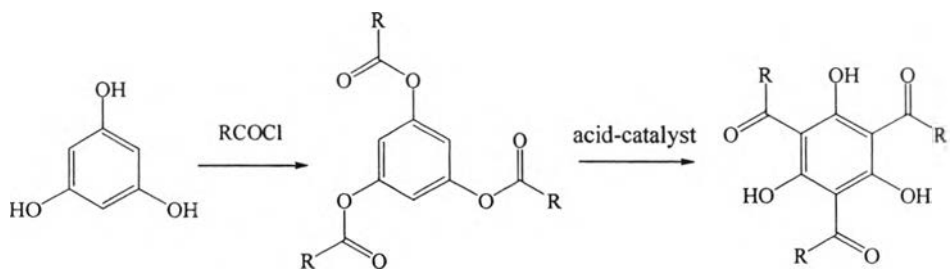
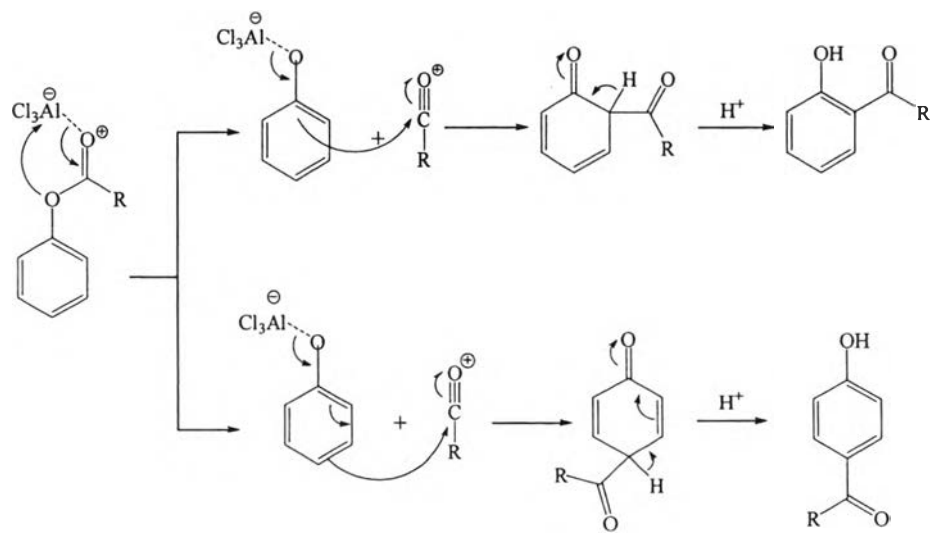
CHAPTER III

RESULTS AND DISCUSSION

The general syntheses of hexasubstituted benzene derivatives were done through triple O-alkylation between one mole equivalent of phloroglucinol dihydrate and excess of various electrophiles such as acid chlorides and aliphatic halide at reflux temperature (**Scheme 3.1**). The product of alkylations then underwent Fries rearrangement[52] to *ortho* or *para*-positions upon treatment of about five equivalents of acid catalyst. The mechanism of this rearrangement is shown in **Scheme 3.2**. The processes will be discussed in detail in the following sections.



Scheme 3.1 Synthesis of hexasubstituted benzene from phloroglucinol



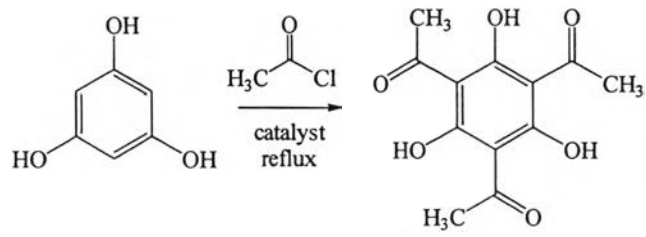
Scheme 3.2 Mechanism of the Fries rearrangement of acyloxybenzene to hydroxy alkophenone derivatives

3.1 Synthesis of 1,3,5-Trisubstituted-2,4,6-trihydroxybenzene

The reaction conditions for the synthesis of compound 1,3,5-triacetyl-2,4,6-trihydroxybenzene **60** were varied through 2 factors: the types of acid-catalysts and the reaction time (**Table 3.1**). Among acid catalysts used, the most efficient acid-catalyst was found to be $AlCl_3$, yielding the product up to 85% (entry 1). Much lower yields were obtained with $TiCl_4$, $FeCl_3$ and conc. H_2SO_4 and no product formed at all with $ZnCl_2$ after 7 hours (entry 2-5). The well known hard Lewis acid $AlCl_3$ could perhaps accepted electrons from oxygen atom on the substrate and initiated the reaction towards the desired product better than $TiCl_4$ and $FeCl_3$ while $ZnCl_2$ was too soft to catalyze any rearrangement. Concentrated H_2SO_4 was not effective either, giving the product in very low yield together with some other intermediates such as mono- and di-ester and large amount of recovered substrate.

As for the time dependence of this reaction, the reaction was held at reflux temperature (approximately 52 °C) for 1, 2 and 4 hours using $AlCl_3$ as the catalyst (**Table 3.1**, entry 1, 6 and 7). The product yield did not improve with the prolonged refluxing time of more than 1 hour. The hexasubstituted benzene product must have reached its optimum yield early but due to its highly steric crowd between neighboring groups, the reaction could reverse back to intermediates in equilibrium at long reaction time and produce several byproducts in the reaction.

Table 3.1 Conditions for the synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **60**

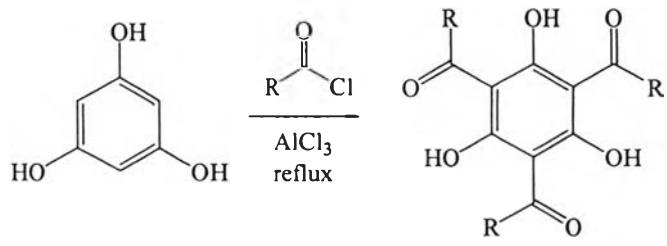


60

Entry	Catalyst	Reaction time (h)	% Yield of product
1	$AlCl_3$	1	85
2	$TiCl_4$	1	40
3	$FeCl_3$	1	32
4	$ZnCl_2$	7	ND[a]
5	conc. H_2SO_4	4.5	14
6	$AlCl_3$	2	60
7	$AlCl_3$	4	70

[a]ND = no product detected

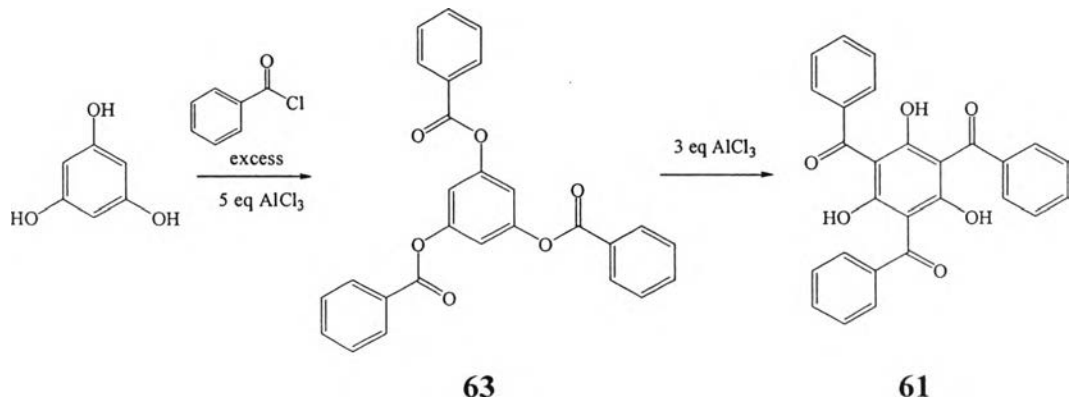
The synthesis of hexasubstituted benzene derivatives had been extended to using benzoyl chloride and octanoyl chloride as electrophile and solvent in place of acetyl chloride. Although the expected products from these two acid chlorides could be obtained by the same method, but the yields were relatively poor; only 37% and 14% yields were obtained for the case of benzoyl and octanoyl chloride, respectively.



60 : R = CH_3 85%
61 : R = C_6H_5 37%
62 : R = C_7H_{15} 14%

Scheme 3.3 Synthesis of hexasubstituted benzene derivatives from 3 types of acid chlorides

During the initial attempt to synthesize compound **61**, the benzoyl groups initially attached as triester intermediate **63** were somehow prevented it from the rearrangement to **61** by the remaining benzoyl chloride, providing 1,3,5-tribenzoyloxybenzene **63** as the product. Subjecting the isolated triester to the rearrangement using anhydrous $AlCl_3$ (0.44 g, 3.3 mmol) at 150 °C without solvent for 3 hours under nitrogen atmosphere gave the desired product in 13% yield and 10% overall yield from phloroglucinol. Later, the synthesis of compound **61** was retried by using benzoyl chloride 6 eq and added chlorobenzene as a solvent. The desired product could be synthesized under this condition in 37% yield.



63 **61**

Scheme 3.4 Stepwise synthesis of 1,3,5-tribenzoyl-2,4,6-trihydroxybenzene **61**

From ^{1}H-NMR spectra analysis, the signal of phenolic protons of **60** appeared as a singlet at δ 17.2 ppm (lit. 17.09 ppm[53], **Figure A.1** in Appendix) indicating that the molecule was not arranged in an *ababab* geometric pattern (see chapter I; p.

2). It was perhaps assumed to be relatively flat platform with strong three intramolecular hydrogen bonds of all the three *ortho*-hydroxy groups to the adjacent carbonyl groups of the acyl aromatics (**Figure 3.1**). Similar to **60**, compound **61** and **62** also showed their proton signals of the phenolic groups relatively downfield due to such intramolecular hydrogen bonds, although at perhaps weaker strength at δ 14.6 (lit. 14.56)[29] and 17.2 ppm (**Figure A.5** and **A.9**), respectively.

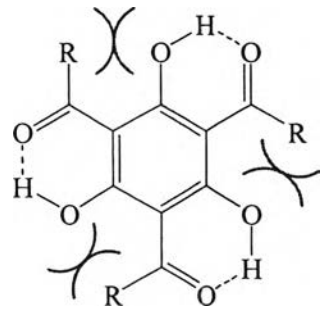


Figure 3.1 Intramolecular hydrogen bonds of the *ortho*-hydroxyacyl aromatics and steric crowd between neighboring groups

The planarity of *ortho*-hydroxyacyl aromatic molecules could possibly be compared among their derivatives. The evidence for such planarity has been suggested to correlate with the chemical shift of the proton signal of phenolic OH in ^{1}H-NMR spectra. It was found that as the sizes of the α-substituents of acyl groups were increased, the planarity of the molecule would decreased due to congestion around the aromatic ring, resulting in less favored arrangements of the intramolecular hydrogen bonds of the *ortho*-hydroxy groups to carbonyl groups of the neighboring acyl groups. Benzoyl group carring a phenyl ring would be the bulkiest among the 3 compounds, as reflected in the more upfield shift of its phenolic OH proton signal in ^{1}H-NMR spectra, possibly corresponding to the weakest intramolecular hydrogen bond in the molecule comparing to the acetyl and octanoyl derivatives.

Preparations of other derivatives with smaller size of acyl groups have been attempted. Ethyl formate and *N,N*-dimethylformamide (DMF) were investigated as the acyl donor reagents to synthesize formyl hexasubstituted benzene using similar strategy and expecting formyl groups to be attached on the 1,3 and 5-positions of the product to become 1,3,5-triformyl-2,4,6-trihydroxybenzene **64**. In the case of ethyl formate, this reagent did not react with phloroglucinol during two days under the reaction condition. Its boiling point of 52 °C and its much lower reactivity than acid

chlorides might have limited the rate of the reaction. The higher boiling DMF showed some reaction with phloroglucinol using $AlCl_3$ as the catalyst but a very complicate mixture was obtained that could not be characterized by ^{1}H-NMR data. Next, benzyl chloride was used as the electrophile in the above condition and expected to observe 1,3,5-tribenzyl-2,4,6-trihydroxybenzene **65**. However, the reaction gave a high yield of unexpected polymer that was assumed to be the formation of polyphenylenemethylene polymer from repeated substitutions of the benzyl groups onto the *para*-positions of another benzyl groups.

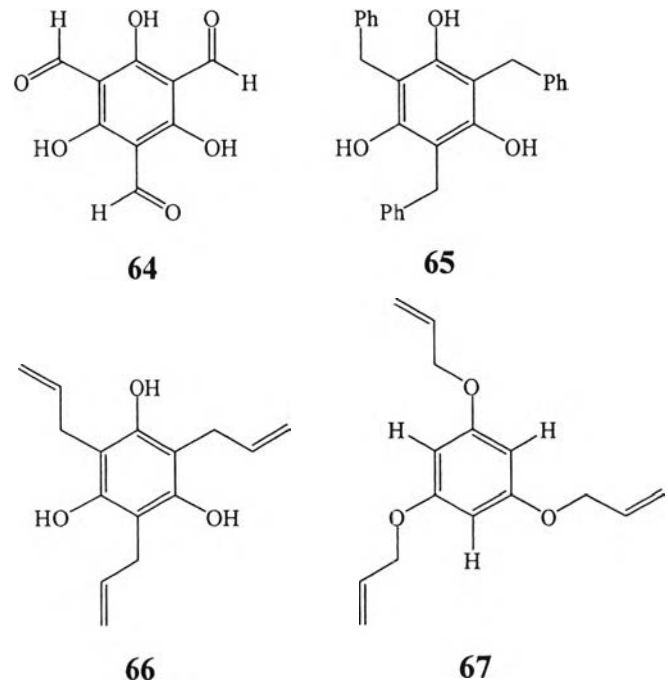
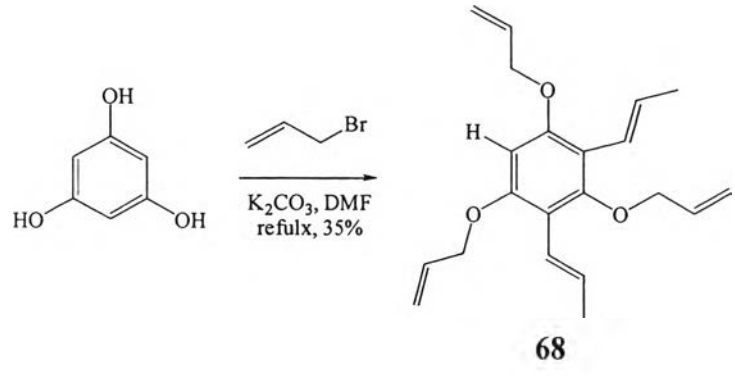


Figure 3.2 Other expected hexasubstituted benzene derivatives

Allyl bromide, a non-aromatic alkyl halide, was then used to form the 1,3,5-triallyl-2,4,6-trihydroxybenzene **66** through 1,3,5-triallyloxybenzene intermediate **67** by alkylation condition followed by rearrangement of the allyl groups to desired product. Surprisingly, the allyl groups had already rearranged during the alkylation process giving a product that was roughly characterized to be 1,3,5-triallyloxy-2,4-di(1-propenyl)benzene **68**. Various conditions were tried including performing the reactions with other bases such as K_2CO_3, Na_2CO_3, KOH, NaOH; other solvents such as MeCN, acetone, DMF; and at different temperature: 0 °C, RT and reflux, which were all yet unsuccessful. The yellow oil of the product **68** was best obtained using K_2CO_3 as the base, DMF as the solvent, reflux temperature, and the reaction time of 3.5 hours. The product was purified by column chromatography (90:10

hexane/EtOAc) to obtain the isolate yield of 35% (**Scheme 3.5**). A cleaner condition could be performed at 0 °C but yielded the compound **68** in only 26%.

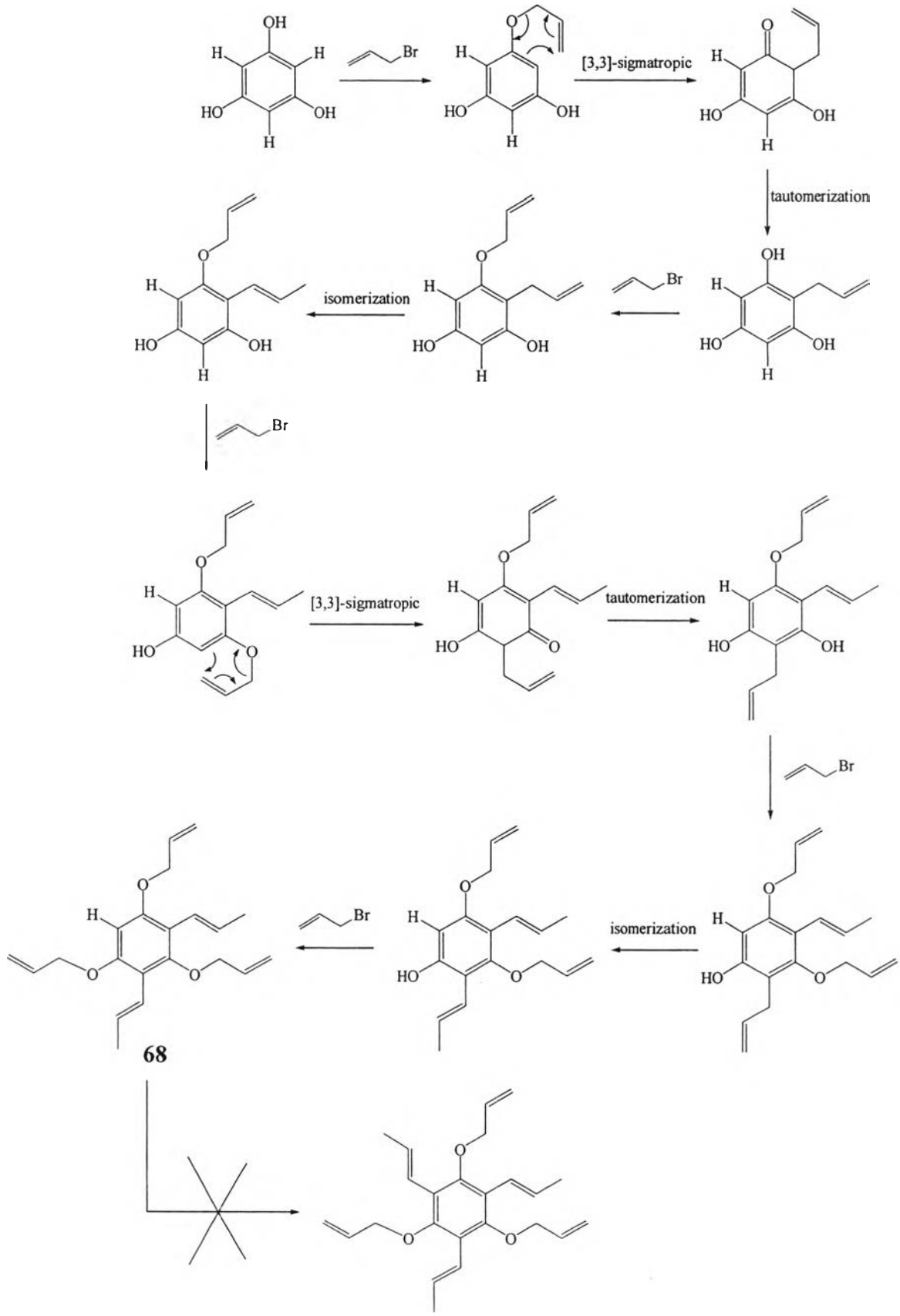


68

Scheme 3.5 Synthesis of 1,3,5-triallyloxy-2,4-di(1-propenyl)benzene **68**

The product **68** was characterized by ^{1}H-NMR and Mass Spectroscopy. The ^{1}H-NMR showed very complicate signals that might arise from many possible conformations. A singlet signal at 5.65 ppm (**Figure A.17**) was assumed to be the lone aromatic proton of the pentasubstituted benzene. The allyl group signals were showed as two groups at 5.98 and 5.55 ppm. In addition, the signals at 2.48 and 2.68 ppm indicating that the product should have isomerized some allyl groups from external to more stable internal alkenes which increased conjugation to the aromatic ring. The uneven integrals of these signals may be due to the presence of other forms of conformers. For ^{13}C-NMR data, the signals appeared to confirm above structure including alkyl carbons, alkoxy carbons, olefinic carbons, although the presence of extra signals at 197 and 210 ppm (**Figure A.18**) were assumed to be an unknown impurity.

The mechanism of the formation of this perallylated benzene **68** was expected to go through the initial O-allylation, then the allyl groups were rearranged to their *ortho*-positions by [3,3]-sigmatropic or Claisen rearrangement[54] (**Scheme 3.6**). The free hydroxyl groups were further allylated and the allyl groups attached to the aromatic ring isomerized to the more stable internal alkenes in the presence of base. The last rearrangement of allyl group onto the aromatic ring was assumed to be too geometrically difficult, restricted by high steric factors of the pentasubstituted benzene product.



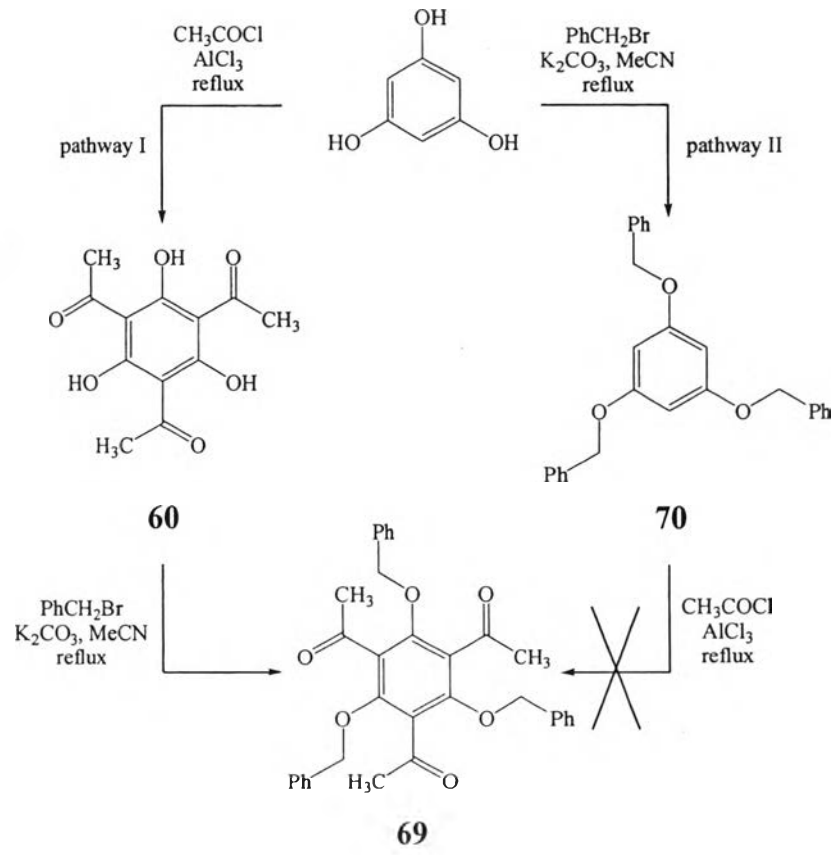
Scheme 3.6 Proposed mechanism of allylation and rearrangement of allyl groups

3.2 Functionalization of 1,3,5-triacetyl-2,4,6-trihydroxybenzene 60

1,3,5-triacetyl-2,4,6-trihydroxybenzene **60** was modified to *ababab* geometry by functionalization to various derivatives. The functionalization had been done in two pathways: alkylations on the phenolic hydroxy groups and additions on the carbonyl of ketone groups.

3.2.1 Functionalization of the Phenolic Hydroxy Groups

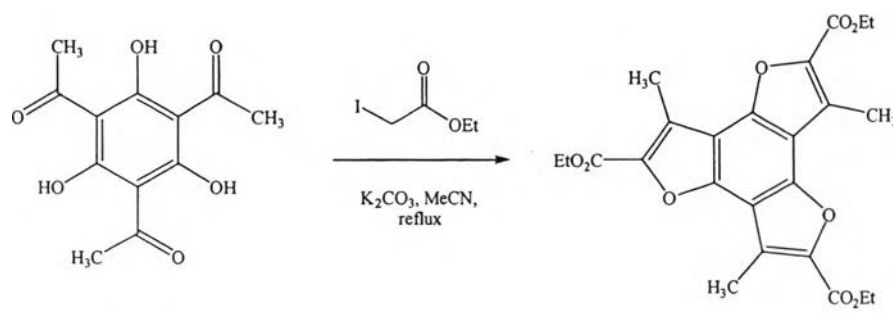
Compound **60** was benzylated using benzyl bromide in basic condition to provide 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene **69**. The ^{1}H-NMR characterization was confirmed a symmetric structure of the desired product obtained up to 65% yield (**Scheme 3.7**, pathway I). The proton signals showed a singlet of methyl, benzyl protons and multiplet of aromatic protons at δ 2.5, 4.9 and 7.4 ppm (**Figure A.21**), respectively. The overall yield of this pathway from phloroglucinol was 55%. Prolonged reaction has showed that this highly congested product might be lose its substituents and provided mono- and/or dibenzylated byproducts that affected the yield of the desired product.



Scheme 3.7 Two synthetic pathways of compound **69**

The compound **69** could also be synthesized by switching the acetylation and benzylation steps (**Scheme 3.7**, pathway II). The benzylation of phloroglucinol gave the tribenzyloxy intermediate **70** in 69% yield. The intermediate was acetylated with acetyl chloride and $AlCl_3$ for 1 hour. The product of the reaction was, however, not the compound **69** but appeared to be the precursor **60,** obtained in 46% yield together with some polymers of the benzyl groups after purified by column chromatography. This result supported that the benzyl groups could be released and polymerized in the presence of $AlCl_3$, similar to the earlier reaction of phloroglucinol and benzyl chloride.

Other O-alkylated products were investigated by using ethyl iodoacetate and *N*-benzyl iodoacetamide. These reagents were synthesized in 2 steps from the reactions of chloroacetyl chloride with ethanol and benzylamine, respectively, followed by iodide substitution, yielding 89% of ethyl iodoacetate and 94% of *N*-benzyl iodoacetamide. The reaction of ethyl iodoacetate with compound **60** were found to occur but immediately condensed further with *ortho*-neighboring groups to provide a symmetric platform of trifuranyl triester derivative **71** in 18% yield (**Scheme 3.8**). The structure of the product was characterized by NMR data confirmed by 4 lines of aromatic carbons (**Figure A.33**). The reaction with *N*-benzyl iodoacetamide, however, gave no identifiable product.

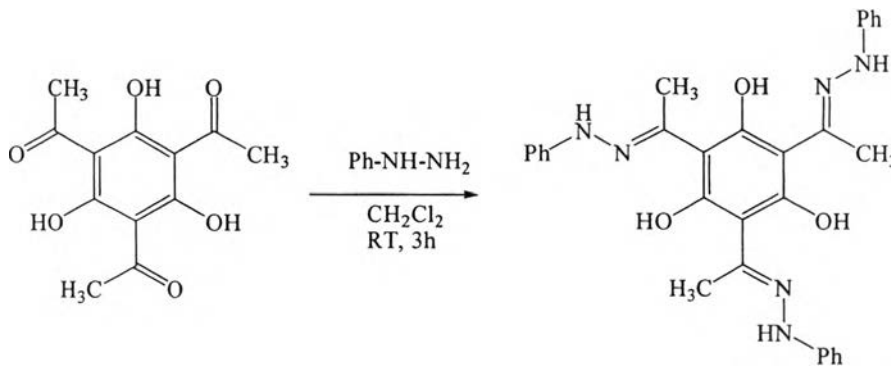


60 **71**

Scheme 3.8 Alkylations of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **60** with iodo ethylacetate to trifuranyl triester derivative **71**

3.2.2 The Functionalization of the Ketone Carbonyls

The ketone groups of compound **60** were functionalized into hydrazone derivative using phenylhydrazine for 3 hours. The 1,3,5-tris(1-[(2-phenylhydrazono) ethyl])-2,4,6-trihydroxy benzene **72** product was obtained in 18% yield. The intramolecular hydrogen bonds between the hydroxyl group and C=N were also present, as showed by the downfield signals of the phenolic hydroxy protons showed at 15.4 ppm while as the methyl protons showed at 2.5 ppm and aromatic protons appeared at 6.9, 7.0 and 7.3 ppm (**Figure A.36**).



60 **72**

Scheme 3.9 Formation of the hydrazone derivative **72**

Compound **72** has been tested to form complexes with $FeCl_3$, $Cu(OAc)_2$, $Co(OAc)_2{\cdot}4H_2O$ and $Zn(OAc)_2{\cdot}2H_2O$ by mixing compound **72** and each salt together in EtOAc. The observed the changes of color of the solution are shown in **Table 3.2**.

Table 3.2 The color changes of the salt solution upon complexation with compound **72** in EtOAc

Compounds	Original Color	Color of the mixture with 72
compound **72**	yellow	-
$FeCl_3$	yellow	orange
$Cu(OAc)_2$	blue	green
$Co(OAc)_2{\cdot}4H_2O$	pink	orange
$Zn(OAc)_2{\cdot}2H_2O$	colorless	yellow

The solution and mixture of metal-ligand complexes were characterized by UV-Visible spectrophotometry. About 15 times excess of metal salt to ligand **72** in EtOAc were used, providing the spectra showed in **Figure 3.3-3.6**. Compound **72** absorbed with λ_{max} at 323 nm and a shoulder peak at 301 nm. $FeCl_3$ absorbed at 272 and 344 nm while the mixture of ligand and $FeCl_3$ absorbed at 287 nm and had a shoulder peak at 324 nm (**Figure 3.3**). For Cu-complex, the λ_{max} of $Cu(OAc)_2$ spectra showed at 275 nm while the spectrum of the complex appeared at 287 nm with a shoulder at longer wavelength (**Figure 3.4**). These results indicated that compound **72** could form complexes with Fe(III) and Cu(II). The mixture of **72** with Co and Zn did not show the λ_{max} shift in the UV spectra, only the decrease of the absorbance due to dilution (**Figure 3.5** and **3.6**)

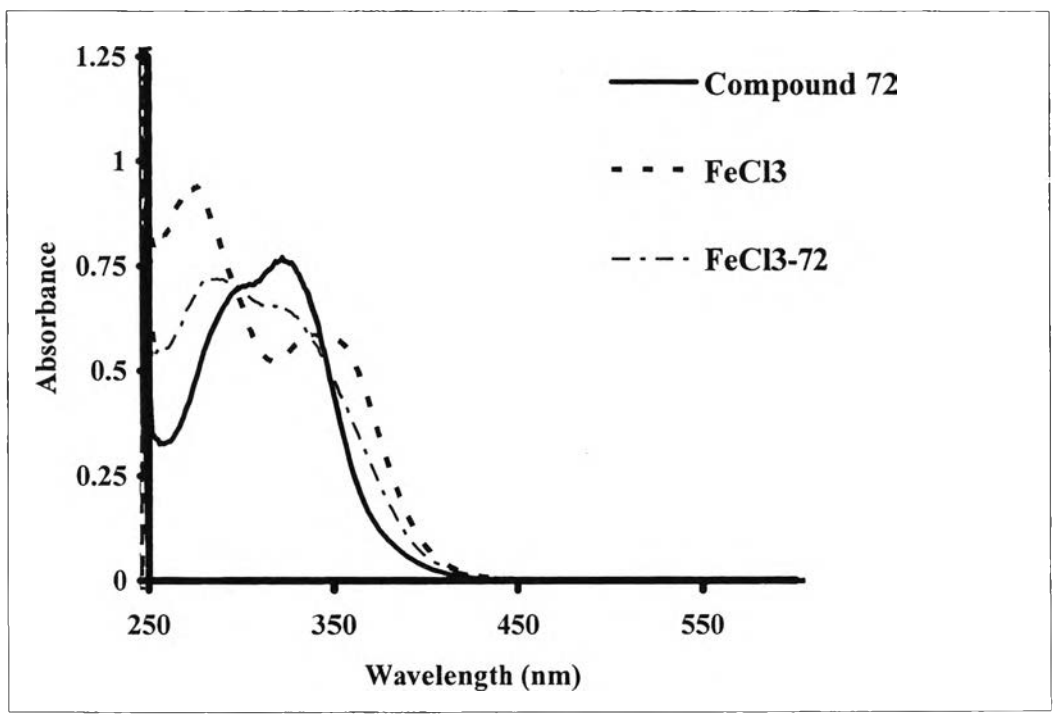


Figure 3.3 Absorption spectra of compound **72**, $FeCl_3$ and their complex

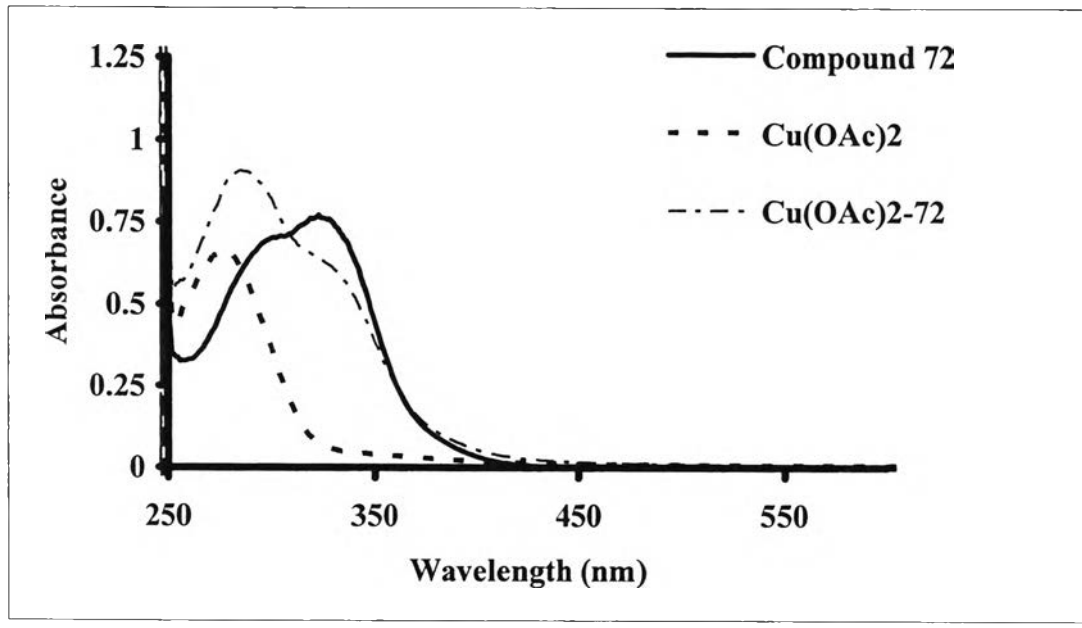


Figure 3.4 Absorption spectra of compound **72**, $Cu(OAc)_2$ and their complex

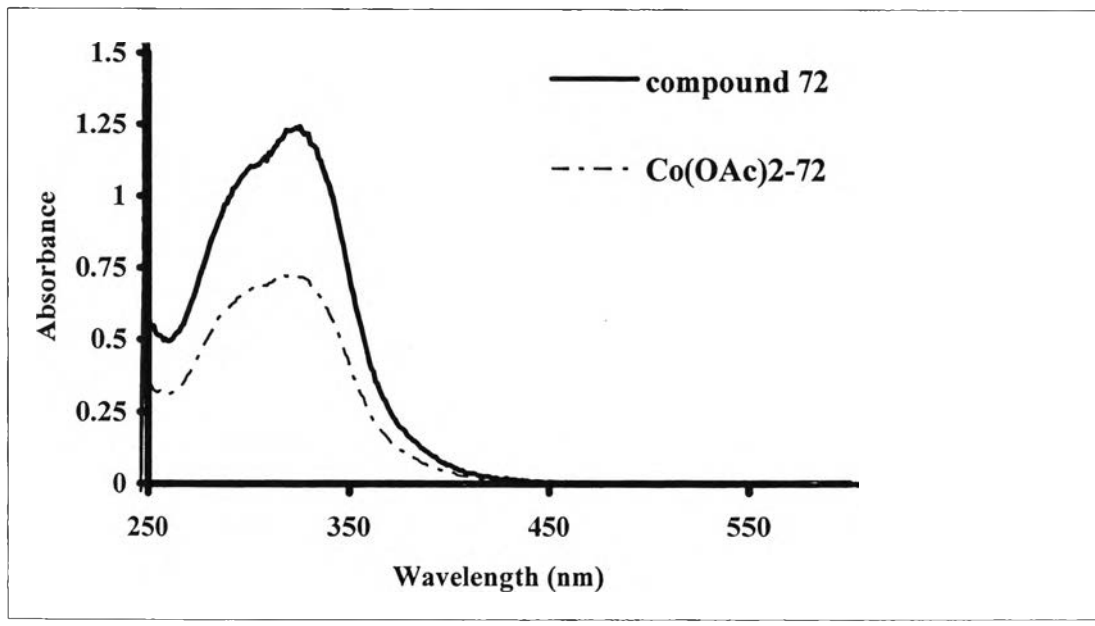


Figure 3.5 Absorption spectra of compound **72**, $Co(OAc)_2$ and their mixture

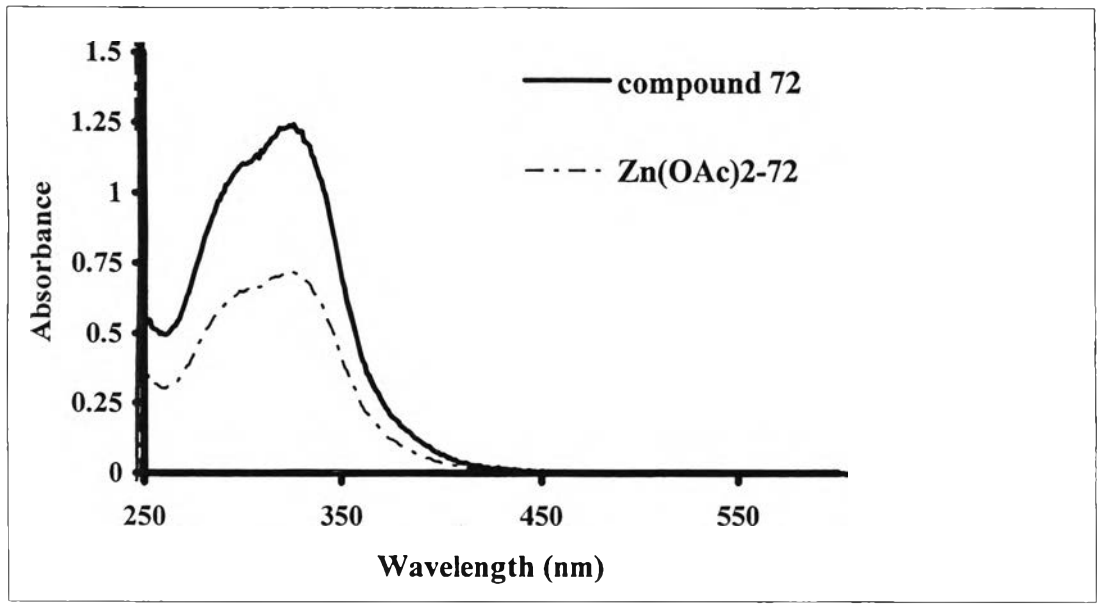


Figure 3.6 Absorption spectra of compound **72**, $Zn(OAc)_2$ and their mixture

The complexes of compound **72** were analyzed in $CDCl_3$ with ^{1}H-NMR technique. The ^{1}H-NMR spectra of $FeCl_3$-**72** and $Cu(OAc)_2$-**72** showed broad peaks and the chemical shifts of the methyl and aromatic protons of compound **72** were changed. For Fe -complex, the methyl protons shifted downfield to 2.8 ppm and all aromatic protons grouped at 7.3 ppm. The methyl protons of Cu-complex shifted downfield to 2.7 ppm as broad peak and aromatic protons shifted to 7.3 ppm and the singlet signal at 2.1 ppm was free acetate which was released by $Cu(OAc)_2$. ^{1}H-NMR spectrum of $Zn(OAc)_2 \cdot 2H_2O$-**72** showed broad peaks in which methyl protons appeared 2.1, 2.5 and 2.8 ppm and aromatic proton remained the same as compound **72**. The spectrum of $Co(OAc)_2 \cdot 4H_2O$ showed very broad peaks and was similar to Zn-complex.

Table 3.3 ^{1}H-NMR signals of compound **72** and its complexes

Compound	^{1}H-NMR signals
Compound **72**	2.5(9H, s), 6.9(3H, t), 7.0(6H, d), 7.3(6H, t), 15.4(3H, s, br)
$FeCl_3$-**72**	2.8(br), 7.3(br)
$Cu(OAc)_2$-**72**	2.1(s), 2.7(br), 7.3(br)
$Zn(OAc)_2$-**72**	2.1(br), 2.5(br), 2.7(br), 7.0(br), 7.3(br), 15.4(br)
Co(OAc)-**72**	2.1(br), 2.5(br), 2.7(br), 7.0(br), 7.3(br), 15.4(br)

Also, the functionalization on ketone groups with above reagent were tried on compound **68** and not at all product was appeared from the reaction. Since compound **68** was contained many steric features of benzyl groups so the increasing of steric by functionalize on ketone groups was rejected. From above results found that the functionalization at α-atom around benzene ring were difficult to perform since these positions were increased the steric features between neighboring groups so the β-position of substituents were interested to functionalize because the steric effects of that position was decreased and expected to functionalize easier than α-position.