การประยุกต์เฮกซะโบรโมแอซีโทนสำหรับโพรเทกชัน ดีโพรเทกชันของแอซีทัลและคีทัล และสำหรับโบรมิเนชันของแอลเคน และสารประกอบไดคาร์บอนิล

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APPLICATIONS OF HEXABROMOACETONE FOR PROTECTION-DEPROTECTION OF ACETALS AND KETALS AND FOR BROMINATION OF ALKANES AND DICARBONYL COMPOUNDS

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A Dissertation Submitted in Partial Fulfillment of the Requirements
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Thesis Title	APPLICATIONS OF HEXABROMOACETONE FOR PROTECTION-DEPROTECTION OF ACETALS AND KETALS AND FOR BROMINATION OF ALKANES AND DICARBONYL COMPOUNDS
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Field of Study	Chemistry
Thesis Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

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กิตติชัย ไชยสีดา : การประยุกต์เฮกซะโบรโมแอซีโทนสำหรับโพรเทกชัน ดีโพรเทกชันของแอซีทัลและคีทัล และสำหรับโบรมิเนชันของแอลเคน และสารประกอบไดคาร์บอนิล (APPLICATIONS OF HEXABROMOACETONE FOR PROTECTION-DEPROTECTION OF ACETALS AND KETALS AND FOR BROMINATION OF ALKANES AND DICARBONYL COMPOUNDS) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.วรินทร ชวศิริ, 112 หน้า.

เฮกซะโบรโมแอซีโทนได้ค้นพบมามากกว่า 100 ปี แต่มีรายงานการนำไปใช้ประโยชน์ค่อนข้างน้อย โดยทั่วไปพันธะระหว่างคาร์บอนและโบรมีนไม่แข็งแรงมากและสามารถแตกได้ด้วยการฉายรังสียูวีเพื่อให้เกิดอนุมูลอิสระที่นำไปใช้กระตุ้นปฏิกิริยาต่างๆ ได้ ในงานวิจัยนี้ ได้ใช้เฮกซะโบรโมแอซีโทนเป็นตัวเร่งปฏิกิริยาสำหรับโพรเทกชันกลีเซอรอลด้วยแอซีโทนเพื่อเตรียมโซลเคทัล โพรเทกชันเบนซัลดีไฮด์ด้วยเมทานอล โพรเทกชันแอลดีไฮด์และคีโทนด้วย 1,3-โพรเพนไดไทออล ดีโพรเทกชันเบนซัลดีไฮด์ไดเมทิลแอซีทัลและแอซีทัล และดีออกซีเมชันของออกซีม โพรเทกชันและดีโพรเทกชันเกิดได้เร็วมากและได้ผลิตภัณฑ์ที่ต้องการในปริมาณสูงในเกือบทุกกรณี โดยใช้เฮกซะโบรโมแอซีโทนในปริมาณน้อยมาก การตรวจสอบด้วยสารจับอนุมูลอิสระแสดงให้เห็นว่า ปฏิกิริยามีอนุมูลอิสระเป็นสารมัธยันตร์ นอกจากนี้ เฮกซะโบรโมแอซีโทนยังสามารถนำไปใช้เป็นโบรมิเนทิงเอเจนต์สำหรับโบรมิเนชันของแอดาแมนเทนและไดเอทิลมาโลเนต ที่อุณหภูมิห้อง ภายใต้รังสียูวี โบรมิเนชันของแอดาแมนเทน ได้ 1-โบรโมแอดาแมนเทนในปริมาณสูง ด้วยความเลือกจำเพาะยอดเยี่ยม ขณะที่สามารถเลือกให้เกิดปฏิกิริยาโมโนและไดโบรมิเนชันของไดเอทิลมาโลเนตได้ โดยการควบคุมระยะเวลาของปฏิกิริยาและปริมาณเฮกซะโบรโมแอซีโทน โดยประมาณแล้วอะตอมของโบรมีนที่ใช้โบรมิเนชันได้คือ 4 อะตอมจาก 6 อะตอม

ภาควิชา เคมี ลายมือชื่อนิสิต .....

สาขาวิชา เคมี ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KITTICHAI CHAISEEDA: APPLICATIONS OF HEXABROMOACETONE FOR PROTECTION-DEPROTECTION OF ACETALS AND KETALS AND FOR BROMINATION OF ALKANES AND DICARBONYL COMPOUNDS. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 112 pp.

Hexabromoacetone (HBA) has been discovered for over a hundred years, but only a few of its applications have been reported. The carbon-bromine bond is generally weak and could be cleaved by UV irradiation, generating radicals that could be used for activating various reactions. In this research, HBA was used as a catalyst for protection of glycerol with acetone to form solketal, protection of benzaldehyde with methanol, protection of a variety of aldehydes and ketones with 1,3-propanedithiol, deprotection of benzaldehyde dimethyl acetal and other acetals, and deoximation of various oximes. The protection and deprotection were very fast and in most cases provided very high yields of the desired products using very small amount of HBA. Tested by a radical trapping reagent, the reactions likely proceeded via radical intermediates. Additionally, HBA was utilized as a brominating agent for the bromination of adamantane and diethyl malonate at room temperature under UV irradiation. The bromination of adamantane provided good yield and excellent selectivity of 1-bromoadamantane, while diethyl malonate can be both mono- and dibrominated depending on the reaction time and amount of HBA. Approximately 4 out of 6 bromine atoms of HBA can be used for bromination.

Department: Chemistry Student's Signature .....
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%	Percent
[bmim]HSO_4	1-Butyl-3-methylimidazolium hydrogen sulfate
°C	Degree Celsius
δ	Chemical shift (NMR)
µL	Microliter(s)
^{13}C NMR	^{13}C Nuclear magnetic resonance spectroscopy
^{1}H NMR	^{1}H Nuclear magnetic resonance spectroscopy
2,3-DhaTph	2,3-Dihydroxyterephthalaldehyde/5,10,15,20-tetrakis(4-aminophenyl)-21*H*,23*H*-porphine
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Al_2O_3	Aluminum oxide
$AlCl_3$	Aluminum chloride
atm	Standard atmosphere
benzyl-THP	2-benzyl tetrahydropyranyl ether
BF_3	Boron trifluoride
Bn	Benzyl
Br_2	Molecular bromine
BrCN	Cyanogen bromide
Bu_4NBr	Tetra-*n*-butylammonium bromide
Bz	Benzoyl
cat.	Catalyst
CBr_4	Carbon tetrabromide
$CBrCl_3$	Bromotrichloromethane
CCBCs	Core-confined bottlebrush copolymers
CCl_4	Carbon tetrachloride
CF_3COOH	Trifluoroacetic acid

CH_2Br_2	Dibromomethane
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CH_3NO_2	Nitromethane
CH_3OH	Methanol
$CHCl_3$	Chloroform
Cl_3CCN	Trichloroacetonitrile
CsHPW	Cesium salt of phosphotungstic acid
$Cu(NO_3)_2 \cdot 3H_2O$	Copper(II) nitrate trihydrate
DCE	1,2-Dichloroethane
DFT	Density functional theory
DMA	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
eq, equiv	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
EtSH	Ethanethiol
$Fe(acac)_3$	Tris(acetylacetonato) iron(III)
g	Gram
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
gem	Geminal
GOAP	Phosphotungstic acid immobilized on amine-grafted graphene oxide
h	Hour(s)
h	Planck constant
H_2	Hydrogen gas

HBA	Hexabromoacetone
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HCO_2H	Formic acid
HOBr	Hypobromous acid
HTIB	[Hydroxy(tosyloxy)iodo]benzene
I_2	Molecular iodine
IDCP	Iodonium dicollidine perchlorate
$KMnO_4$	Potassium permanganate
Li_2MnO_3	Lithium manganese (IV) oxide
$LiAlH_4$	Lithium aluminum hydride
$LiBF_4$	Lithium tetrafluoroborate
$Lu(OTf)_3$	Lutetium triflate
M	Molarity
M.B.	Mass balance
Me	Methyl
Me_2BBr	Dimethylboron bromide
MeOH	Methanol
min	Minute(s)
mL	Milliliter(s)
mmol	Millimole(s)
$Mo(CO)_6$	Molybdenum hexacarbonyl
mol%	Mole percentage
MoO_3	Molybdenum trioxide
MWI	Microwave irradiation
ν	Frequency
N_2	Nitrogen gas
Na_2SO_4	Sodium sulfate
$NaBH_4$	Sodium borohydride
$NaBrO_3$	Sodium bromate
$NaClO_2$	Sodium chlorite

$NaHCO_3$	Sodium bicarbonate
NaI	Sodium iodide
$NaNO_2$	Sodium nitrite
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-Butyllithium
NCS	*N*-Chlorosuccinimide
NH_4OH	Ammonium hydroxide
NHPI	*N*-hydroxyphthalimide (2-hydroxy-1H-isoindole-1,3-dione
$NiAlPO_4$	Nickel aluminum phosphate
NIS	*N*-Iodosuccinimide
nm	Nanometer(s)
OSDA	Organic-structure-directing agent
P_2O_5	Phosphorus pentoxide
PAFs	Porous aromatic frameworks
Ph_3P	Triphenylphosphine
PhF	Fluorobenzene
Pr	Propyl
PSPM	Poly-3-sulfopropyl methacrylate
PTSA	*p*-Toluenesulfonic acid
PWA	Phosphotungstic acid
rt	Room temperature
$RuCl_3$	Ruthenium(III) chloride
s	Second(s)
sat.aq.	Saturated aqueous
SbF_5	Antimony pentafluoride
S-COCC	Sym-collidinium chlorochromate
SiO_2	Silicon dioxide
$SnCl_2$	Tin(II) chloride

TBATB	Tetrabutylammonium tribromide
TBDPS	tert-Butyldiphenylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
$TiCl_4$	Titanium tetrachloride
TiF_4	Titanium tetrafluoride
TLC	Thin-layer chromatography
TUD-1	Technische Universiteit Delft
UV	Ultraviolet
$VOCl_2$	Vanadium chloride oxide
$VOCl_3$	Vanadium(V) oxychloride
W	Watt
XRD	X-ray diffraction

CHAPTER I
INTRODUCTION

1.1 Hexabromoacetone

1,1,1,3,3,3-Hexabromoacetone or hexabromoacetone (HBA) is a derivative of acetone with 3 bromines on each of the two terminal carbons (Figure 1.1). Its information including physical and chemical properties, preparation, handling, and utilization were summarized in e-EROS Encyclopedia of Reagents for Organic Synthesis.[1] It is a white solid at room temperature with a melting point of 107–109 °C. With six bromines on the molecule, HBA is rich with bromine in a single molecule and, therefore, can potentially be a good source of bromine in an easy to use form, unlike molecular bromine, Br_2, which is poisonous and difficult to handle.

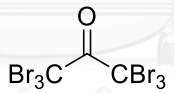


Figure 1.1 Hexabromoacetone (HBA)

The very first report available about HBA was from 1879.[2] Herzig reacted urea with HBA to produce α- and β-cyanuric acids. However, several years later, in 1886 Senier presented two publications in which he repeated Herzig's experiment with further examinations and found that α- and β-cyanuric acids that Herzig found were identical with ordinary cyanuric acid.[3, 4] Since then very few publications on HBA have been reported. Several decades later, Heller *et al*. reported the formation of HBA

from the reaction of excess bromoacetic acid with 2,6-diacetamidoquinone.[5] Ralph and Robertson also reported the synthesis of HBA from 2,4,5-trihydroxyphenylglyoxylic acid and bromine water in 1950.[6] Shvarts *et al*. in 1960 reported that a mixture of penta- and hexabromoacetone were prepared from the reaction of citric acid and acetonedicarboxylic acid with bromine water in the presence of $VOCl_3$, $VOCl_2$, or $KMnO_4$ with the addition of HCl and $TiCl_4$.[7] The method used for the preparation of HBA in this research was first reported by Gilbert.[8] Acetone is brominated using Br_2 and NaOAc as a base in acetic acid at 90 ℃ as shown in Figure 1.2.

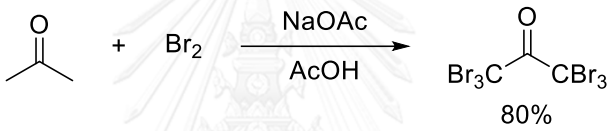


Figure 1.2 Synthesis of HBA

The first report for using HBA as a brominating agent was published by Oppolzer and Mirza in 1984.[9] They used HBA/Ph_3P in sulfolane for the conversion of an allylic alcohol to a bromide (Figure 1.3), which was subsequently used for *N*-alkylation of amide.

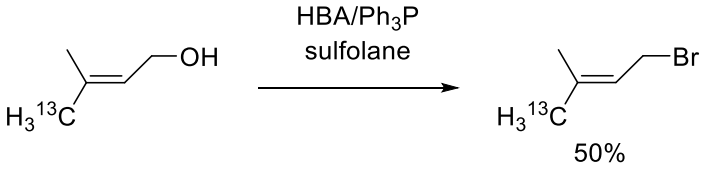


Figure 1.3 Conversion of an allylic alcohol to a bromide using HBA/Ph_3P in sulfolane

In 1990, Sugano *et al*. used HBA as a reagent for producing pentabromopropen-2-yl tribromo- and dibromoacetate, active compounds found in the extract of the red alga *Asparagopsis taxiformis* by treating HBA with tribromo- or dibromoacetyl chloride and Zn(0) in dry acetonitrile (Figure 1.4).[10]

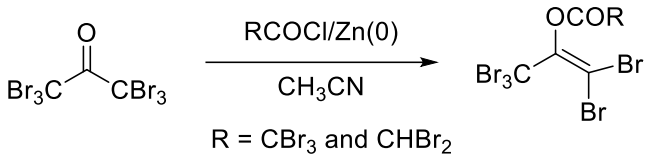


Figure 1.4 Synthesis of pentabromopropen-2-yl tribromo- and dibromoacetate

Recently, several more publications on the utilization of HBA have been reported. In 2008, Tongkate *et al*. used HBA and ethyl tribromoacetate as a reagent for bromination of various alcohols providing high yields of the corresponding alkyl bromides under mild reaction conditions in a short time (Figure 1.5).[11] A competitive study between brominating agents and Cl_3CCN also revealed that the activity of HBA was 9 times higher than that of CBr_4.

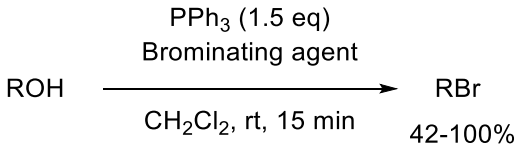


Figure 1.5 Use of HBA and other brominating agents for bromination of alcohols

A year later, Menezes *et al*. reported the use of HBA as tribrominating agent of alcohols and amines (Figure 1.6) and also as mediator for the formation of amides from carboxylic acids in the presence of PPh_3 (Figure 1.7).[12] For tribromoacetylation of

alcohols, the yields ranged from 55-65% after 10 h in DMF at 60 °C. The tribromoacetylation of amines also gave relatively high yields of the corresponding products, ranging from 48 to 74%. However, in the cases of *i*-propylamine and *s*-butylamine, the 2,2-dibromo-*N*-alkylacetamide byproducts were also formed along with 2,2,2-tribromo-*N*-alkylacetamides as shown in Figure 1.6b.

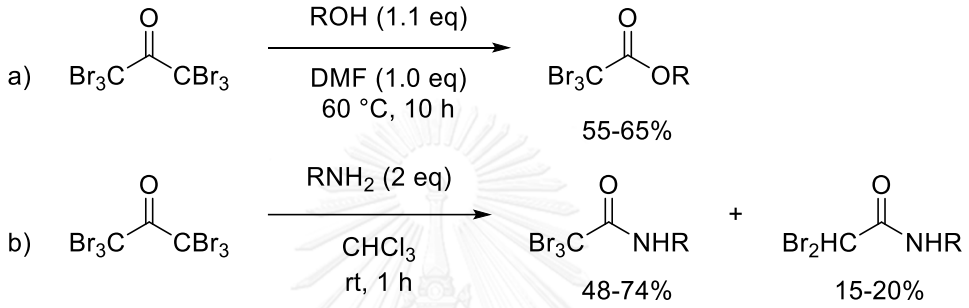


Figure 1.6 Use of HBA as tribrominating agent of a) alcohols and b) amines

When HBA was used as brominating agent in the presence of PPh_3 in CH_2Cl_2 for the conversion of carboxylic acids and then, subsequently, amidation of the corresponding acid bromides (Figure 1.7), the authors showed several examples that produced over 50% yields of the amides. The reactions can be performed in one-pot without the need to separate or purify the acid bromide intermediates.

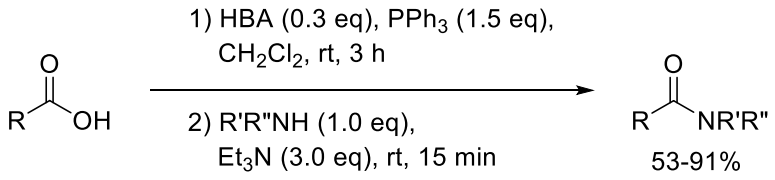


Figure 1.7 Use of HBA as mediator for the formation of amides from carboxylic acids in the presence of PPh_3

In 2011, Joseph and Larraza-Sanchez reported the conversion of alcohols to bromides similar to that previously reported by Tongkate *et al*. but focused more on benzyl alcohol and its derivatives with various electron-withdrawing and electron-donating groups as substituents (Figure 1.8).[13] In all presented substrates, the yields of the corresponding bromides were very high, 75-100 %, though in several cases the reaction temperature had to be raised to 40 °C. The steric hindrance by a substituent on the *ortho* position also affected the efficiency, resulting in lower yields of the products. They also tried other heterocyclic analogues and the yields were very high. Several solvents including THF, DCE, toluene, acetonitrile, and dichloromethane were tested and they all produced yields over 80%.

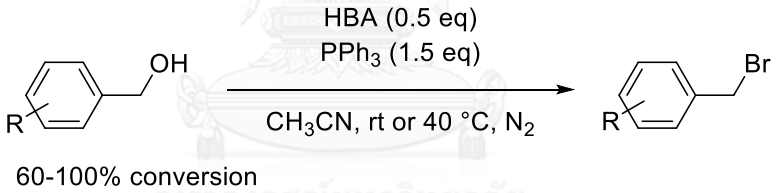


Figure 1.8 Conversion of benzyl alcohol derivatives to the corresponding bromides using HBA and PPh_3

Since the publication of the above methods and HBA is now commercially available, more researchers have adopted these methods for synthesizing complex molecules. For example, Murphy *et al*. used HBA and PPh_3 for converting alcohols to bromides in one of the steps in their preparation of new deoxycytidine kinase inhibitors (Figure 1.9).[14] There are several other functional groups on the starting compounds but the authors did not report any complication and the yields were 74-92%.

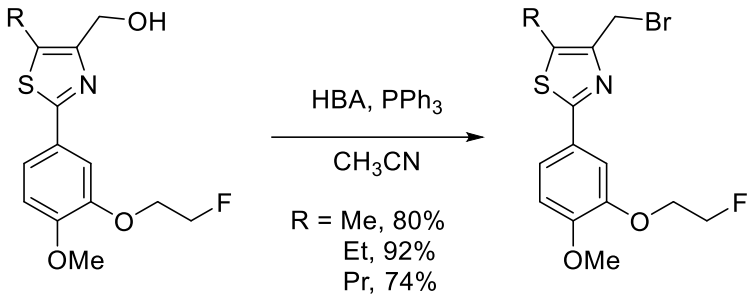


Figure 1.9 Conversion of alcohols to the corresponding bromides using HBA and PPh_3

In another example, Rosokha *et al*. used HBA for the preparation of tribromoacetamide by reacting HBA with NH_4OH in which CBr_3 acted as a leaving group (Figure 1.10).[15] Tribromoacetamide was later dehydrated with P_2O_5 to form tribromoacetonitrile.

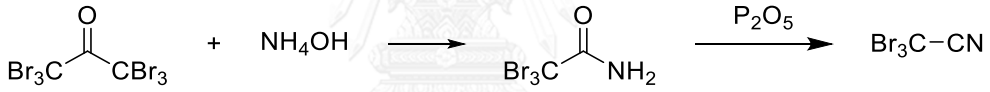


Figure 1.10 Preparation of tribromoacetamide and tribromoacetonitrile from HBA

1.2 Objectives

As seen from the previous section, despite having been discovered over a hundred years ago, the application of HBA has not been explored much. One of the main topics of research emphasized in our lab is the methodology for converting from one functional group to another using small organobromine and organochlorine compounds such as HBA,[11] trichloroacetonitrile,[16-18] CBr_4,[16, 17] ethyl tribromoacetate,[11, 19-21] hexachloroethane,[22] and trichloroacetamide.[17, 23-25]

Therefore, in this research, utilization of HBA as a catalyst and brominating agent will be explored for the following reactions:

1. Protection of alcohols and carbonyl compounds
2. Deprotection of acetals and ketals and conversion of oximes to carbonyl compounds
3. Bromination of alkanes and 1,3-dicarbonyl compounds

CHAPTER II

PROTECTION OF HYDROXYL AND CARBONYL COMPOUNDS BY HBA

2.1 Introduction and literature reviews

One of the problems frequently encountered during the functional group transformation in a multifunctional molecule is the incompatibility of the selected method with other functional group(s) in the molecule; therefore, protection of this functional group is required before conversion of the desired functional group is performed. For instance, in Figure 2.1 the direct reduction of methyl 4-oxocyclohexane-1-carboxylate with lithium aluminum hydride ($LiAlH_4$) will result in the reduction of both the ester and the ketone to the corresponding alcohols.[26] If one wants to selectively reduce only the ester then the ketone needs to be protected. In this example, ethylene glycol, catalyzed by an acid, is used to protect the ketone to form a dioxolane. Subsequently, when the product is reduced by $LiAlH_4$ then only the ester is reduced to the corresponding alcohol since $LiAlH_4$ cannot reduce the dioxolane. To recover the original ketone, an aqueous acid is used to convert the dioxolane to the ketone, a process called deprotection. This will give the product that only the ester is reduced to an alcohol.

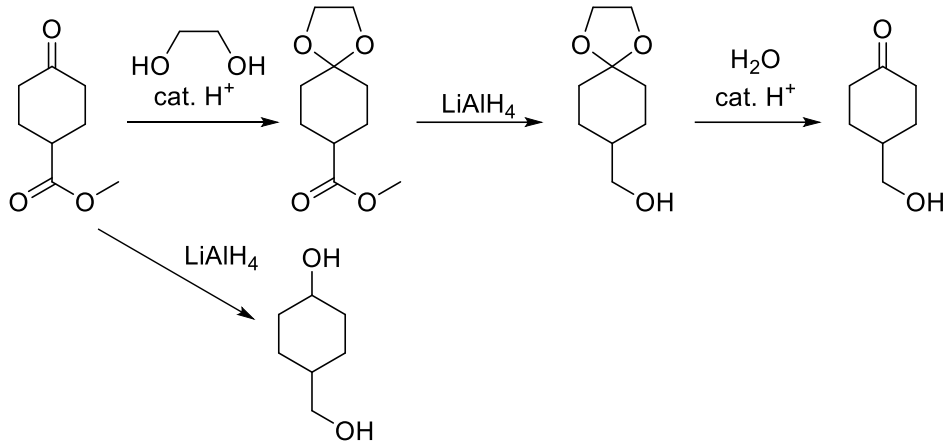


Figure 2.1 Acetal protection of a ketone during reduction of an ester vs. reduction to a diol when unprotected

This protection-deprotection process is not without a criticism since it adds additional steps to the overall synthesis and various researchers have tried to perform the conversion without protection-deprotection.[27-30] However, protection-deprotection is unavoidable in most cases and is still the method of choice. Many protective and deprotective methods have been reported. However, “no protective group is the best protective group,”[31] as it depends on the substrate that is being worked on and selectivity is mostly the key. Researchers still try to find a more selective, convenient, fast, and economical method. A good protective group should have the following properties:[31]

- It must selectively react with the substrate in good yield and the protected substrate must be stable in the desired reaction.
- The protective group must be selectively removed in good yield by readily available reagents that do not attack the regenerated functional group.

- The protective group should produce a derivative (without creating a new stereogenic center) that can be easily separated from side products from its formation or cleavage.
- The protective group should have a minimum of additional functionality to avoid side reactions.

Depending on the reaction performed, functional groups that are normally required to protect are hydroxyl, amine, carbonyl, carboxylic acid, phosphate, and terminal alkyne. In this research, hydroxyl, primarily 1,2- and 1,3-diols, and carbonyl compounds are the main focus.

2.1.1 Protection of hydroxyl compounds

When the compound that is being worked on has a hydroxyl group and there is a need to do a transformation on another functional group in the molecule such as oxidation, acylation, halogenation with phosphorus or hydrogen halides, and dehydration then this hydroxyl group likely requires to be protected.[31] Hydroxyl compounds are normally protected by converting them to ethers or esters, while 1,2- and 1,3-diols can be protected by making cyclic acetals and ketals. Among various cyclic acetals and ketals that have been reported, the formation of acetonide (isopropylidene ketal) would be the main focus and it is the most commonly used protection for 1,2- and 1,3-diols. In carbohydrate chemistry, there are many hydroxyls and the acetonide has been extensively used to protect the desired group. The use of

acetone, which is cheap, readily available and easy to remove, and other small molecules also makes this method attractive as a protective group. Because of its advantages and popularity, 33 preparative methods using various reagents and catalysts were listed in the latest edition of Greene's Protective Groups in Organic Synthesis, while the classical method is the reaction of diol with acetone using an acid as a catalyst.[31] From this list, here are some of the examples that are related, particularly those that used HBr, halogens or halogenated compounds, to the method that will be reported in this research.

Corey *et al*. used 0.5 equivalent of dry HBr as a catalyst and excess 2-methoxypropene in dichloromethane at 0 °C for 16 h and then selective methanolysis of the isolated product with Amberlite IRC-50 in methanol at 20 °C for 12 h to give 75% of the acetonide ester for the total synthesis of erythronolide B (Figure 2.2).[32]

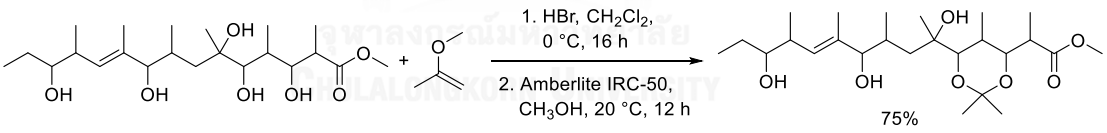


Figure 2.2 Formation of acetonide ester using HBr as a catalyst

The next 4 examples used molecular iodine (I_2) as a catalyst. The very first report was published by Kartha in 1986 in which I_2 and acetone were used for the ketalization of sugars.[33] Various sugars were tested and the yields were around 70-85% in 25 min to 4.5 h. When the reactions were performed at refluxing temperature the reaction time was significantly reduced. For example, for L-arabinose the reaction

was reduced from 2 h to 20 min giving 85% yield of the corresponding product under both conditions. Since these sugars are nearly insoluble in acetone, the reaction was found to be complete when the sugars went into solution.

Another example used acetone and polymer-bound Ph_3P/I_2 complex (Figure 2.3).[34] The advantages of this method are the ease of purification, non-equilibrium reaction condition, and mild condition. The authors compared their method with previously published results and this method gave better yields in nearly all substrates.

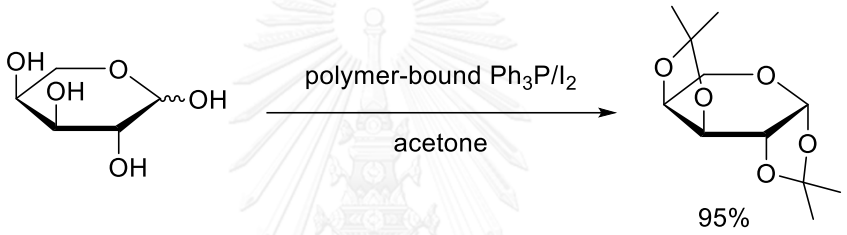


Figure 2.3 Ketalization of L-arabinose using acetone and polymer-bound Ph_3P/I_2 complex

In 2007, Mukherjee *et al*. reported the use of I_2 with enolacetates for the tandem ketalization-acetylation of sugars and related derivatives (Figure 2.4).[35] The 1,2-*cis* diols formed the corresponding acetal/ketals while the remaining hydroxyl groups are acetylated and the yields were 62-91%. The reactions preferentially produced acetonide acetate at lower temperature whereas at high temperature the major products were peracetate.

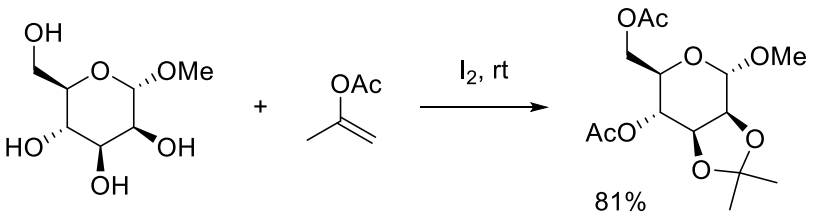


Figure 2.4 Tandem acetalation-acetylation of sugars with enolacetates using molecular iodine as a catalyst

The other example using I_2 was reported by Houston and Koreeda (Figure 2.5).[36] They first tried various alcohols in THF for ribosylation reactions promoted by I_2. After the solvent was changed from THF to acetone, acetonides were partly formed and with the use of only dry acetone without an alcohol, only the acetonide shown in Figure 2.5 was obtained at 91% yield without the ribosylation product.

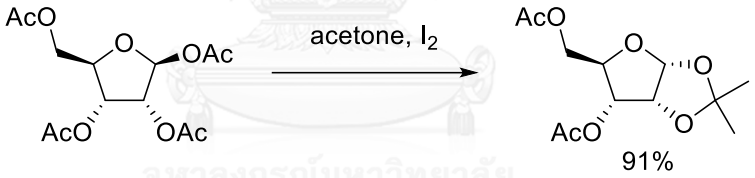


Figure 2.5 Acetonide formation using acetone and I_2

In 1995, Madsen and Fraser-Reid reported the use of iodonium dicollidine perchlorate (IDCP) or various *N*-halosuccinimides with Lewis or protic acid for the formation of ketals.[37] For the case of NBS/BF_3•OEt_2, the reaction took only 5 min to give 94% of the product without affecting the existing functional groups as shown in Figure 2.6. The other advantages of this method are the mild reaction conditions and

its compatibility with highly acid labile substrates while the ketal protective groups present in the substrate are neither scrambled nor exchanged.

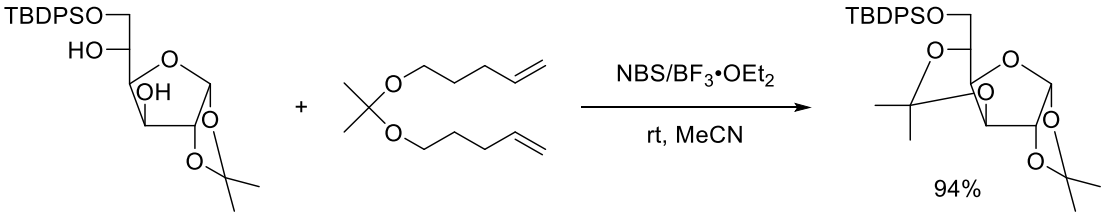


Figure 2.6 Ketalization using $NBS/BF_3•OEt_2$ as a catalyst

Acetalization is not only for protection of hydroxyl group, but it also can be used for producing fine chemicals. For instance, with the recent popularity of biodiesel, large excess glycerol byproduct is being produced and one way to convert this excess glycerol to a fine chemical is to make its ketal, called solketal, as shown in Figure 2.7. Solketal is a valuable chemical and being utilized as a solvent, plasticizer, surfactant, flavor enhancer, pharmaceutical intermediate, and fuel additive.[38]

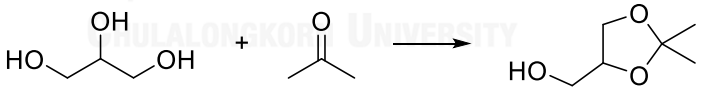


Figure 2.7 Conversion of glycerol to solketal

Here are some latest examples of publications on the production of solketal from glycerol. In Figure 2.8, Pierpont *et al*. reported the use of $Lu(OTf)_3$ to catalyze the formation of solketal from glycerol and acetone.[39] The reaction fully converted glycerol to solketal as a sole product within 1-3 h depending on the source of glycerol and acetone. The variation in reaction time was attributed to the amount of water that

may be present in the reagents. In addition, the authors used DFT computations to explain the regioselective preference toward the five-membered ring 1,3-dioxolane (solketal) over the six-membered ring product (1,3-dioxane). According to their speculation, because of the symmetry of the intermediates, only solketal product was possible.

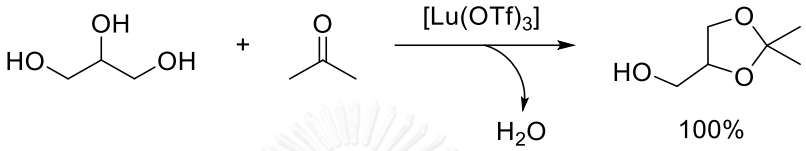


Figure 2.8 Lutetium triflate catalyzed ketalization of acetone with glycerol

Solketal was also synthesized by a batch process using sulfonic ion exchange resin Lewatit GF101.[40] Esteban *et al*. optimized the condition including stirring rate, external and internal mass transfer, particle size of the resin, temperature, ratio of acetone to glycerol, and catalyst loading. In another example, Li *et al*. used metal-containing TUD-1 mesoporous silicates as solid acid catalysts.[41] The metals used included Sn, Zr, and Hf. The selectivity of solketal was very high at over 99% for all metals while the conversion was 44-52%.

Ramazanov *et al*. used β and Y zeolites and KU-2 and Amberlyst 70 cation-exchange resins as catalysts and found that zeolites were better catalyst than cation-exchange resins and the rate of the reaction over β zeolite was lower than Y zeolite.[42] M-$AlPO_4$/x$AlPO_4$ (x = Zn, Cu, Ni, or Co) solid acid catalysts were also used by Zhang *et al*.[43] The catalysts of various metals gave solketal 57-75% in 1 h and M-

$NiAlPO_4$ gave the highest yield at 75% with the best selectivity at 75% as well. Various types of Brønsted solid acid catalysts including various forms of zeolites, Amberlyst-15, cesium salt of phosphotungstic acid (CsHPW), Montmorillonite K-10, molybdenum oxide supported on silica (MoO_3/SiO_2) were tested by Manjunathan *et al*. and they found that H-Beta zeolite had the highest catalytic activity with 86% glycerol conversion and 98.5% selectivity of solketal.[44] Jose da Silva *et al*. used $SnCl_2$ to catalyze the reaction, but the reaction of acetone and glycerol gave quite low yield with high selectivity when performed in acetonitrile solution.[45] They tested other ketones as well and found that cyclohexanone showed the highest conversion. All ketones gave much higher conversion when performed under solvent-free condition. The catalyst can be recovered and recycled several times without losing activity.

Aluminum triflate-grafted MCM-41 was synthesized for the ketalization of glycerol with acetone by Tayade *et al*.[46] Since the reaction produces water as a co-product, they modified this mesoporous solid acid catalyst to be more water-tolerant. The catalyst gave high conversion of glycerol (over 86%) under various conditions and when recycled still retained its high reactivity. Another example is the use of organic-inorganic hybrid catalyst.[47] Sandesh *et al*. prepared organic-inorganic hybrid catalyst from organic ammonium salt and heteropoly acid and used for solketal production. $(C_3H_7)_4N^+$/PWA showed higher activity than other solid acid catalysts giving 94% glycerol conversion and 98% selectivity for solketal. The catalyst was also water-tolerant and can be recycled multiple times.

2.1.2 Protection of carbonyl compounds

Several protective methods are available for the protection of carbonyl compounds such as aldehydes and ketones and one of them is to convert them to acetals or ketals.[31, 48] Classical method for making acetals or ketals uses an acid to catalyze and the mechanism is generally well-known as shown in Figure 2.9. The use of acid is sometimes not compatible with the intended substrate and the reaction generally requires the use of the Dean-Stark apparatus to remove water and shift the equilibrium toward the product.

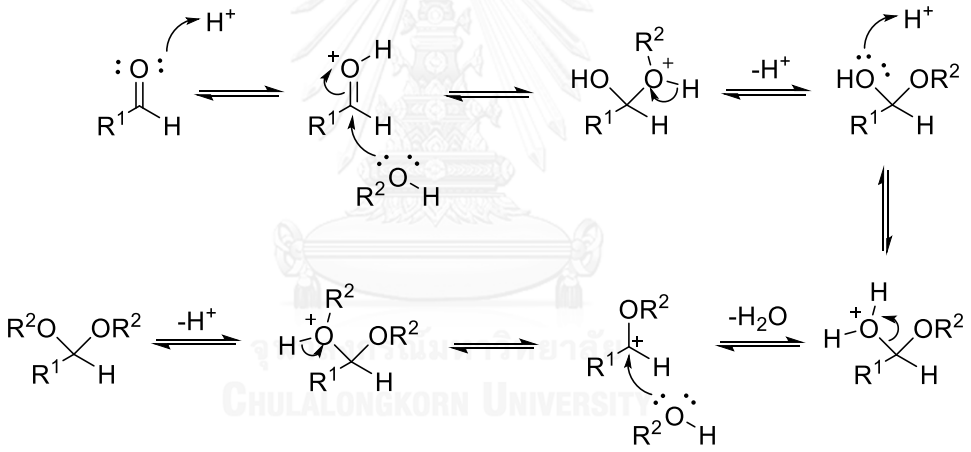


Figure 2.9 Mechanism of acetalization using acid as a catalyst

Many methods have been reported for the preparation of acetals and ketals. Some examples will be shown here. The first example reported by Khan *et al*. used (bromodimethyl)sulfonium bromide as a catalyst for acetalization, thioacetalization (discussed below) and transthioacetalization under solvent-free conditions (Figure 2.10).[49] The catalyst is very versatile and can be used for a wide range of substrates

giving products 65-98% yield at room temperature. To make acetals, alcohols or diols and triethyl orthoformate were used as the protective species while for dithioacetals thiol or dithiols was used. They were also able to convert from *O,O*-acetals to the corresponding dithioacetals using the same conditions. The reaction conditions were mild and compatible with other protective groups. They did not notice brominations when substrates with double bond or α to the keto position or aromatic ring were used. The authors proposed that the true catalyst was likely to be HBr generated *in situ*. They also found that the reaction was selective toward aldehydes when ketones are present.

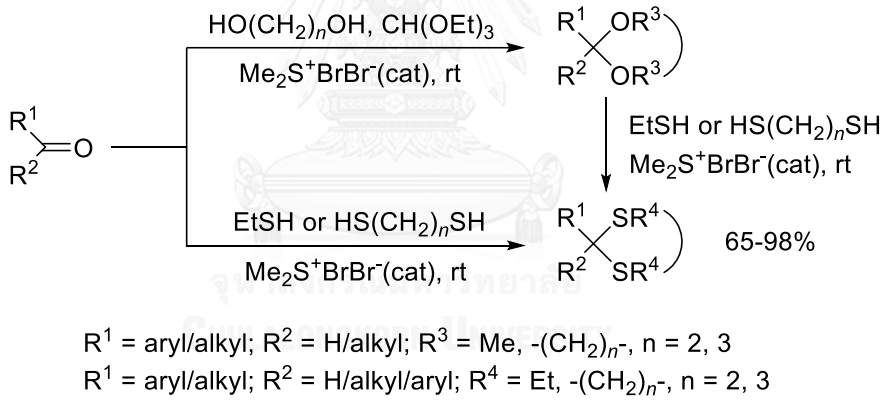


Figure 2.10 Acetalization, thioacetalization and transthioacetalization using (bromodimethyl)sulfonium bromide as a catalyst under solvent-free conditions

Myles *et al*. developed various Brønsted acidic imidazolium salts that can be used for acetalization and thioacetalization (Figure 2.11).[50, 51] The best catalyst for acetalization is shown below and using only 0.1 mol% of the catalyst the acetalization of benzaldehyde with methanol gave 94% of the acetal product in 24 h. The

advantages of their catalysts are that they are recyclable and more active than previously reported aprotic salts.

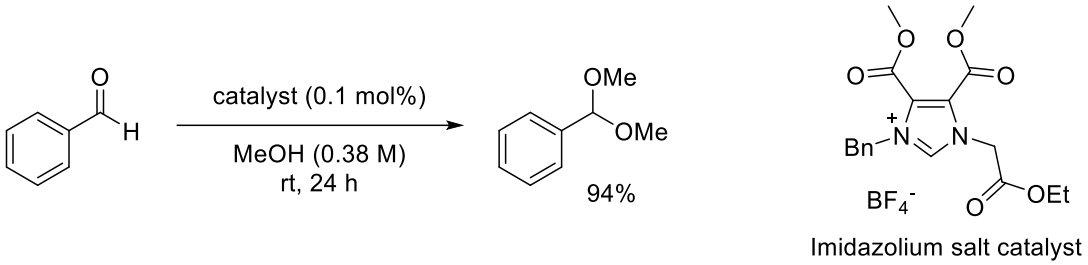


Figure 2.11 Use of Brønsted acidic imidazolium salts as a catalyst for protection of benzaldehyde with methanol

Another method that has gained more interest is the use of metal organic frameworks (MOFs) as solid heterogeneous catalysts. Dhakshinamoorthy *et al*. compared various MOFs for the protection of benzaldehyde and other carbonyl compounds with methanol (Figure 2.12).[52] $Cu_3(BTC)_2$ (BTC=1,3,5-benzenetricarboxylic acid) was the best MOFs giving 63% of the acetal in 2 h. The authors also compared $Cu_3(BTC)_2$ with several other homogeneous and heterogeneous catalysts for the acetalization of aldehydes and ketalization of ketones and found that $Cu_3(BTC)_2$ was better than most catalysts except $Cu(NO_3)_2 \cdot 3H_2O$. The catalyst was characterized with X-ray powder diffraction (XRD) before and after the reaction to determine its reusability and the crystallinity of $Cu_3(BTC)_2$ was maintained after the reaction. $Cu_3(BTC)_2$ was used to catalyze a variety of aldehydes and ketones but not all of them were successful. Reaction of benzaldehyde with glycerol gave the five-membered ring as the major

product. Comparative study of benzaldehyde and acetophenone showed that the protection of the aldehyde was preferred.

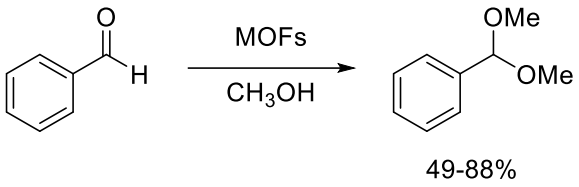


Figure 2.12 Use of MOFs as a catalyst for protection of benzaldehyde with methanol

Wang *et al.* also reported the use of MOFs.[53] Hybrid nanoflowers from boron nitride nanosheets (BNNSs) and the metal–organic framework (MOF)MIL-53 was prepared for the acetalization of benzaldehyde with methanol. This hydrid nanoflowers showed higher activity than just MOFs.

Another popular method that is commonly used for protection of the carbonyl group is to convert to thioacetal or thioketal, the sulfur analog of acetal and ketal. As seen in Figure 2.13., cyclic thioacetal is called 1,3-dithiane when *n* = 3 and 1,3-dithiolane when *n* = 2.

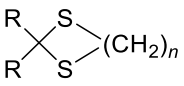


Figure 2.13 1,3-Dithiane (n = 3) and 1,3-dithiolane (n = 2)

The reagents generally used for the formation of 1,3-dithiane and 1,3-dithiolane are 1,3-propanedithiol and 1,2-ethanedithiol, respectively. These reagents have a foul smell and occasionally produced by products that are difficult to remove during

deprotection. However, its benefits outweigh its disadvantages. 1,3-Dithiane and 1,3-dithiolane are exceptionally stable in acidic condition compared to the dioxolane or 1,3-dioxane groups.[31] In addition, the dithianes or ditholanes formed from aldehydes can be deprotonated by *n*-BuLi to produce an anion that can react with various electrophiles to form a carbon-carbon bond, a very useful method for synthesizing larger molecules (Figure 2.14).[54] Moreover, there are several other reagents that can be used in place of 1,3-propanedithiol and 1,2-ethanedithiol, which will help avoiding the stench smell.[31]

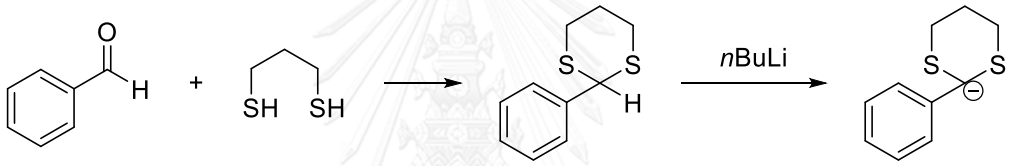


Figure 2.14 An example of the preparation of an anion from a dithiane

According to Greene's Protective Groups in Organic Synthesis, there are 3 main methods for making 1,3-dithiane and 1,3-dithiolane including Lewis acid-catalyzed methods, uses of solid-supported reagents, and methods that form an acid *in situ*.[31] Several of these catalysts are also used for the preparation of dioxolane or 1,3-dioxane groups. Here are examples of some methods that used halides or halogenated compounds.

In the first example, Naik *et al*. reported the use of tetrabutylammonium tribromide (TBATB) for chemoselective thioacetalization and transthioacetalization (Figure 2.15).[55] Only 2 mol% of TBATB was used and the reactions produced 45-97%

of the corresponding 1,3-dithiolane and 1,3-dithiane from various aldehydes and ketones. The reaction time varied from 0.08-3 h. Comparative studies also found that the reactions were more selective toward aldehydes than ketones similar to the method by Khan *et al*. In addition, the reactions were also more selective toward aromatic aldehydes with electron-donating substituents than those with electron-withdrawing substituent. For transthioacetalization, 1 mol% of TBATB was sufficient for the conversion.

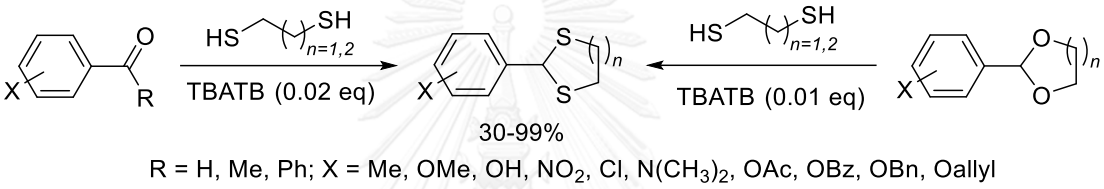


Figure 2.15 Thioacetalization and transthioacetalization using tetrabutylammonium tribromide (TBATB) as a catalyst

The next two examples both used I_2 as a catalyst and were published almost at the same time. The first one was by Samajdar *et al*. and the reactions were simple, fast, and mild and gave very high yields of the products (Figure 2.16).[56] Like other methods, the authors found that the reactions were more selective toward aldehydes than ketones. They also found that it was more selective toward aliphatic ketones than aromatic ketones. When they tried to protect the carbonyl groups in androstane, dithioacetal was formed only on the six-membered ring ketone and not on the five-membered ring ketone, which was more sterically hindered as well.

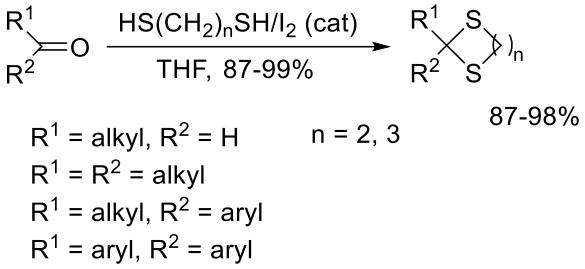


Figure 2.16 Thioacetalization using I_2 as a catalyst

The other example by Deka and Sarma used I_2 supported on neutral alumina under solvent-free conditions (Figure 2.17).[57] For most carbonyl compounds tested, the reactions were very fast, mostly around 10 min, with very good yields of the corresponding products. Only benzophenone and camphor took very long time, over 4 h, and had to be performed under refluxing dichloromethane.

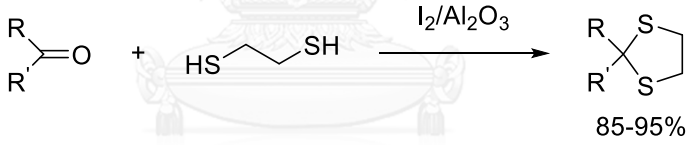


Figure 2.17 Thioacetalization using I_2 and alumina as a catalyst

Kamal *et al*. reported the use of NBS as a catalyst for oxathioacetalization, thioacetalization and transthioacetalization in two publications (Figure 2.18).[58, 59] The yields were quite high but mostly not as high as other methods. However, they can be accomplished in a short period of time in most cases. Selectivity was the same as other methods in which it was more selective toward aldehyde than ketone as well as more selective toward aliphatic ketone than aromatic ketone. When the molecule had both a ketone and an ester, only the ketone was protected.

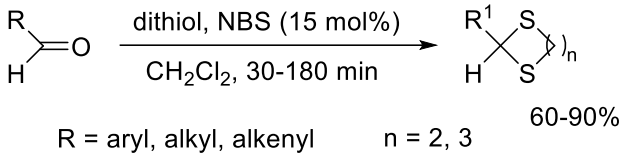


Figure 2.18 Thioacetalization using NBS as a catalyst

2.2 Objectives

To use HBA as a catalyst for the protection of hydroxyl and carbonyl compounds.

2.3 Experimental

2.3.1 Instruments and equipment

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus NMR spectrometer or a Varian Mercury NMR spectrometer with an Oxford YH400 magnet operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. GC analysis was performed using a Varian CP-3800 Gas Chromatograph equipped with SGE BP1 or BP21 column. The home-made UV reactor consists of eight UV lamps (6 W, 254 nm, Sylvania G6W T5) and a fan for ventilation (Figure 2.19 and Figure 2.20). A magnetic stirrer was placed underneath the UV reactor to stir the reaction. For the reactions under UV irradiation, the reactions were performed in custom-made quartz tube for maximum UV transmission (Figure 2.21). Sonication was performed using Elma Transsonic T460/H ultrasonic unit.

Figure 2.19 Home-made UV reactor

Figure 2.20 Home-made UV reactor showing UV lamps

Figure 2.21 Custom-made quartz tubes and their stand

2.3.2 Chemicals

Chemicals and solvents were purchased from standard suppliers and were used without further purification. HBA was either synthesized[8] or obtained from Sigma-Aldrich.

2.3.3 Synthesis

2.3.3.1 Synthesis of HBA

Acetic acid (35 mL) was added to a 100-mL two-necked round-bottom flask. NaOAc 11.0 g (133 mmol) was then added small-portion-wise so it did not form a chunk and the mixture was vigorously stirred at room temperature for 30 min. The mixture became white and viscous. Acetone 1.4 mL (19 mmol) was added drop-wise. Br_2 6.88 mL (133 mmol) was added to an addition funnel attached on the side neck of the round-bottom flask. The mixture was heated to 60 °C and then Br_2 was added

from the addition funnel to the reaction mixture drop-wise. The temperature was raised to 90 °C and the mixture was refluxed for 5 h. The solution was cooled down to room temperature and poured into 50 mL cold water. The precipitate was filtered using suction flask and rinsed with cold water. The crude product was recrystallized using hexane. The yield was 40-60% based on acetone used. ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6 (C=O) and 24.8 (CBr_3).[8]

2.3.4 General procedure

2.3.4.1 Conversion of glycerol to solketal

Representative procedure for the conversion of glycerol to solketal: To a 25-mL quartz tube was added the specified amount of glycerol, HBA, and acetone. The reaction mixture was stirred and irradiated by a home-made UV reactor for the desired time at room temperature. To quantify the product using GC, the specified amount of naphthalene was added as an internal standard.

2.3.4.2 Protection of benzaldehyde with methanol

Representative procedure for protection of benzaldehyde with methanol: To a 25-mL quartz tube was added the specified amount of benzaldehyde, HBA, and methanol. The reaction mixture was stirred and irradiated by a home-made UV reactor for the desired time at room temperature. To quantify the product using GC, the specified amount of biphenyl was added as an internal standard.

2.3.4.3 Protection of carbonyl compounds with 1,3-propanedithiol

Representative procedure for the protection of carbonyl compounds with 1,3-propanedithiol: To a 25-mL quartz tube was added the specified amount of aldehyde or ketone, HBA, and 1,3-propanedithiol. The reaction mixture was stirred under various conditions as specified for the desired time. To quantify the product using GC, the specified amount of biphenyl was added as an internal standard.

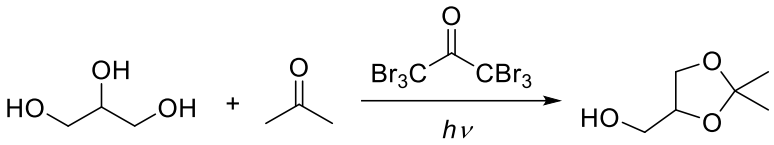
2.4 Results and discussion

2.4.1 Conversion of glycerol to solketal by HBA

For the protection of glycerol with acetone (Table 2.1), using 2.5 mol% of HBA the yield of solketal was 75% after only 1 min (entry 1) and 87% after 5 min (entry 2). Increasing the reaction time to 10 and 30 min, the yields did not change much (entries 3 and 4). Reaction conditions were then changed to improve the product yield. Since the formation of acetal generally generates water, to drive equilibrium to the solketal product, a drying agent could be added to absorb water. However, in this case when 50 mg of molecular sieves type 4A was added to the reaction mixture, the yield of solketal did not improve (entry 5). Doubling the amount of HBA still did not increase the product yield (entry 6) while doubling the amount of acetone only slightly increased the product yield (entry 7). It should be noted that under UV irradiation and without HBA (entry 8), with HBA and without UV irradiation (entry 9), and without HBA and UV irradiation (entry 10), only trace amount or none of solketal was detected by

GC. Overall, HBA was successfully used to catalyze the conversion of glycerol to solketal with acetone and only 2.5 mol% of HBA was used. Using higher amount of acetone would give higher amount of solketal product.

Table 2.1 Conversion of glycerol to solketal by HBA



Entry	Time (min)	Remaining Glycerol (%)[a]	Yield of Solketal (%)[a]	M.B.[b] (%)[a]
1	1	15	75	90
2	5	8	87	95
3	10	10	88	98
4	30	10	85	95
5[c]	10	12	86	98
6[d]	10	14	86	100
7[e]	10	5	90	95
8[f]	10	99	1	100
9[g]	10	100	0	100
10[f,g]	10	100	0	100

Reaction conditions: 1 mmol glycerol, 1 mL acetone, 0.025 mmol (2.5 mol%) HBA, rt.

[a] Determined by GC.

[b] Mass balance.

[c] 50 mg of molecular sieves type 4A was added to the reaction mixture.

[d] 0.050 mmol (5 mol%) HBA was used.

[e] 2 mL acetone was used.

[f] Without HBA.

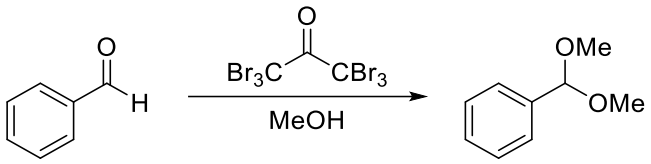
[g] Without UV irradiation.

2.4.2 Protection of benzaldehyde with methanol using HBA as a catalyst under UV irradiation

2.4.2.1 The effect of the amount of methanol for protection of benzaldehyde with methanol

The amount of methanol was varied for the protection of benzaldehyde using HBA as a catalyst. Since this reaction is generally reversible, increasing the amount of methanol should shift the reaction toward the product. As shown in Table 2.2, when the amount of methanol increased from 0.5 mL to 16 mL, the amount of benzaldehyde dimethyl acetal did increase. The amount of the product reached a plateau of about 95% after 8 mL of methanol was used. The reactions were performed under UV irradiation for 10 min.

Table 2.2 The effect of the amount of methanol for protection of benzaldehyde with methanol



Entry	MeOH (mL)	Remaining Aldehyde (%)[a]	Yield of Acetal (%)[a]	M.B.[b] (%)[a]
1	0.5	29	71	100
2	1	15	84	99
3	2	12	88	100
4	4	10	89	99
5	8	4	95	99
6	16	5	95	100

Reaction conditions: 1 mmol benzaldehyde, 0.025 mmol (2.5 mol%) HBA, 10 min UV irradiation, rt.

[a] Determined by GC.

[b] Mass balance.

2.4.2.2 The effect of the amount of HBA for protection of benzaldehyde with methanol

The amount of HBA was also varied from 0.63 to 5 mol% in order to find the optimal amount (Table 2.3). The reactions were performed under UV irradiation for 10 min using 8 mL of methanol. At 0.63 mol%, only 66% of benzaldehyde dimethyl acetal was formed, indicating that this was too small amount (entry 1). When the amount of HBA was raised to 1.25 to 5 mol%, the yields increased to above 90%, but were not over 95% (entries 2-4). This means that using between 1.25 and 2.5 mol% of HBA

should be sufficient for this reaction. In addition, for control experiments, when the reactions were performed either without HBA or UV irradiation (entries 5-7), there was no acetal produced at all. This indicates that both HBA and UV irradiation are required.

Table 2.3 The effect of the amount of HBA for protection of benzaldehyde with methanol

Entry	HBA (mol%)	Remaining Aldehyde (%)[a]	Yield of Acetal (%)[a]	M.B.[b] (%)[a]
1	0.63	33	66	99
2	1.25	9	91	100
3	2.5	4	95	99
4	5.0	10	90	100
5[c]	2.5	100	0	100
6	0	100	0	100
7[c]	0	100	0	100

Reaction conditions: 1 mmol benzaldehyde, 8 mL MeOH, 10 min UV irradiation, rt.

[a] Determined by GC.

[b] Mass balance.

[c] Without UV irradiation.

In summary, protection of benzaldehyde with methanol by HBA produced very high yield of the acetal product in very short time. Higher amount of methanol used will result in higher yield of the product. The amount of HBA can be reduced to as low as 1.25 mol% and the reaction still can produce high yield of the product.

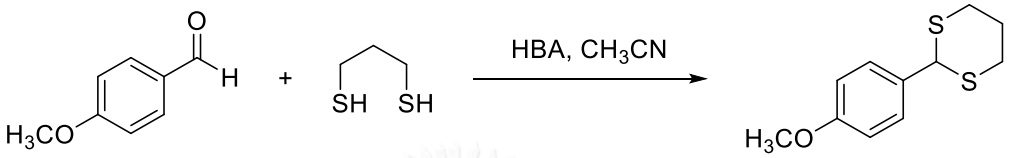
2.4.3 Protection of *p*-anisaldehyde with 1,3-propanedithiol by HBA

2.4.3.1 The effect of UV irradiation and HBA on protection of p-anisaldehyde with 1,3-propanedithiol

Protection of *p*-anisaldehyde with 1,3-propanedithiol was tested under various conditions to find the optimal reaction conditions as well as to see the effect of UV irradiation and HBA (Table 2.4). Without UV irradiation and HBA, there was not any dithiane product formed at all after 1 or 20 min (entries 1 and 2). When the reaction was performed under UV irradiation without HBA for 1 min, small amount of the product was detected by GC (entry 3). Prolonging the reaction time to 10 and 20 min increased the amount of dithiane product significantly, reaching 95% after 20 min (entries 4 and 5). According to literature search, protection of carbonyl compounds using thiol or dithiol under UV irradiation has never been reported. When HBA was added at 2.5 mol%, in only 1 min, 96% of the product was already formed (entry 6) and when the reaction time was increased to 20 min, all *p*-anisaldehyde was converted to the product (entry 7). Using both UV irradiation and HBA for 1 min (entry 8), the yield did not improve from the condition without UV irradiation (entry 6). Based on these results, protection of *p*-anisaldehyde with 1,3-propanedithiol was possible under UV irradiation even without HBA. The addition of HBA significantly reduced the reaction time and produced excellent yield of product, while using both UV irradiation and HBA did not improve the yield. It should be noted that for the reaction under UV irradiation

without HBA, ketone substrate such as acetophenone was attempted but there was no ketal product. Therefore, this condition could be applicable only with the aldehyde substrates.

Table 2.4 The effect of UV irradiation and HBA on protection of *p*-anisaldehyde with 1,3-propanedithiol



Entry	HBA (mol%)	UV Irradiation	Time (min)	Remaining Aldehyde (%)[a]	Yield of Dithiane (%)[a]	M.B.[b] (%)[a]
1	-	-	1	100	0	100
2	-	-	20	100	0	100
3	-	Yes	1	99	1	100
4	-	Yes	10	36	63	99
5	-	Yes	20	15	87	100
6	2.5	-	1	5	95	100
7	2.5	-	20	0	100	100
8	2.5	Yes	1	5	95	100

Reaction conditions: 1 mmol *p*-anisaldehyde, 1.1 mmol 1,3-propanedithiol, 1 mL CH_3CN, rt.

[a] Determined by GC.

[b] Mass balance.

2.4.3.2 The effect of the amount of HBA on protection of p-anisaldehyde with 1,3-propanedithiol by HBA

For economical reason, the amount of HBA was reduced from 2.5 to 1 and 0.5 mol% (Table 2.5). The yield of the dithiane product was still quite high in both cases, 93 and 89% for 1 and 0.5 mol%, respectively (entries 2 and 1). This showed that smaller amount of HBA could be used for protection of *p*-anisaldehyde with 1,3-propanedithiol.

Table 2.5 Effect of amount of HBA on protection of *p*-anisaldehyde with 1,3-propanedithiol

Entry	HBA (mol%)	Remaining Aldehyde (%)[a]	Yield of Dithiane (%)[a]	M.B.[b] (%)[a]
1	0.5	10	89	99
2	1	7	93	100
3	2.5	5	95	100

Reaction conditions: 1 mmol *p*-anisaldehyde, 1.1 mmol 1,3-propanedithiol, 1 mL CH_3CN, 1 min without UV irradiation, rt.

[a] Determined by GC.

[b] Mass balance.

2.4.4 Protection of various carbonyl compounds with 1,3-propanedithiol by HBA

HBA was subsequently applied for the protection of various aldehydes and ketones with 1,3-propanedithiol using 2.5 mol% of HBA as a catalyst in 1 mL

acetonitrile (Table 2.6). For benzaldehyde and 2-methoxybenzaldehyde, within 1 min all substrates were converted to the desired dithiane products without UV irradiation (entries 1 and 2). Salicylaldehyde was more difficult to protect and after 30 min under UV irradiation the yield was 93% (entry 3). For aldehyde with an electron-withdrawing group at the *ortho* position such as 2-nitrobenzaldehyde, the reaction without UV irradiation for 1 min gave only 4% of the product (entry 4), while the addition of UV irradiation increased the yield to 10% (entry 5); increasing the reaction time to 1 h increased the yield to 93% (entry 6). Despite having an electron-donating substituent at the *para* position, 4-diethylaminobenzaldehyde gave only trace amount of dithiane product after 1 min without UV irradiation (entry 7). Addition of UV irradiation (entry 8) or prolonging the reaction time (entry 9) did not help improve the yield much and the yield was only 10% after 1 h. This indicated that this method might not be compatible with an amine. Aliphatic aldehyde was also protected rapidly as seen in the case of 2-ethylbutyraldehyde which was underwent the protection completely within 1 min without UV irradiation (entry 10). Cyclic aliphatic ketone could also be protected and within 20 min under UV irradiation the reaction gave the dithiane product in 100% yield (entry 11). As mentioned in the previous section, protection of ketones is more difficult, especially aromatic ketones, and when the reaction was performed with acetophenone with HBA and without UV irradiation only 1% of the dithiane was formed (entry 12). This result was similar to other reports which found that the formation of dithiane of aldehydes is more facile and faster than ketones.[49, 55, 56, 58, 59] When

applying UV irradiation to the reaction, the yield increased to 6% (entry 13) and when the reaction was increased to 1 h, the yield was 74% (entry 14). Propiophenone also behaved similarly. In 1 h under UV irradiation, the reaction produced 73% of the dithiane product (entry 15). Having an electron-donating group at the *para* position increased the yield as seen in the case of 4′-methoxyacetophenone compared to acetophenone. For 1 min reaction time the yield was 1% (entry 16); adding UV irradiation increased the yield to 12% (entry 17), which was twice as much as acetophenone. After 1 h of irradiation, the yield was 80% (entry 18), which was also higher than that of acetophenone. The reaction could also be applied to α-tetralone and after 1 h under UV irradiation the yield was 89% (entry 19).

Table 2.6 Protection of various carbonyl compounds with 1,3-propanedithiol by HBA

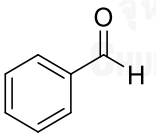
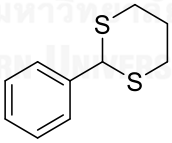
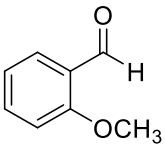
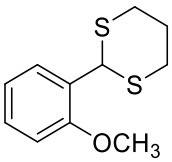
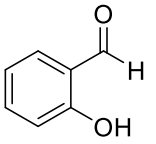
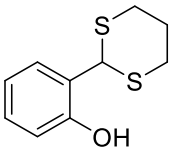
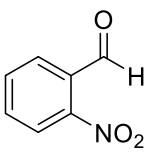
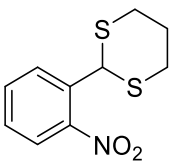
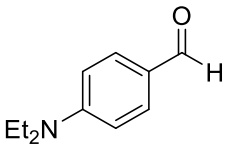
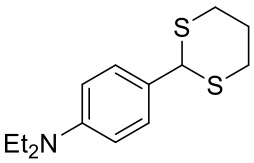
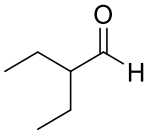
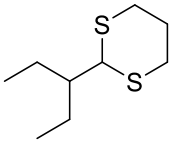
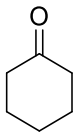
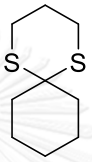
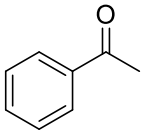
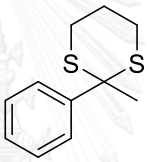
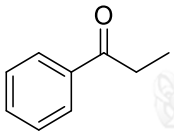
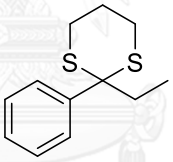
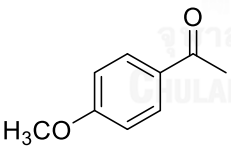
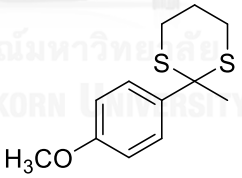
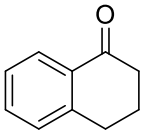
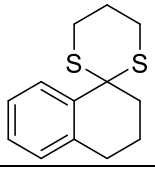
Entry	Reagent	Product	Time (min)	Product (%)[a]
1			1	100
2			1	100
3			30[b]	93
4			1	4
5			1[b]	10
6			60[b]	93

Table 2.6 (*Continued*)

Entry	Reagent	Product	Time (min)	Product (%)[a]
7			1	1
8			1[b]	2
9			60[b]	10
10			1	100
11			20[b]	100
12			1	1
13			1[b]	6
14			60[b]	74
15			60[b]	73
16			1	1
17			1[b]	12
18			60[b]	80
19			60[b]	89

Reaction conditions: 1 mmol substrate, 1.1 mmol 1,3-propanedithiol, 0.025 mmol (2.5 mol%) HBA, 1 mL CH_3CN, rt.

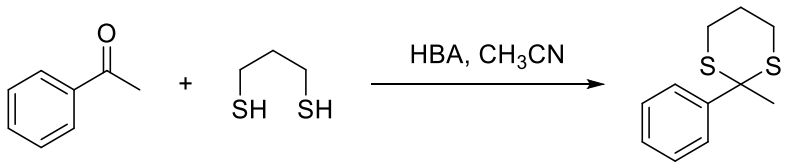
[a] Determined by GC.

[b] Under UV irradiation.

2.4.5 Variation of reaction conditions for protection of acetophenone with 1,3-propanedithiol by HBA

Since the protection of ketones with 1,3-propanedithiol by HBA is more difficult than protection of aldehydes, in order to improve the yield, various conditions were tested for protection of acetophenone (Table 2.7). As a reference, when the reaction was performed at room temperature for 1 h without UV irradiation, the yield was only 66% (entry 1). Under UV irradiation, the yield of dithiane increased to 74% (entry 2) and performing the reaction at refluxing acetonitrile gave 90% yield (entry 3). When the reaction mixture was sonicated for 1 h, the yield was also relatively high at 88% (entry 4).

Table 2.7 Variation of reaction condition for protection of acetophenone with 1,3-propanedithiol by HBA



Entry	Condition	Remaining Acetophenone (%)[a]	Yield of Dithiane (%)[a]	M.B.[b] (%)[a]
1	rt, no UV	34	66	100
2	rt, UV irradiation	26	74	100
3	Reflux	10	90	100
4	Sonication	12	88	100

Reaction conditions: 1 mmol acetophenone, 1.1 mmol 1,3-propanedithiol, 1 mL CH_3CN, 1 h reaction time.

[a] Determined by GC.

[b] Mass balance.

2.4.6 Comparison with other methods

Using only 2.5 mol% of HBA as a catalyst, solketal can be prepared from glycerol for up to 90% yield within 10 min at room temperature. Since HBA is now commercially available, there is no need for catalyst preparation; therefore, using HBA has a major advantage over other methods. For example, the catalysts used by Tayade *et al*. and Sandesh *et al*. required many steps of preparation and several methods of characterization.[46, 47] The 10-min reaction was also very fast compared to 4 h by Tayade *et al*. which gave similar results (up to 92% yield at room temperature).

For benzaldehyde protection with methanol by HBA, the amount of HBA can be reduced to as low as 1.25 mol% and still produced very high yield of protected product. The method by Myles *et al*. took 24 h but for HBA it took only 10 min to produce over 90% yield.[50, 60] MOFs prepared by Dhakshinamoorthy *et al.* produced only 63% yield in 2 h and also were difficult to make and characterize.[52]

The protection of *p*-anisaldehyde with 1,3-propanedithiol could also be achieved rapidly and efficiently. In terms of reaction time and yield, HBA was similar to other methods. [55, 57-59] However, the advantage of HBA is that it can be used to protect both aldehydes and ketones by changing reaction conditions while some other methods can only be used to protect aldehyde.

2.5 Conclusion

HBA has been proven to be very efficient for the protection of hydroxyl and carbonyl compounds. In most cases, the yields were very high in a very short period of time. The formation of dithiane of aldehyde under UV irradiation without any catalyst is very interesting and has never been reported. Addition of HBA greatly reduced the reaction time for the formation of dithiane. UV irradiation also accelerated the formation of dithiane of various ketones. Having electron-donating substituents at the *ortho* and *para* position increased the yield of the corresponding dithiane, while the presence of an electron-withdrawing group hampered the reaction. Aldehydes are easier to protect than ketones, which could be a benefit when selectivity is required

for the protection of aldehydes. Aliphatic ketones were also more readily protected than aromatic ketones.

CHAPTER III

DEPROTECTION OF ACETALS AND KETALS AND CONVERSION OF OXIMES TO CARBONYL COMPOUNDS BY HBA

3.1 Introduction and literature reviews

3.1.1 Deprotection of acetals and ketals

After protection of the susceptible group and transformation of the desired group, the next step is restoration of the original functional group, a process called deprotection. Traditionally, deprotection of acetal uses acid as a catalyst and its mechanism is the reversal of protection mechanism (Figure 3.1).

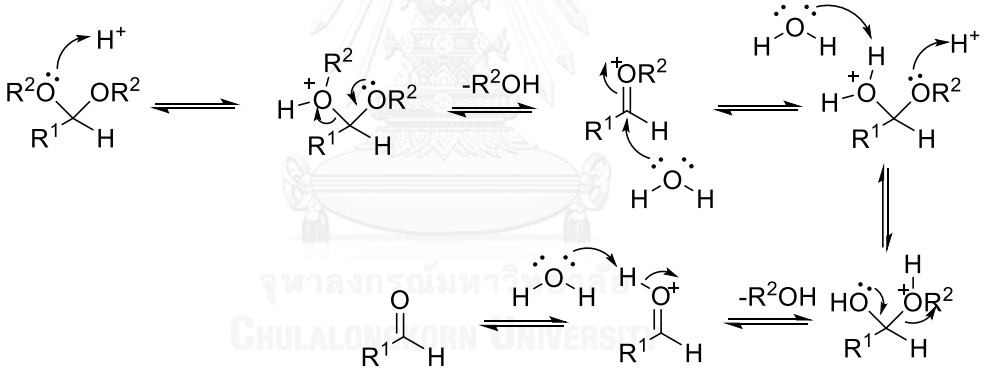


Figure 3.1 Mechanism of acetal deprotection using acid as a catalyst

Other reagents or catalysts that can be used for the deprotection of acetals and ketals include CF_3COOH, PTSA, $LiBF_4$, HCO_2H, Amberlyst-15, Me_2BBr, and I_2.[31] More recently, these catalysts have been reported. In the first example, Moschetta *et al*. used zeolite ZSM-5 embedded in the walls of hollow fibers as flow reactors for deprotection of benzaldehyde dimethyl acetal.[61] The method showed 100%

conversion at 60 °C (Figure 3.2). In addition, the fibers can also be used to support other catalysts such as APS-functionalized silica for base-catalyzed Knoevenagel condensations and [Rh_2(*S*-DOSP)$_4$]-fibers for C-H insertion and cyclopropanation. Embedding the catalysts on the walls of the fibers also allows better flow and avoids large pressure drops compared to packed-bed reactor.

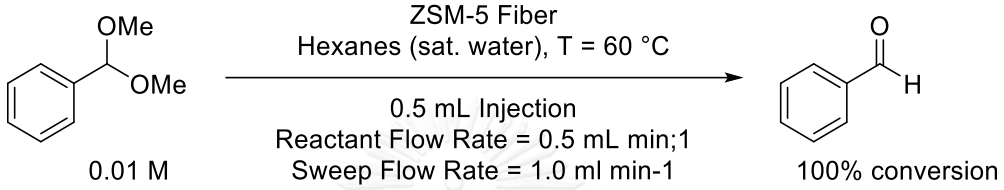


Figure 3.2 Deprotection of benzaldehyde dimethyl acetal by zeolite ZSM-5 embedded in the walls of hollow fibers

Chloral hydrate in hexane was efficiently used by Chandrasekhar and Shrinidhi for deprotection of various acetals, dithioacetals, and tetrahydropyranyl (THP) ethers under ambient conditions.[62] The reaction time was as short as 30 min, producing the corresponding products mostly over 80% yields. However, large amount of chloral hydrate was used, 1.5-6 equivalents.

In another interesting example, Williams *et al*. reported that various aliphatic and aromatic dimethyl and diethyl acetals and ketals can be hydrolyzed when heated at 80 °C in neat water or aqueous medium without a catalyst or additive.[63] Most cyclic acetals were not deprotected. They then showed selective deprotection when both acyclic and cyclic acetals were present in a molecule. The addition of 20% THF was necessary for the deprotection of the desired acetal to occur (Figure 3.3).

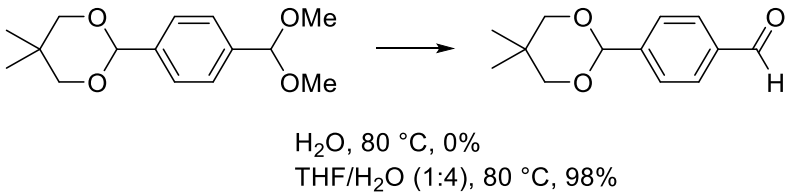


Figure 3.3 Selective hydrolysis of acyclic acetal

Jung *et al*. used TiF_4 to catalyze the conversion of dimethyl acetals into *gem*-diacetates (**Figure 3.4**).[64] However, in some cases the yield of the aldehyde was as low as 16%.

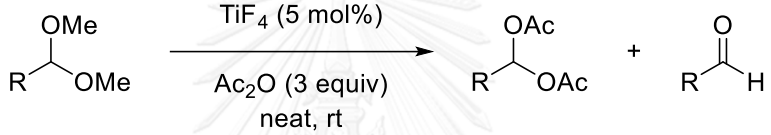


Figure 3.4 Titanium(IV)-catalyzed conversion of dimethyl acetals into gem-diacetates

Li *et al*. showed the deacetalization of various acetals and ketals with trifluoroacetic acid (TFA).[65] More interestingly, they used ^{1}H NMR experiments to prove that water is not required for the deprotection of acetals and ketals with TFA and proposed the mechanism.

Recently, there have been growing interests in multistep cascade reactions and the conversion of acetal to aldehyde has been a part of several multistep cascade reactions. Here are some of the latest examples. Shinde *et al*. reported the use of bifunctional (acid/base) catalytic sites in the crystalline organocatalytic porous covalent organic frameworks (2,3-DhaTph) for deprotection of benzaldehyde dimethyl

acetals and its derivatives.[66] The catalyst had high selectivity and reusability and it can be used for the cascade reaction that included acid-catalyzed deacetalization and base-catalyzed Knoevenagel condensation reaction very well, giving 96% of the desired product. Liu *et al*. also used organic pillared MFI zeolite for acetal hydrolysis followed by a Knoevenagel condensation.[67] The first reaction step of this cascade reaction used acid sites, which can be supplied by the framework Al–O(H)–Si sites in the MFI layers, for deacetalization.

Yang *et al*. also reported one-pot deacetalization-reduction cascade reaction.[68] They used Pickering emulsion system to separate incompatible catalysts for one-pot cascade reactions. For deacetalization-reduction cascade reaction, the system included HCl and $NaBH_4$. In addition, this remarkable catalytic systems can also be used in three other one-pot cascade reactions including the deacetalization-Knoevenagel cascade reaction in the presence of HCl/ethanolamine pair, the deacetalization-Henry cascade in the presence of HCl/ethylenediamine pair, and the diazotization-iodization cascade in the presence of $NaNO_2$/NaI pair.

Another example was the use of trifunctional mesoporous silica-based catalyst by Biradar *et al*.[69] The catalyst contained amine, sulfonic acid and Pd nanoparticle catalytic groups anchored on the pore walls of SBA-15 (Figure 3.5). The sulfonic acid was used for the deacetalization. Overall, the process allowed approximately 100% conversion and 92% selectivity of the final product.

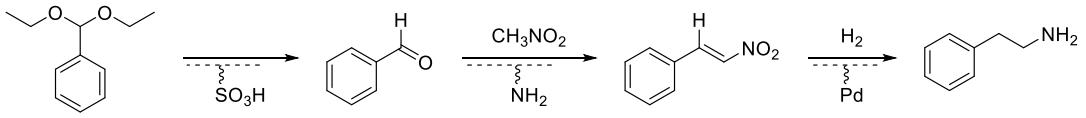


Figure 3.5 A one-pot, three-step cascade deacetalization, Henry and hydrogenation reactions catalyzed by a trifunctional catalyst

Elmekawy *et al*. prepared solid bifunctional acid-base catalysts on an amorphous silica support and used them for a two-stage cascade reaction that included acid-catalyzed deacetalization of benzaldehyde dimethyl acetal to benzaldehyde and the subsequent base-catalyzed Henry reaction with nitromethane to form nitrostyrene.[70] Dual functionalization of porous aromatic frameworks (PAFs) was also shown by Zhang *et al*. to be able to catalyze both the deacetalization and Henry reaction in one-pot as well.[71] Additionally, Xiong *et al*. made core-confined bottlebrush copolymers (CCBCs) that included two incompatible groups, acidic *para*-toluenesulfonic acid (PTSA) and basic 4-(dimethylamino)pyridine (DMAP) groups, for a one-pot cascade reaction that included deacetalization and Knoevenagel condensation.[72] Xu *et al*. reported the preparation and characterization of multilayered zeolites with organic-structure-directing agent (OSDA) molecules occluded within micropores that can be used for one-pot tandem deacetalization-Knoevenagel condensation and one-pot tandem aerobic oxidation-Knoevenagel condensation reaction.[73] The systems can produce the desired products at approximately 90% over 2 steps. Amine-functionalized graphene oxide was prepared by Zhang *et al*. by a facile one-step silylation approach for an acid–base bifunctional

catalyst in one-pot cascade reactions consisting of deacetalization and Knoevenagel condensation.[74] The activity and selectivity of the catalytic system was very high and the authors suggested that this method could be applied to other systems as well. A series of acid-base bifunctional catalysts with different matches of acidity and basicity formed from immobilization of proline onto Al-SBA-15 were prepared by Guan *et al*. for one-pot deacetalization-Knoevenagel reaction, one-pot deacetalization–Henry reaction, nitroaldol reaction, and aldol reaction.[75] They found that weak acid matching weak base was beneficial to the Knoevenagel reaction and nitroaldol reaction, while moderately strong acid matching weak base was good for the one-pot deacetalization-Knoevenagel reaction, one-pot deacetalization-Henry reaction, and aldol reaction. Phosphotungstic acid immobilized on amine-grafted graphene oxide (GOAP) was prepared by silylanization and electrostatic interaction and characterized and then used as acid/base bifunctional catalyst for one-pot tandem reaction that included deacetalization and nitroaldol reaction.[76] The conversion was 100% and the yield of the final product was also nearly 100%. Merino *el al*. used porous aromatic frameworks that had been functionalized with sulfonic acid and primary amine for one-pot deacetalization-Knoevenagel reaction.[77] The catalyst was recycled 7 times and it still showed high conversion of the substrate and around 80% yield of the product.

Ricciardi *et al*. reported the preparation of sulfonic acid-bearing polymer brushes (PSPM) used in continuous flow micro-reactors for the hydrolysis of benzaldehyde dimethyl acetal and deprotection of 2-benzyl tetrahydropyranyl ether

(benzyl-THP).[78] The catalytic system can continuously run over 7 days without significant loss of activity.

3.1.2 Conversion of oximes to carbonyl compounds

Formation of oximes is another way to protect carbonyl compounds, even though it is not very popular because it still possesses an acidic hydrogen and a quite reactive C=N.[31] They can then be cleaved by oxidation, reduction, or hydrolysis in the presence of another carbonyl compound.[31, 79] Many methods have been reported and over 60 methods were summarized in Greene's Protective Groups in Organic Synthesis.[31] It should be noted that carbonyl compounds are also byproducts for Beckmann rearrangement by various catalysts.[80-83] Here are the latest discoveries that have been reported. Hao and Zhao used $NaClO_2$ in water for deprotection of oximes and for cyclohexanone oxime, the yield was 91% in 5 min.[84] Liu *et al*. used ruthenium trichloride and *p*-toluenesulfonic acid (PTSA) in a mixture of dimethylacetamide and water for deoximation (Figure 3.6).[85] They varied different solvents as well as additives to find the optimal reaction conditions. With DMA/H_2O (20:1) and PTSA (60 mol%), the conversion was 100% and selectivity was 94% of cyclohexanone oxime. They then successfully used this condition for various other oximes.

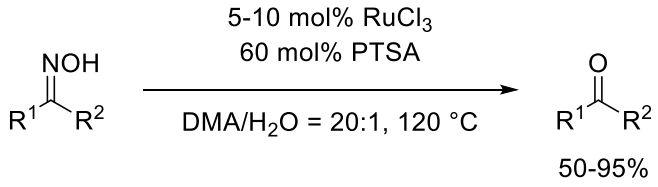


Figure 3.6 Deoximation by ruthenium trichloride

Lumb *et al*. used sodium bromate in the presence of acidic ionic liquid [bmim]HSO_4 at 60 °C for deprotection of oximes, hydrazones, phenyl hydrazones, tosylhydrazones, Schiff's bases and azines to their corresponding carbonyl compounds (Figure 3.7).[86] The products can be simply isolated in high yield and the ionic liquid can be recovered and recycled as well.

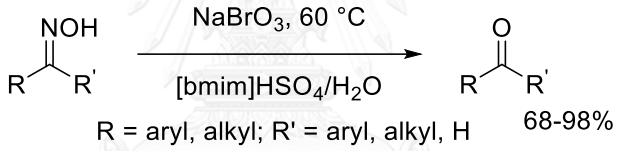


Figure 3.7 Deoximation by $NaBrO_3$

p-Chloroperbenzoic acid was used by Dewan and Sharma for deoximation under microwave irradiation.[87] The authors claimed that the reaction was very fast (90 s) and the yield was 79%. Garcia-Ortiz *et al*. discovered that mixed iron and copper hexacyanocolbatate was found to be a suitable heterogeneous and recoverable catalyst for aerobic deoximation in water-ethanol 1-1 mixture.[88] The catalyst was compared with other double metal hexacyanocobaltates and iron and copper hexacyanocolbatate was the best, giving 100% conversion of acetophenone oxime and

100% yield of acetophenone. Another efficient catalyst that has been used for deoximation was sym-collidinium chlorochromate (S-COCC).[89] The reaction gave 90% cyclohexanone product in 10 min at room temperature.

In another example, nano-manganese-catalyst and *N*-hydroxyphthalimide (2-hydroxy-1H-isoindole-1,3-dione; NHPI) under oxygen pressure was used for the aerobic deoximation without the need of any reducing agent.[90] The reactions took 1-4 h and gave mostly over 90% of the carbonyl compound products. Anhydrous $AlCl_3$ supported on nano silica was used by Zeynizadeh and Karimkoshteh for deprotection of oximes to carbonyl compounds and in 60 min at 70-80 °C, the yields were over 90%.[91]

3.2 Objectives

To explore its potential applications, HBA will be used for the following purposes.

1. To deprotect acetals and ketals.
2. To convert oximes to carbonyl compounds.

3.3 Experimental

3.3.1 Instruments and equipment

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus NMR spectrometer or a Varian Mercury NMR spectrometer with an Oxford YH400 magnet operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. GC analysis was performed using a Varian CP-3800 Gas Chromatograph equipped with SGE BP1 or BP21 column. The home-made UV reactor consists of eight UV lamps (6 W, 254 nm, Sylvania G6W T5)

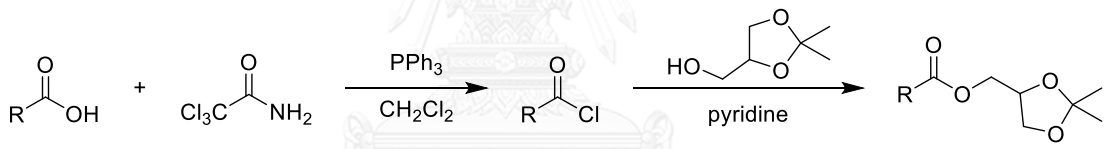
and a fan for ventilation. A magnetic stirrer was placed underneath the UV reactor for stirring the reaction. For the reactions under UV irradiation, the reactions were performed in custom-made quartz tube for maximum UV transmission.

3.3.2 Chemicals

Chemicals and solvents were purchased from standard suppliers and were used without further purification. HBA was both synthesized[8] and obtained from Sigma-Aldrich. Oximes were prepared according to literature.[92]

3.3.3 Synthesis

3.3.3.1 Synthesis of dioxolane derivatives



To a 250-mL round-bottomed flask was added the corresponding carboxylic acid (25 mmol), 8.12 g trichloroacetamide (50 mmol), 13.11 g PPh_3 (50 mmol), and dichloromethane (100 mL) to give a colorless solution. The mixture was stirred and heated at reflux for 1 h. Then 3.11 mL solketal (25 mmol) and 6.04 mL pyridine (75 mmol) were added to the resulting acid chloride solution and the reaction mixture was heated at reflux until completion as indicated by TLC (approximately for 4 h). After completion, the solution was extracted with 10% HCl and sat.aq. $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified with silica gel column eluting with 5% EtOAc/hexanes.

3.3.4 General procedure

3.3.4.1 Deprotection of acetals and ketals

Representative procedure for the deprotection of acetals and ketals: To a 25-mL quartz tube was added the specified amount of benzaldehyde dimethyl acetal, HBA, and the desired solvent. The reaction mixture was stirred and irradiated by a home-made UV reactor for the desired time at room temperature. To quantify the product using GC, the specified amount of biphenyl was added as an internal standard. To obtain isolated yield, solvent was evaporated and the crude product was purified using silica gel column.

3.3.4.2 Conversion of oximes to carbonyl compounds

Representative procedure for deoximation: To a 25-mL quartz tube was added the specified amount of oxime, HBA, and the desired solvent. The reaction mixture was stirred and irradiated by a home-made UV reactor for the desired time at room temperature. To quantify the product using GC, the specified amount of naphthalene was added as an internal standard.

3.4 Results and discussion

3.4.1 Deprotection of benzaldehyde dimethyl acetal by HBA

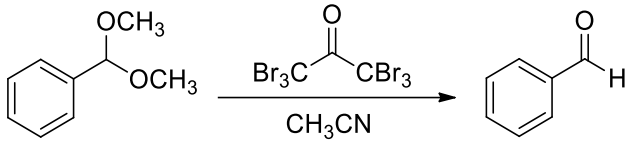
To demonstrate that HBA can deprotect acetals or ketals and is truly responsible for the deprotection and to investigate reaction parameters including the reaction time, molar ratio of HBA to substrate, and the amount of solvent (reaction

concentration), various experiments were performed using the commercially available benzaldehyde dimethyl acetal as a model compound.

3.4.1.1 The effect of the amount of HBA and UV irradiation

The first set of experiments was to confirm that HBA is responsible for the deprotection of acetal (Table 3.1). Stirring just benzaldehyde dimethyl acetal (1 mmol, 150 µL) in acetonitrile (5 mL) without HBA and under either the dark condition (entry 1) or UV irradiation (entry 2) for 5 min, there was no reaction and approximately 100% of the acetal was recovered. Adding 0.025 mmol (2.5 mol%) of HBA to the reaction without UV irradiation, there was also no reaction and there was no peak of benzaldehyde in GC chromatogram (entry 3). Addition of HBA as well as performing the reaction under UV irradiation gave almost quantitative amount of the benzaldehyde product (entry 4). This indicates that UV irradiation is needed to activate the reaction. Without it, no product was formed. These results also indicate that HBA can deprotect acetal under UV irradiation. Note that for the reactions under UV irradiation, quartz test tubes were used in order to maximize UV light transmitted to the reaction mixture.

Table 3.1 Controlled experiments for the deprotection of benzaldehyde dimethyl acetal by HBA



Entry	HBA (mmol)	UV Irradiation (min)	Remaining Acetal (%)[a]	Yield of Benzaldehyde (%)[a]	MB[b] (%)[a]
1[c]	0	0	100	0	100
2	0	5	101	0	101
3[c]	0.025	0	100	0	100
4	0.025	5	5	97	102

Reaction conditions: 1 mmol (150 μL) benzaldehyde dimethyl acetal, 0.025 mmol (2.5 mol%) HBA (if applicable), 5 mL CH_3CN, 5 min, rt.

[a] Determined by GC.

[b] Mass balance.

[c] The reaction tube was wrapped with aluminum foil.

3.4.1.2 Time-course investigation of the deprotection of benzaldehyde dimethyl acetal by HBA

The deprotection of benzaldehyde dimethyl acetal was found to be very fast. To investigate this, the reaction was quenched with sat.aq. $NaHCO_3$ after 0.25, 0.5, 1, and 5 min and the amounts of benzaldehyde dimethyl acetal and benzaldehyde were quantified by GC. Within 15 seconds the yield was already over 90% (Figure 3.8).

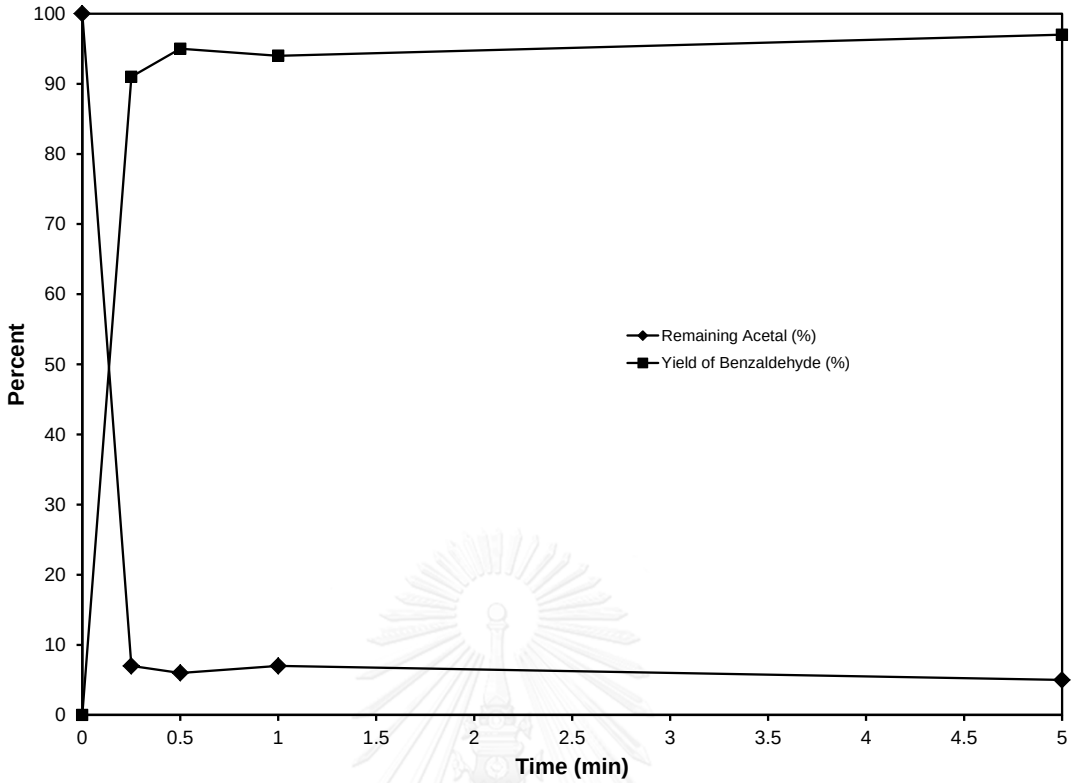


Figure 3.8 Time-course investigation of the deprotection of benzaldehyde dimethyl acetal by HBA

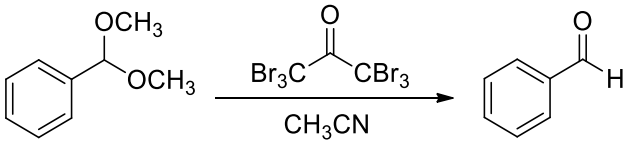
Reaction conditions: 1 mmol (150 μL) benzaldehyde dimethyl acetal, 0.025 mmol (2.5 mol%) HBA, 5 mL CH_3CN, under UV irradiation, rt. The amounts of the substrate and product were determined by GC.

3.4.1.3 The effect of the amount of HBA on the deprotection of benzaldehyde dimethyl acetal by HBA

HBA was also found to be very efficient in the deprotection of benzaldehyde dimethyl acetal. As shown in Table 3.2, when the amount of HBA was reduced to 1 mol%, the yield of benzaldehyde was still 92% in 1 min (entry 2). However, in 15 s the yield of benzaldehyde was only 9% (entry 1). When the amount of HBA was 2.5 mol% the benzaldehyde product was over 90% from 15 s (entries 3 and 4). Therefore, there

is a tradeoff between the amount of HBA used and the reaction time. Higher amount of HBA would take less time and *vice versa*.

Table 3.2 The effect of the amount of HBA on the deprotection of benzaldehyde dimethyl acetal by HBA



Entry	HBA (mol%)	UV Irradiation (min)	Remaining Acetal (%)[a]	Yield of Benzaldehyde (%)[a]	MB[b] (%)[a]
1	1	0.25	91	9	100
2	1	1	8	92	100
3	2.5	0.25	7	91	98
4	2.5	1	7	94	101

Reaction conditions: 1 mmol (150 µL) benzaldehyde dimethyl acetal, 5 mL CH_3CN, rt.
a Determined by GC.
b Mass balance.

3.4.1.4 The effect of the amount of solvent on the deprotection of benzaldehyde dimethyl acetal by HBA

The effect of the amount of solvent was investigated to find the optimal amount used and it strongly affected the yield of benzaldehyde product. As shown in Figure 3.9, increasing the volume of CH_3CN also increases the yield of the product. This could be because MeOH produced from the reaction is more diluted in higher amount

of solvent and, therefore, the competing reverse reaction is much slower, giving higher amount of product.

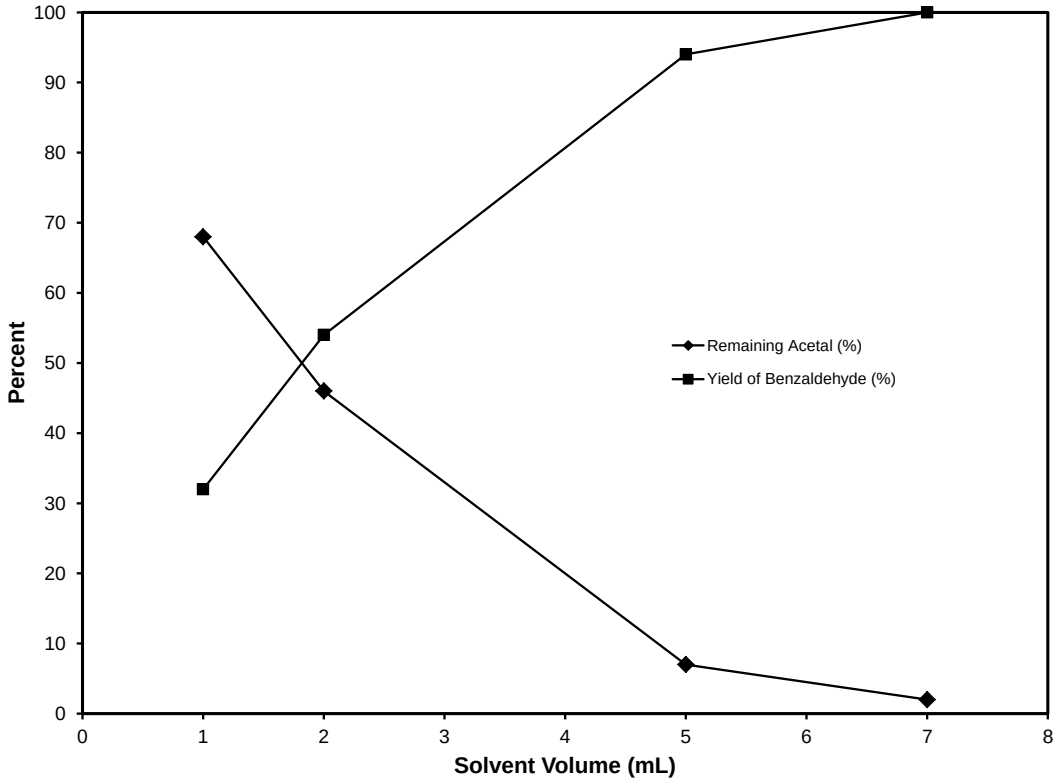


Figure 3.9 The effect of the amount of solvent on the deprotection of benzaldehyde dimethyl acetal by HBA

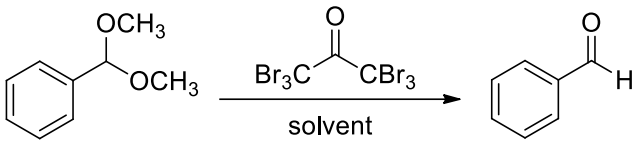
Reaction conditions: 1 mmol (150 μL) benzaldehyde dimethyl acetal, 0.0125 mmol (1.25 mol%) HBA, 1 min UV irradiation, rt. The amounts of the substrate and product were determined by GC.

3.4.1.5 The effect of solvent on the deprotection of benzaldehyde dimethyl acetal by HBA

Changing the solvent used in the reaction also changed the effectiveness of HBA as shown in Table 3.3. Chlorinated solvents gave the highest yields of benzaldehyde (entries 1 and 2). Further investigation found that benzaldehyde

dimethyl acetal was not very stable in this type of solvent. Upon irradiation under UV light in either DCE or CH_2Cl_2 without HBA, benzaldehyde dimethyl acetal was converted to benzaldehyde, though at a considerably lower rate than with HBA (62 and 35% yield of benzaldehyde in DCE and CH_2Cl_2, respectively, after 5 min). Without UV irradiation, 11% of benzaldehyde was formed in DCE and trace amount of benzaldehyde was formed in CH_2Cl_2 after 5 min. Acetonitrile was also a good solvent, giving 94% of benzaldehyde (entry 3). Acetone, THF, Et_2O, benzene, and hexane gave less yield of benzaldehyde (entries 4-8). Using MeOH as a solvent, no benzaldehyde product was formed (entry 9), indicating that the reverse reaction was dominating. In addition, when EtOH was used as a solvent (entry 10), transetherification occurred and benzaldehyde diethyl acetal was obtained as a major product (80%).

Table 3.3 The effect of solvent on the deprotection of benzaldehyde dimethyl acetal by HBA.



Entry	Solvent	Remaining Acetal (%)[a]	Yield of Benzaldehyde (%)[a]	M.B.[b] (%)[a]
1	DCE	0	98	98
2	CH_2Cl_2	1	97	98
3	CH_3CN	7	94	101
4	Acetone	16	88	104
5	THF	1	86	87
6	Et_2O	13	63	86
7	Benzene	30	63	93
8	Hexane	21	58	79
9	MeOH	95	0	95
10	EtOH	2	17	19

Reaction conditions: 1 mmol (150 μL) benzaldehyde dimethyl acetal, 0.025 mmol (2.5 mol%) HBA, 5 mL solvent, 1 min UV irradiation, rt.

[a] Determined by GC.

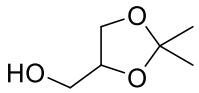
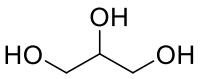
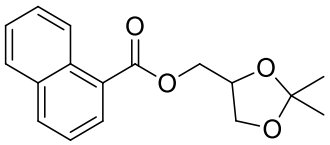
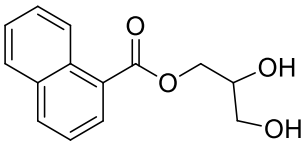
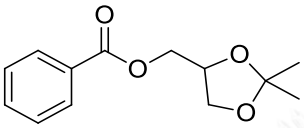
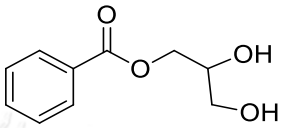
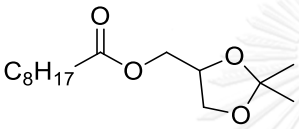
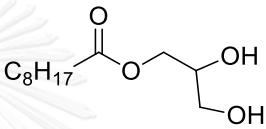
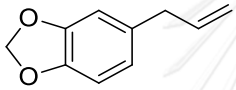
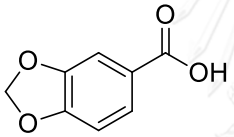
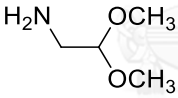
[b] Mass balance.

3.4.2 Deprotection of other acetals and ketals by HBA

To further explore the potential of HBA for the deprotection of acetals and ketals, HBA was also successfully used to deprotect some acetals and ketals as shown in Table 3.4. For the deprotection of solketal, the reaction took much longer time than that of benzaldehyde dimethyl acetal (entry1). MeOH was found to be the best

solvent. At first, several modifications of reaction conditions were tried including raising the amount of HBA, varying the amount of solvent, and increasing reaction time, but the yield of glycerol did not improve. When the product was prepared for compound characterization using ^{1}H NMR, evaporation under reduced pressure was needed to evaporate solvent. It was found that there was no solketal left. Sun *et al*. also stated that because of equilibrium between the substrate and the product, it was necessary to raise the temperature for the reaction to proceed to completion.[93] However, in this case after simple evaporation under reduced pressure a quantitative yield of glycerol was obtained (entry 1). HBA can also cleave solketal that has been esterified with 1-naphthoic, benzoic, and nonanoic acids giving the corresponding product in high yields (entries 2-4). In addition, 1-naphthoic acid was not detected from the reaction indicating that the ester bond was not cleaved. However, dioxolanes of safrole and piperonylic acid were not cleaved (entries 5 and 6) and bromine addition products were not detected in the case of safrole. HBA also cannot deprotect an acetal with amine functional group such as 2,2-dimethoxyethanamine (entry 7).

Table 3.4 Deprotection of acetals and ketals by HBA

Entry	Reagent	Product	Product Yield (%)
1			100[a]
2			96[b]
3			90[b]
4			98[b]
5		No reaction[c]	-
6		No reaction[c]	-
7		No reaction[c]	-

Reaction conditions: 1 mmol substrate, 10 mol% HBA, 5 mL MeOH, 30 min UV irradiation (rt) and followed by evaporation under reduced pressure.

[a] 2.5 mol% HBA, determined by GC.

[b] Isolated yield.

[c] Checked by ^{1}H NMR spectroscopy.

3.4.3 Conversion of oximes to carbonyl compounds

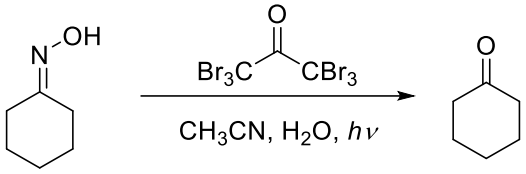
To investigate the scope of substrates that can be deprotected by HBA, this reagent was tested for the conversion of oxime to ketone.

3.4.3.1 Conversion of cyclohexanone oxime to cyclohexanone by HBA

Similar to the other investigations mentioned above, in addition to HBA, solvent also plays an important role. In the conversion of cyclohexanone oxime to cyclohexanone, when CH_3CN, DCE, Et_2O, and MeOH were used as solvent, only trace amount of cyclohexanone was detected. When H_2O was used together with CH_3CN the yield was much better. Several publications also used H_2O in combination with other organic solvents and found that it was a crucial factor.[94-97] It was also found that, for this reaction, the reaction required longer time and larger amount of HBA than that of the deprotection of acetals and ketals. After varying the ratio of CH_3CN and H_2O, 4 mL CH_3CN and 1 mL H_2O was a suitable ratio. As shown in Table 3.5, when 20 mol% of HBA was used the yield of cyclohexanone was 51% after 2 h (entry 1). Increasing the reaction time did not improve the yield much (entries 2 and 3). However, when the amount of substrate is lower (lower substrate concentration), the yield is much higher (entry 4), but increasing the amount of HBA did not improve the yield (entry 5). It appeared that HBA became ineffective after some period of time. Therefore, HBA was added in 2 portions and the yield of cyclohexanone dramatically increased to 91% (entry 6). As a controlled reaction, cyclohexanone oxime was irradiated for 2 h without HBA and only 6% of ketone was formed (entry 7). In comparison to some recently reported methods for the oxidation of oxime into

ketone,[88, 90, 98, 99] this method produces ketone product in very high yield in a short time, uses relatively mild condition, and is also metal-free.

Table 3.5 Conversion of cyclohexanone oxime to cyclohexanone by HBA



Entry	Oxime (mmol)	HBA (mol%)	UV Irradiation Time (h)	Remaining Oxime (%)[a]	Yield of Ketone (%)[a]	MB[b] (%)[a]
1	1	20	2	32	51	83
2	1	20	4	39	60	99
3	1	20	14	27	59	87
4	0.25	20	4	15	87	101
5	0.25	80	2	7	78	85
6[c]	0.20	20 x 2	1 x 2	5	91	96
7	1	-	2	91	6	97

Reaction conditions: 4 mL CH_3CN and 1 mL H_2O, rt.

[a] Determined by GC.

[b] Mass balance.

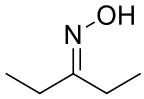
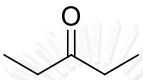
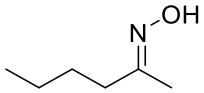
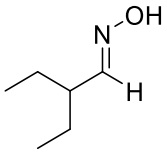
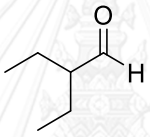
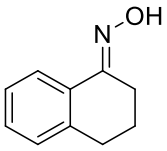
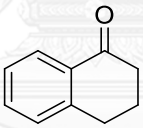
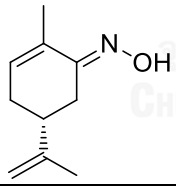
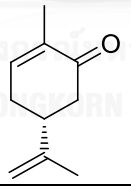
[c] HBA was added in 2 portions at the specified amount and the reaction was stirred for 1 h for each portion.

3.4.3.2 Conversion of other oximes to ketones by HBA

In addition to cyclohexanone oxime, HBA was evaluated for the conversion of other oximes using the above method as shown in Table 3.6. HBA could effectively convert 3-pentanone oxime, 2-hexanone oxime, and 2-ethylbutyraldehyde oxime to

the corresponding carbonyl compounds (entries 1-3). However, for the cases of α-tetralone oxime and (-)-carvone oxime, only small amounts of products were obtained (entries 4 and 5), suggesting that conjugated oximes are difficult to convert.

Table 3.6 Conversion of oximes to ketones by HBA

Entry	Oxime	Product	Remaining Oxime (%)[a]	Product Yield (%)[a]	MB[b] (%)[a]
1			2	92	94
2			13	87	100
3			9	91	100
2			88	12	100
3			86	5	91

Reaction conditions: 0.40 mmol oxime, 20 mol% HBA added twice (total 40 mol%, second addition after 1 h stirring), UV irradiation for 2 h total, 8 mL CH_3CN and 2 mL H_2O, rt.

[a] Determined by GC.

[b] Mass balance.

3.4.4 Comparison with other methods

The reaction time of only 1 min for deprotection of benzaldehyde dimethyl acetal by HBA was much faster than other methods. For instance, the use of chloral hydrate took 4.5 h and gave only 82% yield of benzaldehyde.[62] In addition, the use of titanium(IV) halide by Jung *et al*. took several hours and the reaction had to be performed at 60 °C.[64]

For deoximation, the drawback of HBA could be the need for higher amount of HBA. However, the reaction condition is favorable. When HBA is used, the reaction can be performed at room temperature, but for acidic ionic liquid [bmim]HSO_4, the reaction must be performed at 60 °C.[86] or for ruthenium trichloride and PTSA, it must be done at 120 °C.[85]

3.5 Mechanism investigation

Based on the results in Table 3.1, UV irradiation was required for the reactions. Therefore, the reactions were expected to take place via radical intermediates. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) radical was used as a radical trap for the reaction in entry 4 of Table 3.1 as shown in Figure 3.10. While the reaction without TEMPO was nearly complete within 5 min, when TEMPO was added only 6% of benzaldehyde product was formed, reaffirming that radical intermediates were formed after UV irradiation and trapped by TEMPO, inhibiting the reaction.

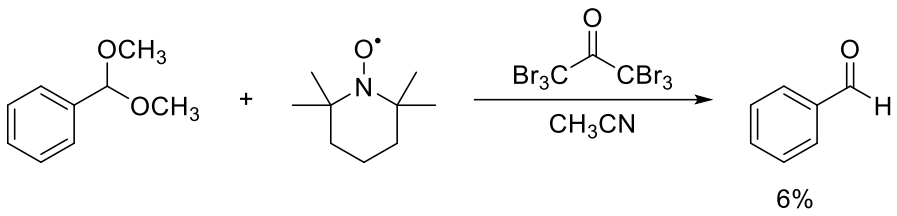


Figure 3.10 Using TEMPO as a radical trap for the deprotection of benzaldehyde dimethyl acetal by HBA

Based on the information available, bromine radical is likely formed by UV irradiation from HBA (Figure 3.11). The bromine radical could form a bond with CH_3 from benzaldehyde dimethyl acetal to produce methyl bromide. GC-MS could be used to verify this by checking for methyl bromide produced. Further born formation and cleavage as shown in Figure 3.11 would produce benzaldehyde. The remaining radicals could help propagate more deprotection.

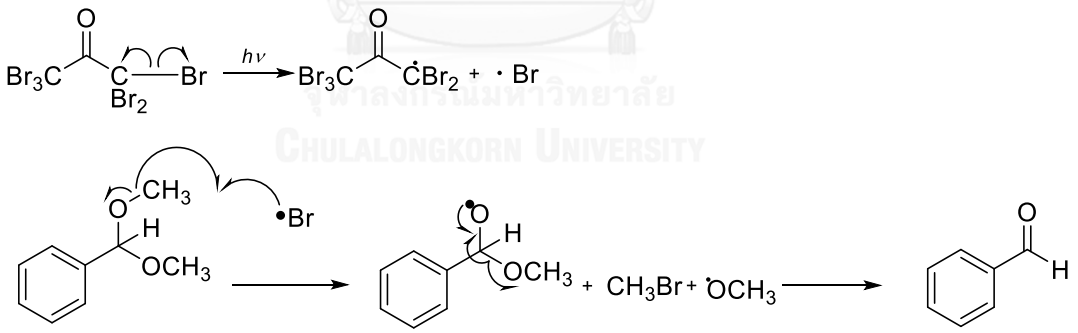


Figure 3.11 Proposed mechanism for deprotection of benzaldehyde dimethyl acetal by HBA

3.6 Conclusion

In summary, HBA was efficiently used as a deprotective agent of benzaldehyde dimethyl acetal, solketal, and some other acetals and ketals. In most cases, the

reaction was very fast and very small amount of HBA was needed. HBA was also effectively used for deoximation. Solvent was found to have impact on the efficiency of HBA and it was crucial to choose the right solvent or solvent combination for each type of substrate and reaction.

CHAPTER IV

BROMINATION OF ADAMANTANE AND DIETHYL MALONATE BY HBA

4.1 Introduction and literature reviews

Organobromines are important intermediates in organic synthesis. In chemistry, they are mainly used in nucleophilic substitution, coupling reaction, Grignard reaction, and dehydrobromination, while in industries they are generally used as fire-retardants, fumigants, biocides, dyes, and pharmaceutical compounds.[100] They are excellent building blocks or intermediates for organic reactions. Organobromides are traditionally synthesized using HBr or Br_2 but other brominating reagents such as *N*-bromosuccinimide [101] and CBr_4 [102] have also been used for the bromination of various types of compounds. In this research, adamantane was selected as a model compound for bromination of alkane and diethyl malonate was chosen for bromination of dicarbonyl compound.

4.1.1 Bromination of adamantane

Alkane bromination is generally difficult since the substrate is stable and removing a proton from alkane is difficult. For adamantane, selectivity is also a problem. In addition to 1-bromoadamantane, other brominated products could be formed such as 2-bromoadamantane and other dibrominated products. Here are some of the latest examples of bromination of adamantane that have been reported. Khusnutdinov *et al*. reported bromination of adamantane and its derivatives with

tetrabromomethane catalyzed by iron compounds (Figure 4.1).[103] $Fe(acac)_3$ was found to be the best among various iron compounds and the conversion of adamantane was 66% in 2 h at 90 °C, giving 54% of 1-bromoadamantane and 12% of 1,3-dibromoadamantane.

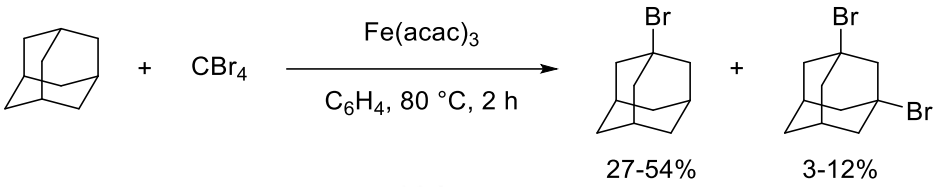


Figure 4.1 Bromination of adamantane using CBr_4 catalyzed by $Fe(acac)_3$

Schmidt *et al*. used *N*-bromoamides and visible light for site-selective aliphatic C-H bromination.[104] Various *N*-bromoamides were tested with several substrates and yields and selectivity were determined. For adamantane, *N*-bromoamides shown in Figure 4.2 was used and in 4 h at room temperature under visible light the overall yield was 58% with the ratio of 1-bromoadamantane to 2-bromoadamantane at 36:1.

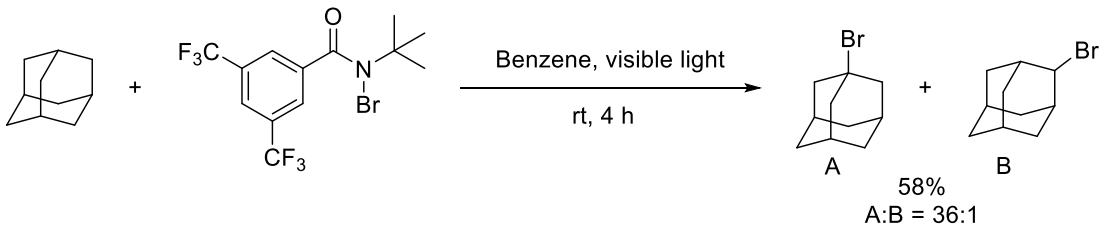


Figure 4.2 Bromination of adamantane using N-bromoamides under visible light

Nishina *et al*. performed direct bromination of hydrocarbons catalyzed by Li_2MnO_3 under oxygen and photo-irradiation conditions.[105] In 24 h under 1 atm

oxygen and at 100 °C in CH_2Cl_2, bromination of adamantane catalyzed by Li_2MnO_3 gave 42% of 1-bromoadamantane and 5% of 2-bromoadamantane. This corresponds to 8.4:1 ratio of the two isomeric products.

Bromination of adamantane and in a system containing *N*-hydroxyphthalimide, oxone, and CBr_4 was shown by Zhuk *et al*.[106] The conversion of adamantane 86.7%, giving 71.6% of 1-bromoadamantane, 7.5% of 2-bromoadamantane, and 7.6% of dibromoadamantane. The authors also proposed the mechanism of the reaction. Several unactivated aliphatic hydrocarbons including adamantane was brominated in a phase-transfer system by Schreiner *et al*.[107] They tested various brominating agents; however, the conversions were not very high despite after several hours.

4.1.2 Bromination of diethyl malonate

α-Bromocarbonyl compounds have been used as an intermediate or a building block for various compounds including bioactive compounds, heterocyclic compounds, and natural products and their derivatives. The synthesis of α-bromocarbonyl compounds was traditionally performed using Br_2 or *N*-bromosuccinimide (NBS) as a bromine source.

The classical method for bromination of diethyl malonate is the use of molecular bromine. The method was previously reported by Palmer and McWherter in Organic Synthesis.[108] Delon *et al*. performed the reaction in CCl_4 and the reaction mixture was initially irradiated with a Tensor lamp and then refluxed for 1 h.[109] The

yield of diethyl bromomalonate was 96%, which was subsequently used for the synthesis of polyfluoroalkyl racemic α-amino acids. Chai *et al*. also used molecular bromine for bromination of diethyl malonate and they obtained 70% of diethyl bromomalonate which they used to synthesize alkoxycarbonyl- and carboxy-piperazine-2,5-diones.[110]

Here are examples of some other methods. Hosseini *et al*. used BrCN as a bromine source (Figure 4.3).[111] However, the yield of diethyl bromomalonate was quite low, only 20.0% when the reaction was performed in diethyl ether and 38.1% when performed in acetone.

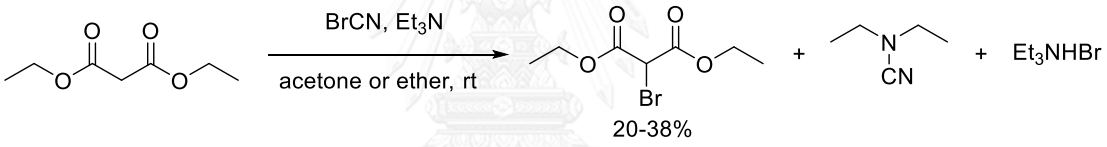


Figure 4.3 Bromination of diethyl malonate with BrCN

Silvestrini *et al*. brominated diethyl malonate with CBr_4 and then used diethyl bromomalonate for cyclopropanation of [60]fullerene in the presence of DBU in a continuous flow system.[112] This example also showed how brominated dicarbonyl compound can be used for the synthesis of more complexed molecules.

NBS was used for bromination of diethyl malonate using *p*-toluenesulfonic acid (PTSA) as a catalyst by Fang *et al*. (Figure 4.4).[113] The reaction gave 92% of diethyl bromomalonate after 15 min at room temperature. Lee *et al*. also reported the use

of NBS catalyzed by PTSA for bromination of diethyl malonate.[114] The reaction in acetonitrile at reflux for 2 h gave 95% of diethyl bromomalonate.

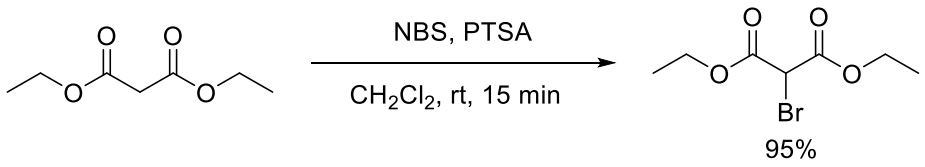


Figure 4.4 Bromination of diethyl malonate with NBS using PTSA as a catalyst

Sreedhar *et al*. also used NBS as a brominating agent as well.[115] However, the reaction was performed in DMSO at room temperature and produced 90% of diethyl bromomalonate after 20 min. This method can also be used with NCS and NIS as well. Overall, NBS produced the highest yields of the corresponding halogenated products followed by NCS and NIS. For all substrates, the yields were over 70%.

Adimurthy *et al*. reported eco-friendly and versatile brominating agent prepared from a liquid bromine precursor.[116] The brominating agent was prepared with 2:1 bromide:bromate from the alkaline intermediate of the conventional bromine recovery process. During the reaction, the reagent is acidified *in situ* to generate HOBr, the reactive species. This brominating agent was also used for bromination and polybromination of phenols, amines, aromatic compounds, bromohydrins and C-H active compounds.

Poly(vinylpyrrolidone)-bromine complex was shown to be a mild and efficient brominating reagent by Lakouraj *et al*.[117] For the bromination of diethyl malonate,

the reaction was performed for 30 min at room temperature in dichloromethane and 88% of diethyl bromomalonate was obtained.

Lee *et al*. reported fast and efficient α-halogenation of carbonyl compounds with [hydroxy(tosyloxy)iodo]benzene (HTIB) followed by magnesium halides under solvent-free microwave irradiation.[118] Diethyl bromomalonate was obtained in 83% yield from diethyl malonate. The general trend also showed that bromination gave the highest yields followed by chlorination and iodination.

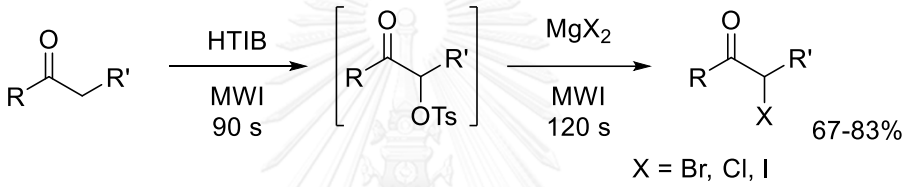


Figure 4.5 α-Halogenation of carbonyl compounds with HTIB followed by magnesium halides under solvent-free microwave irradiation

Cheng *et al*. reported the chlorination and bromination of various carbonyl compounds using either hydrochloric acid or hydrobromic acid and potassium permanganate in acetonitrile.[119] Bromination of diethyl malonate produced 86% yield of diethyl bromomalonate. In another example, trifluoromethanesulfonyl bromide was used as brominating agent and the yield of diethyl bromomalonate was 92%.[120]

4.2 Objectives

To find the optimal reaction conditions for bromination of adamantane and diethyl malonate with HBA.

4.3 Experimental

4.3.1 Instruments and equipment

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus NMR spectrometer or a Varian Mercury NMR spectrometer with an Oxford YH400 magnet operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. GC analysis was performed using a Varian CP-3800 Gas Chromatograph equipped with SGE BP1 or BP21 column. The home-made UV reactor consists of eight UV lamps (6 W, 254 nm, Sylvania G6W T5) and a fan for ventilation. A magnetic stirrer was placed underneath the UV reactor for stirring the reaction. For the reactions under UV irradiation, the reactions were performed in custom-made quartz tube for maximum UV transmission. Sonication was performed using Elma Transsonic T460/H ultrasonic unit. Microwave reaction was performed using CEM Discover microwave reactor.

4.3.2 Chemicals

Chemicals and solvents were purchased from standard suppliers and were used without further purification. HBA was both synthesized [8] and obtained from Sigma-Aldrich.

4.3.3 General procedure

4.3.3.1 Bromination of adamantane

Representative procedure for bromination of adamantane: To a 25-mL quartz tube was added the specified amount of adamantane, HBA, and the desired

solvent. The reaction mixture was stirred under the specified reaction condition for the desired time. To quantify the product using GC, the specified amount of biphenyl was added as an internal standard.

4.3.3.2 Bromination of diethyl malonate

Representative procedure for bromination of diethyl malonate: To a 25-mL quartz tube was added the specified amount of diethyl malonate, HBA, and the desired solvent. The reaction mixture was stirred under the specified reaction condition for the desired time. To quantify the product using ^{1}H NMR, solvent was removed under vacuum, the specified amount of naphthalene was added as an internal standard. The ^{1}H NMR spectrum of the sample was then obtained and the amount of substrate and products were determined.

4.4 Results and discussion

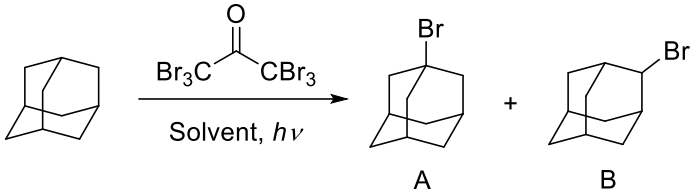
4.4.1 Bromination of adamantane

4.4.1.1 The effect of solvent on bromination of adamantane

Bromination of adamantane was performed in 12 solvents as shown in Table 4.1. The results did not show a clear trend of the most suitable solvent are suitable for this reaction. The solvent that gave the highest yield of 1-bromoadamantane was DCE in 48% with small amount (1%) of 2-bromoadamantane (entry 11). Non-polar solvent including hexane, benzene, and toluene gave 1-bromoadamantane in 7, 26, and 2% yields, respectively, and 2-bromoadamantane in 0, 3, and 1% yields,

respectively (entries 1-3). Both acyclic (Et_2O; entry 4) and cyclic ethers (THF; entry 5) gave very low yield of 1-bromoadamantane (1%) without 2-bromoadamantane. Acetonitrile gave relatively high amount of both 1-bromoadamantane and 2-bromoadamantane in 10% and 5% yields, respectively (entry 6). Methanol gave higher amount of 2-bromoadamantane (2%) than 1-bromoadamantane (1%; entry 7). However, the overall yield was still very low. Four chlorinated solvents were tested including dichloromethane, chloroform, CCl_4, and DCE. As mentioned above, DCE gave the highest yield of 1-bromoadamantane (entry 11), while dichloromethane and CCl_4 gave considerably high amount of 1-bromoadamantane in 21% and 24% yields, respectively (entries 8 and 10). Among these chlorinated solvents, chloroform gave the lowest yield of 1-bromoadamantane (6%) (entry 9). In 4-picoline, the reaction did not give any of the two expected products. The ratio of 1-bromoadamantane to 2-bromoadamantane reflects the selectivity of the developed method toward 1-bromoadamantane, and from the results below, for DCE, the ratio of 48:1 is considered very high.

Table 4.1 Effect of solvent on bromination of adamantane using HBA



Entry	Solvent	Remaining Substrate (%)[a]	Yield A (%)[a]	Yield of B (%)[a]	M.B.[b] (%)[a]	A/B
1	Hexane	87	7	0	93	-
2	Benzene	66	26	3	95	8.7
3	Toluene	114	2	1	117	2.0
4	Et_2O	91	1	0	91	-
5	THF	112	1	0	113	-
6	CH_3CN	81	10	5	95	2.0
7	MeOH	104	1	2	106	0.5
8	CH_2Cl_2	66	21	2	90	10.5
9	$CHCl_3$	91	6	1	98	6.0
10	CCl_4	38	24	4	66	6.0
11	DCE	37	48	1	86	48.0
12	4-Picoline	91	0	0	91	-

Reaction conditions: 0.125 mmol adamantane, 0.125 mmol HBA, 2 mL solvent, 1 h UV irradiation, rt.

[a] Determined by GC.

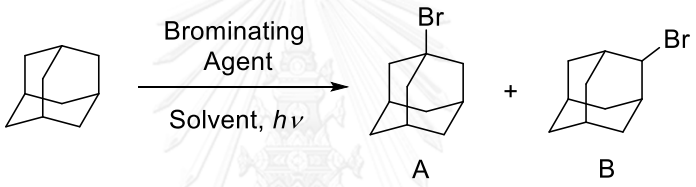
[b] Mass balance.

4.4.1.2 The effect of brominating agents for bromination of adamantane

HBA was also compared with other brominating agents including Br_2, HBr, and CBr_4 (Table 4.2). The reactions were performed in DCE under UV irradiation for 1 h. HBA

was found to be superior to other brominating agents giving 1-bromoadamantane in 48% and 2-bromoadamantane in 1% yields (entry 1). The next best brominating agent was CBr_4 yielding 39% of 1-bromoadamantane and 6% of 2-bromoadamantane (entry 4). Despite using excess of Br_2, because of the difficulty in transferring it to the reaction tube, the yield was only 17% of 1-bromoadamantane and without 2-bromoadamantane (entry 2). HBr gave very low yield of both 1-bromoadamantane and 2-bromoadamantane in 1% yield each (entry 3).

Table 4.2 Effect of brominating agents for bromination of adamantane



Entry	Brominating Agent	Remaining Substrate (%)[a]	Yield A (%)[a]	Yield of B (%)[a]	M.B.[b] (%)[a]	A/B
1	HBA	37	48	1	86	48.0
2	Br_2	68	17	0	85	-
3	HBr	91	1	1	93	1.0
4	CBr_4	77	39	6	122	6.5

Reaction conditions: 0.125 mmol adamantane, 1 eq. brominating agent (except for Br_2 which excess was used), 2 mL DCE, 1 h UV irradiation, rt.

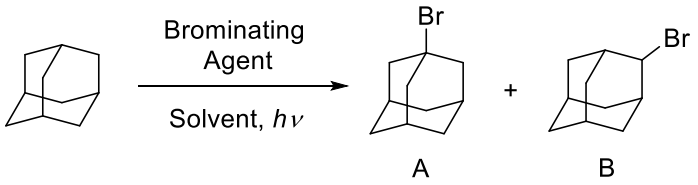
[a] Determined by GC.

[b] Mass balance.

The two best brominating agents, HBA and CBr_4, were tested further by increasing the reaction time to 6 h (Table 4.3). However, their yields only slightly

improved. For HBA, the yield of 1-bromoadamantane increased to 50% while 2-bromoadamantane remained at 1% (entry 1). The yield of 1-bromoadamantane increased to 43%, while 2-bromoadamantane increased to 7% for CBr_4 (entry 2).

Table 4.3 Increasing reaction time of bromination of adamantane



Entry	Brominating Agent	Remaining Substrate (%)[a]	Yield of A (%)[a]	Yield of B (%)[a]	M.B.[b] (%)[a]	A/B
1	HBA	34	50	1	85	50.0
2	CBr_4	33	43	7	83	6.1

Conditions: 0.125 mmol adamantane, 1 eq. brominating agent, 2 mL DCE, 6h UV irradiation, rt.

[a] Determined by GC.

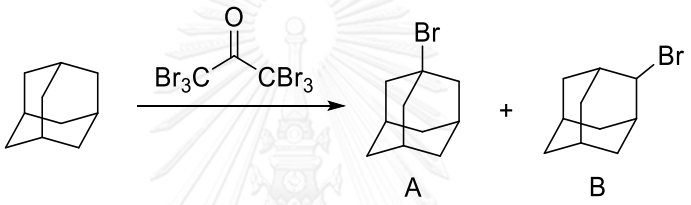
[b] Mass balance.

4.4.1.3 Variation of reaction conditions for bromination of adamantane

In order to improve the yield of the product for bromination of adamantane, various reaction conditions were tested (Table 4.4). However, none of other methods were as good as UV irradiation. It should be noted that running the reaction at room temperature gave 1-bromoadamantane in only 2% yield with no 2-bromoadamantane (entry 2). Increasing the temperature of the reaction to 80 °C increased the yield of 1-bromoadamantane to 6% with 1% of 2-bromoadamantane (entry 3). Under sonication,

only tiny amount of 1-bromoadamantane (1%) was produced with no 2-bromoadamantane (entry 4). For the reactions under microwave irradiation, two conditions were performed, with and without solvent. Under solvent-free condition, 6% yield of 1-bromoadamantane was obtained with no 2-bromoadamantane (entry 5), while in DCE only 1% of 1-bromoadamantane was formed with no 2-bromoadamantane as well (entry 6).

Table 4.4 Variation of reaction conditions for bromination of adamantane



Entry	Condition	Remaining Substrate (%)[a]	Yield of A (%)[a]	Yield of B (%)[a]	M.B.[b] (%)[a]	A/B
1	UV	37	48	1	86	39.9
2	rt	103	2	0	105	4.5
3	80 °C	96	6	1	103	5.2
4	sonication	97	1	0	98	5.5
5	microwave (solvent free)	82	6	0	88	55.0
6	microwave (in DCE)	98	1	0	99	6.0

Reaction conditions: 0.125 mmol (17 mg) adamantane, 0.125 mmol (66 mg) HBA, 2 mL DCE (except solvent free reaction), 1 h reaction time (except microwave, hold at 130 °C for 5 min).

[a] Determined by GC and SGE BP21 column using biphenyl as an internal standard.

[b] Mass balance.

4.4.1.4 Comparison with other methods

Compared to other methods in literature, the use of HBA provided reasonably high yield of the product in a short period of time (Table 4.5). Even though the yields may be lower than some methods, the reaction was performed at room temperature using an easy-to-make UV reactor. In addition, the 1- to 2-bromoadamantane of 48:1 was also very high, indicating high selectivity.

Table 4.5 Bromination of adamantane with various brominating agents

Reagent/Catalyst	Time	Condition	Yield	Reference
HBA	1 h	UV irradiation	48%	This study
$CBrCl_3$, $Mo(CO)_6$	5 h	160 °C	99%	[121]
Br_2, HBr	8 h	10 m, rt; 5 h, 105 °C	88%	[122]
CH_2Br_2, SbF_5	26 h	2 h, -78 °C; 24 h, rt	74%	[123]
CBr_4, NaOH, Bu_4NBr	20 h	PhF, H_2O; 42 °C	17%	[107]
CBr_4, polymetalphenylsiloxanes	1.5 h	150 °C	95%	[102]

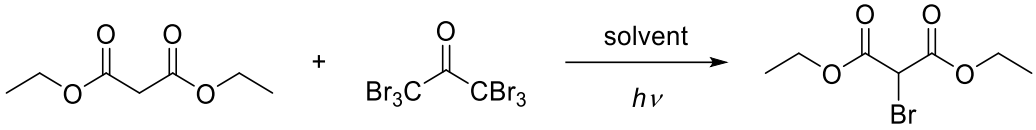
4.4.2 Bromination of diethyl malonate

4.4.2.1 The effect of solvent on bromination of diethyl malonate

To determine which solvent is the best for bromination of diethyl malonate with HBA, 10 solvents including CCl_4, DCE, chloroform, dichloromethane, acetonitrile, methanol, Et_2O, THF, benzene, and hexane were tested (Table 4.6). The reactions were

performed under UV irradiation for 2 h using 0.25 mmol diethyl malonate, 0.125 mmol (0.5 equiv.) HBA, and 1 mL solvent. CCl_4 was found to be the best solvent, giving 98% of diethyl bromomalonate (entry 1). The other three chlorinated solvents also gave considerably high yield of product of 94, 72, and 62% for DCE, chloroform, and dichloromethane, respectively (entries 2-4). Acetonitrile was also a very good solvent for this reaction as well, giving 96% yield of the product (entry 5). Methanol, Et_2O, and THF only gave over 30% yield of diethyl bromomalonate (entries 6-8). There were contrasting results for non-polar solvent as benzene gave very high yield of diethyl bromomalonate at 86% while hexane turned out to be the worst solvent, giving only 23% yield of the product (entries 9 and 10). UV irradiation was found to be crucial and when the reaction in CCl_4 was performed without UV irradiation, no diethyl bromomalonate was detected after 2 h (entry 11).

Table 4.6 Effect of solvents on the bromination of diethyl malonate with HBA



Entry	Solvent	Diethyl Malonate (%)[a]	Diethyl Bromomalonate (%)[a]	M.B.[b] (%)[a]
1	CCl_4	2	98	100
2	DCE	5	94	99
3	$CHCl_3$	29	72	101
4	CH_2Cl_2	34	62	96
5	CH_3CN	1	96	98
6	MeOH	26	36	62
7	Et_2O	54	36	90
8	THF	69	31	100
9	Benzene	14	86	101
10	Hexane	65	23	88
11[c]	CCl_4	100	0	100

Reaction condition: 0.25 mmol diethyl malonate, 0.125 mmol HBA, 1 mL solvent, 2 h UV irradiation, rt.

[a] Determined by ^{1}H NMR.

[b] Mass balance.

[c] Without UV irradiation.

4.4.2.2 Time-course investigation of bromination of diethyl malonate by HBA

To track the reaction progress, the bromination of diethyl malonate was collected every 30 min for 330 min as shown in Figure 4.6. After 30 min, almost 80% of diethyl bromomalonate was produced. The amount of diethyl bromomalonate produced then gradually rose. After 90 min, diethyl dibromomalonate began to appear

and slowly increased. The rate in which the amount of diethyl dibromomalonate rose was much slower than the rise in the amount of diethyl bromomalonate and diethyl dibromomalonate was not formed until nearly all of diethyl malonate had been converted, indicating that, comparatively, diethyl malonate is easier to brominate than diethyl bromomalonate. After 330 min, only around 40% of diethyl dibromomalonate was formed and the amount did not seem to be increasing. To make diethyl dibromomalonate the reaction condition was modified in the next section.

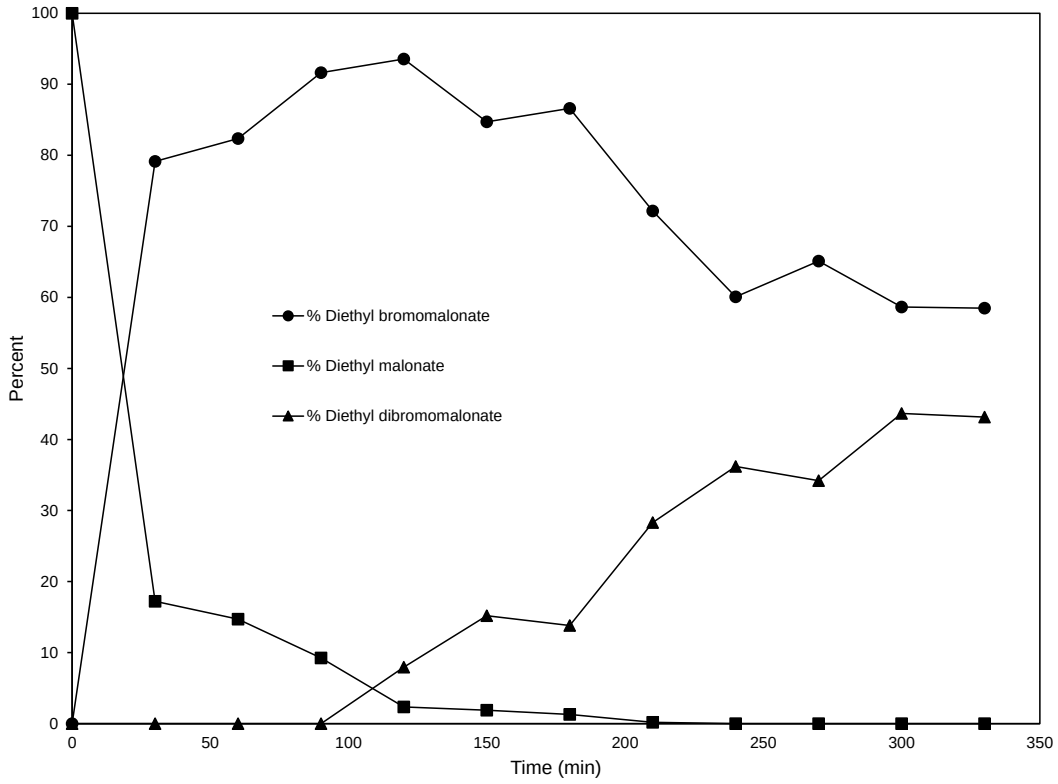
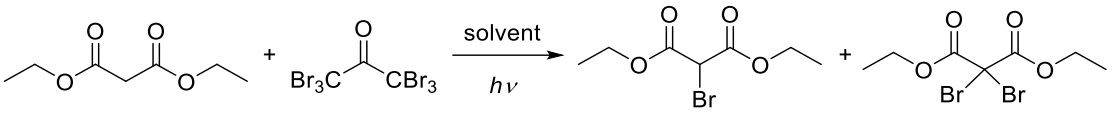


Figure 4.6 Time-course investigation of bromination of diethyl malonate by HBA Reaction condition: 0.25 mmol diethyl malonate, 0.125 mmol HBA, 1 mL CCl_4, rt. The amount of each compound was determined by ^1H NMR.

4.4.2.3 Dibromination of diethyl malonate

In order to make diethyl dibromomalonate, the amount of HBA was increased from 0.5 to 1 equivalent and the reaction time was increased to 18 h (Table 4.7). Three best solvents were chosen to be tested including CCl_4, DCE, and acetonitrile. The results showed that dibromination is also possible with HBA. The amount of diethyl dibromomalonate produced also had the same trend as the production of diethyl bromomalonate. CCl_4 gave the highest amount of diethyl dibromomalonate at 94% with 7% of diethyl bromomalonate and full conversion of diethyl malonate (entry 1). In DCE, the reaction produced 84% of diethyl dibromomalonate and 16% of diethyl bromomalonate with 100% conversion of diethyl malonate (entry 2). The reaction performed in acetonitrile gave 60% yield of diethyl dibromomalonate and 40% yield of diethyl bromomalonate with all diethyl malonate converted (entry 3).

Table 4.7 Bromination of diethyl malonate for 18 h using 1 equivalent of HBA



Entry	Solvent	Diethyl Malonate (%)[a]	Diethyl Bromomalonate (%)[a]	Diethyl Dibromomalonate (%)[a]	M.B.[b] (%)[a]
1	CCl_4	0	7	94	101
2	DCE	0	16	84	100
3	CH_3CN	0	40	60	100

Reaction condition: 0.25 mmol diethyl malonate, 0.25 mmol HBA, 1 mL solvent, 18 h UV irradiation, rt.

[a] Determined by ^1H NMR.

[b] Mass balance.

4.4.2.4 Bromine efficiency of bromination of diethyl malonate

Since one molecule of hexabromoacetone contains 6 bromine atoms, the number of bromine atoms from each molecule used for bromination of diethyl malonate was determined by using 6:1 and 12:1 ratio of substrate:HBA which would be equal to 1 substrate molecule:1 bromine atom and 2 substrate molecules:1 bromine atom, respectively, as shown in Table 4.8. The 6:1 ratio was performed twice (entries 1 and 2) and the 12:1 ratio was performed once (entry 3). For the 6:1 ratio, the bromine efficiency is calculated as follows:

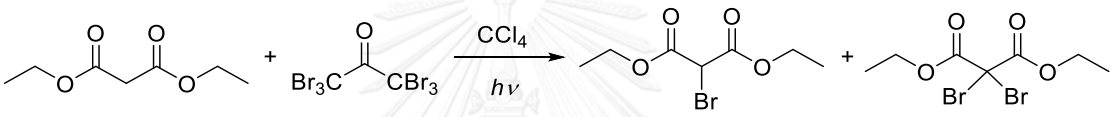
$$\text{Bromine Efficiency} = \frac{\%\text{Diethyl Bromomalonate}}{100} \times 6$$

For the 12:1 ratio, the bromine efficiency is calculated as follows:

$$\text{Bromine Efficiency} = \frac{\%\text{Diethyl Bromomalonate}}{100} \times 12$$

The results showed that bromine efficiency was between 3.8-3.9, indicating that for each molecule of HBA, 3.8-3.9 bromine atoms can be used for bromination of diethyl malonate.

Table 4.8 Bromine efficiency of bromination of diethyl malonate



Entry	Substrate:HBA	Diethyl Malonate (%)[a]	% Diethyl Bromomalonate (%)[a]	M.B.[b] (%)	Bromine Efficiency
1	6:1	27.0	65.7	92.7	3.9
2	6:1	23.7	63.8	87.5	3.8
3	12:1	47.7	31.8	79.5	3.8

Reaction condition: 0.25 mmol diethyl malonate, 1 mL CCl_4, 12 h UV irradiation, rt.

[a] Determined by ^{1}H NMR.

4.4.2.5 Comparison with other methods

Using HBA as a brominating agent produced excellent yields of diethyl bromomalonate in a short period of time similar to some other brominating agents.[113, 115, 117, 119] In addition, it was much better than some reported

methods. When BrCN was used only 38% yield of diethyl bromomalonate was obtained [111] and for HTIB and magnesium bromide, only 83% yield was produced despite using a microwave.[118] This study also optimized reaction conditions for producing diethyl dibromomalonate, which other publications did not report.

4.5 Proposed mechanism

The bromination mechanism likely starts from the cleavage of bromine from HBA by UV irradiation (Figure 4.7). The resulting radical of HBA would then abstract hydrogen radical from adamantane producing adamantane radical. This adamantane radical would form a bond with bromine from HBA, which would propagate more bromination.

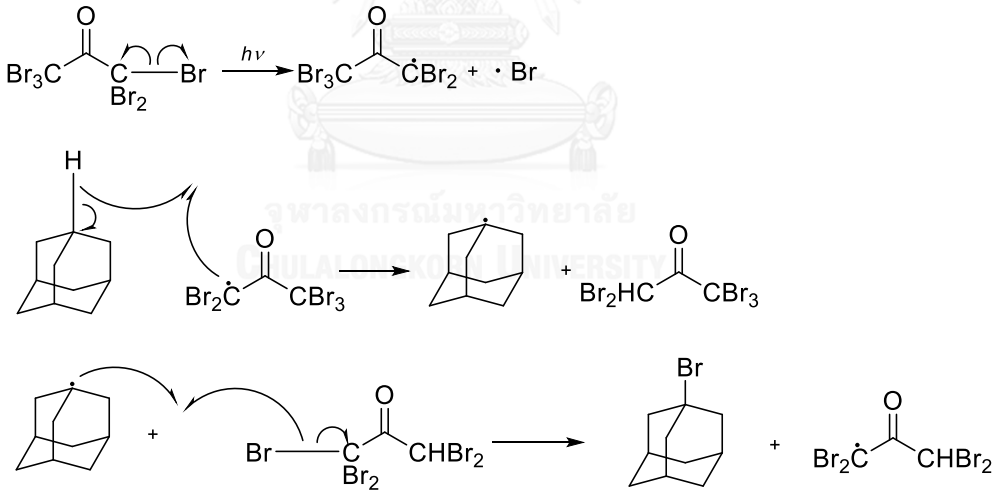


Figure 4.7 Proposed mechanism for bromination of adamantane

4.6 Conclusion

HBA was found to be a very efficient and selective brominating agent for both adamantane and diethyl malonate. For adamantane, which is difficult to brominate,

the yield of 1-bromoadamantane was high and the selectivity was very good. The reaction can be performed under UV irradiation in only 1 h. For diethyl malonate, the reaction was very fast as well and in CCl_4 gave 98% yield of diethyl bromomalonate product. In addition, preparation of diethyl dibromomalonate was also successful and 94% yield of the product was obtained. The bromine efficiency of HBA was determined to be between 3.8-3.9.

CHAPTER V
CONCLUSIONS

In this research, HBA was used as a catalyst for protection of glycerol with acetone to produce solketal, protection of benzaldehyde with methanol, protection of a variety of aldehydes and ketones with 1,3-propanedithiol, deprotection of benzaldehyde dimethyl acetal and other acetals, and deoximation of various oximes.

For protection of glycerol with acetone, 90% of solketal product can be obtained within 10 min using only 2.5 mol% of HBA under UV irradiation. This method could be used for conversion of glycerol by product from biodiesel to produce fine chemicals. For protection for benzaldehyde with methanol, benzaldehyde dimethyl acetal yield was 95% in 10 min under UV irradiation. In both protection cases, the higher the amount of the protective solvent, the higher the yields of the products. Reducing the amount of HBA could also produce high yield of products, but will require longer reaction time.

Dithiane of aldehyde can be produced under UV irradiation without any catalyst and has never been reported. Addition of HBA significantly reduced the reaction time. UV irradiation also accelerated the formation of dithiane of various ketones. Substrates with electron-donating substituents at the *ortho* and *para* position can be protected faster with higher yields of the corresponding dithiane, while electron-withdrawing group impeded the reaction. Aldehydes are easier to protect than ketones, which

could be a benefit when selectivity is required for the protection of aldehydes. Aliphatic ketones were also more readily protected than aromatic ketones.

For deprotection of benzaldehyde dimethyl acetal, solketal, and some other acetals and ketals, in most cases, the reactions were very fast and very small amount of HBA was needed. The products can be easily separated from impurities. HBA was also effectively used for deoximation of various oximes. Solvent was found to have an impact on the efficiency of HBA and it was crucial to choose the right solvent or solvent combination for each type of substrate and reaction. Water was necessary for deoximation. Using TEMPO as a radical trapping agent, it was revealed that the reactions involved radical intermediates.

HBA was found to be a very efficient and selective brominating agent for both adamantane and diethyl malonate. For adamantane, which is difficult to brominate because of unactivated C-H, the yield of 1-bromoadamantane was 48% and the selectivity was very good. The reaction can be performed under UV irradiation in only 1 h. For diethyl malonate, the reaction was very fast as well and in CCl_4 gave 98% yield of diethyl bromomalonate product. In addition, the preparation of diethyl dibromomalonate was also successful and 94% yield of the product was obtained. The selectivity of these two products can be controlled by varying the reaction time and the amount of HBA. The bromine efficiency of HBA was determined to be between 3.8-3.9.

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APPENDIX

VITA

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