CHAPTER III

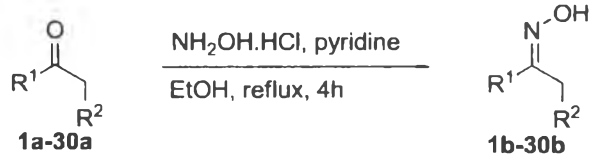
RESULTS AND DISCUSSION

3.1 Preparation of aryl oximes

To test the Trofimov reaction, thirty oximes were prepared by following the known procedure [21] as shown in Scheme 3.1. The condensation between the ketone 1a-30a with hydroxylamine hydrochloride in the presence of pyridine as base gave rise to the formation of the desired oxime 1b-30b in high yields after recrystallization. Notably, aryl oximes **1b-4b, 9b, 11b-19b, 21b, 22b-30b** were obtained from commercially available ketones while **5b-7b, 9b, 20b,** on the other hand, were prepared from the corresponding ketones according to literatures. The synthesis of ketone starting material will be discussed in detail below.

3.1.1 Synthesis of oximes

Table 3.1 Type of oximes used in this work



No.	R^1	R^2	yield (%)
1b	C_6H_5	H	92
2b	CH_3-C_6H_4	H	87
3b	HO-C_6H_4	H	52
4b	CH_3O-C_6H_4	H	99
5b	$CH_3(CH_2)_3O$-C_6H_4	H	95
6b	C_6H_5O-C_6H_4	H	76
7b	TsO-C_6H_4	H	93
8b	NH_2-C_6H_4	H	92
9b	$(CH_3)_2N$-C_6H_4	H	75
10b	CH_3S-C_6H_4	H	77
11b	F-C_6H_4	H	97
12b	Cl-C_6H_4	H	96
13b	Br-C_6H_4	H	95
14b	I-C_6H_4	H	91
15b	NO_2-C_6H_4	H	93

No.	R^1	R^2	yield (%)
16b	CN-C_6H_4	H	91
17b	C_6H_5-C_6H_4	H	97
18b	C_5H_4N-C_6H_4	H	87
19b	C_4H_3S-C_6H_4	H	95
20b	$C_6H_5C{\equiv}CC_6H_4$	H	80
21b	$(OH)_2B$-C_6H_4	H	87
22b	$C_6H_{12}O_2B$-C_6H_4	H	84
23b	α-$C_{10}H_7$	H	90
24b	β-$C_{10}H_7$	H	91
25b	$C_{14}H_9$	H	88
26b	C_6H_5CH=CH	H	87
27b	$(CH_2)_5C$		83
28b	$C_6H_4(CH_2)_3C$		95
29b	$(CH_2)_4CH$=CH	H	35
30b	C_6H_5	CH_3	80

3.1.2 Preparation of arylketones (5a-7a, 9a, 20a)

4-Butoxyacetophenone (5a)

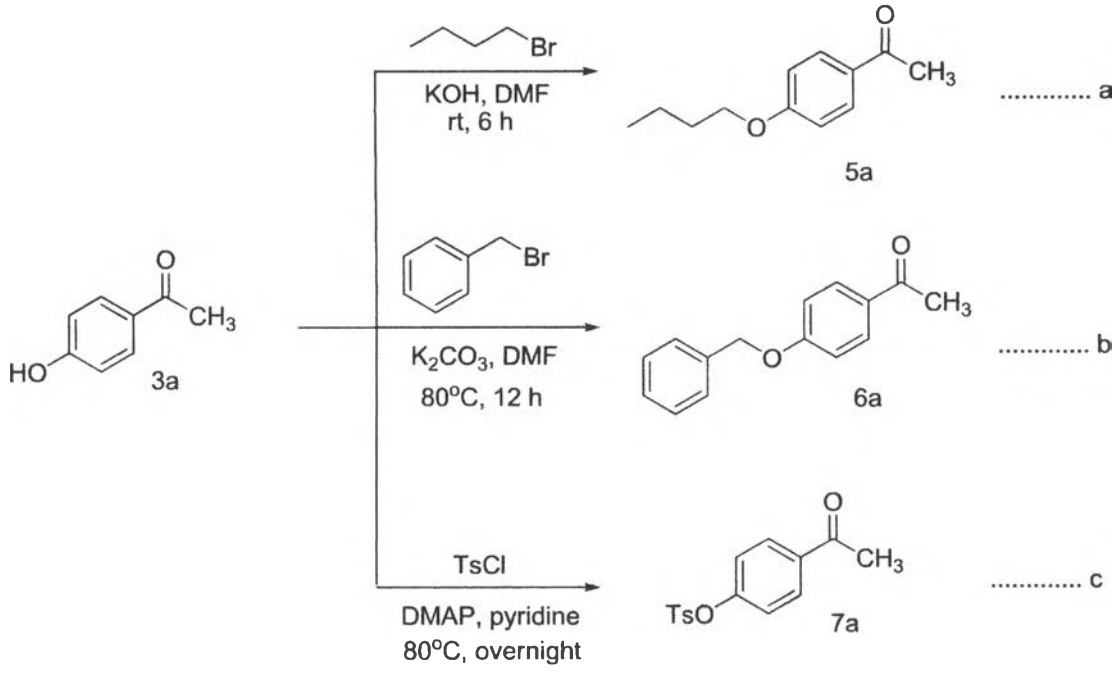
Reaction of 4-hydroxyacetone with n-butyl bromide in DMF and potassium hydroxide at room temperature gave the alkylated product **5a** in 93% yield (Scheme 3.1, a)

4-Benzyloxyacetophenone (6a)

Compound **6a** was synthesized by addition of 4-hydroxyacetone using benzyl bromide in DMF and potassium carbonate at 80°C for 12 h in 90% yield (Scheme 3.1, b)

4-Tosyloxyacetophenone (7a)

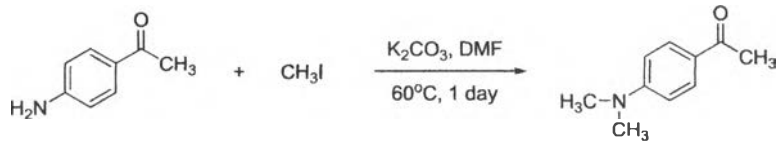
4-Hydroxyacetone was reacted with tolsyl chloride in pyridine and 4-dimethylaminopyridine at 80°C overnight gave compound **7a** in 86% yield (Scheme 3.1, c)



Scheme 3.1 Synthesis of a) 4-butoxyacetophenone **(5a)** b) 4-benzloxyacetophenone **(6a)** c) Tosyloxyacetophenone **(7a)** from 4-hydroxyacetophenone **(3a).**

(4-(Dimethylamino)phenyl)ethanone (9a)

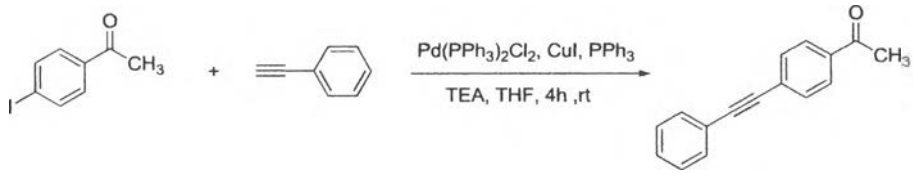
Methylation of (4-aminophenyl)ethanone were accomplished using methyl iodide in DMF and potassium carbonate as base at 60°C for 1 day to give the product **9a** in 75% yield (Scheme 3.2)



Scheme 3.2 Synthesis of (4-(dimethylamino)phenyl)ethanone **(9a)**

(4-(Phenylethynyl)phenyl)ethanone (20a)

Sonogashira coupling of 4-iodoacetophenone with phenyl acetylene in the presence of bis(triphenylphosphine)palladium (II), and triethylamine as base and THF as solvent give the desired product **21a** in 71% yield (Scheme 3.20).



Scheme 3.3 Synthesis of (4-(dimethylamino)phenyl)ethanone **(20a)**

3.2 Trofimov reaction using calcium carbide as a starting material.

3.2.1 Optimization of the reaction conditions

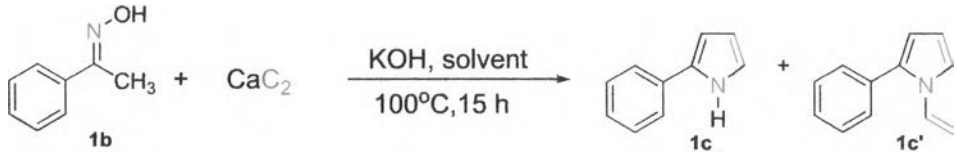
With the 30 oximes in hand, we started the screening of the Trofimov condition with calcium carbide in the hope that our target 2-arylpyrroles. Acetophenone oxime **(1b)** was selected as starting material for optimization studies because of its relative sample of NMR signals. Therefore, the effect of solvents, bases, temperature, additives, amount of CaC_2 and bases and water were studied in the following section.

1) Screening solvents

In this section, we used 100 mg of acetophenone oxime **(1b)**, 6 equiv of calcium carbide, 1.5 equiv of potassium hydroxide and 10 mL of solvent. All the reactions were carried out in a sealed tube and heated at 100°C for 15 h. The results in Table 3.2 indicated that DMSO was sufficient to drive the Trofimov reaction

without recovery of starting material and gave the highest yield of pyrrole **1c** (in 58%) (Table 3.2, entry 1). The reason that DMSO is the best solvent among the other is possibly due to its ability to dissolve KOH. The minor product, 2-phenylvinylpyrrole **(1c')**, was generated from the second addition between pyrrole **1c** and excess acetylene gas as shown in Scheme 3.1.

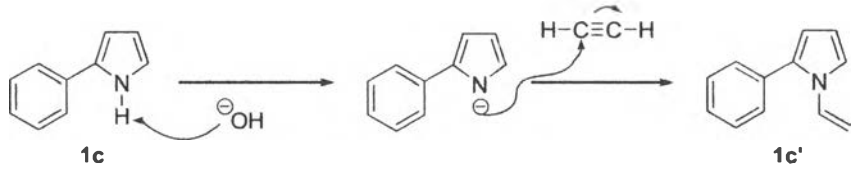
Table 3.2 Effect of solvent



1b 1c 1c'

entry	solvent	yield 1c(%)[a]	yield 1c'(%)[a]
1	DMSO	58	3
2	DMF	0[b]	0[b]
3	EtOH	0[b]	0[b]

[a]Isolated yield, [b]100% recovery starting material



1c 1c'

Scheme 3.4 Mechanism of 2-phenylvinylpyrrole (1c')

All the isolated product pyrrole **(1c)** and vinylpyrrole **(1c')** were characterized by using NMR spectroscopy as shown in Figure 3.1. The ^{1}H NMR of 2-phenylpyrrole **(1c)** and 2-phenylvinylpyrrole **(1c')** are clearly different from oxime **1a**. The singlet peak of methyl in oxime **(1b)** as 2.29 ppm disappeared (Figure 3.1, A), and a new NH peak at 8.45 ppm as well as aromatic signals on the pyrrole ring at 6.87, 6.53 and 6.31 ppm were detected in case of pyrrole **1c** (Figure 3.1, B) while the ethylene peak between 5.11 and 4.63 ppm were observed in case of vinylpyrrole **1c'** (Figure 3.1, C).

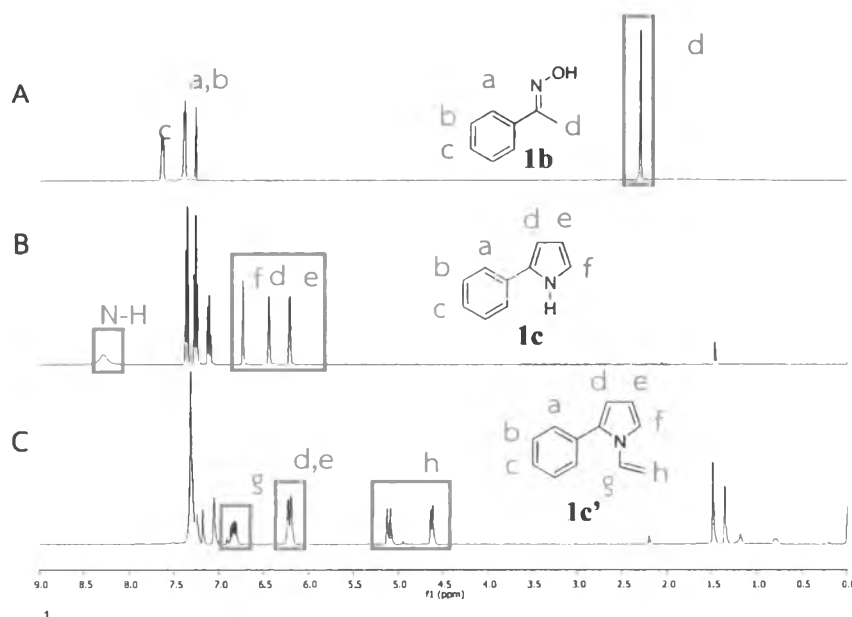
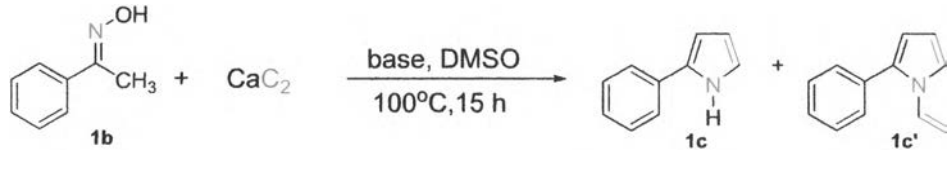


Figure 3.1 ^{1}H NMR spectra of A) acetophenone oxime **(1a)**, B) 2-phenylpyrrole **(1c)** and C) 2-phenylvinylpyrrole **(1c')** in $CDCl_3$

2) Screening type of bases

In this section, we used acetophenone oxime (**1a)** (100 mg), calcium carbide (6 equiv), DMSO (10 mL) in the present of 3 bases (1.5 equiv). All reactions were carried in sealed tube and heated at 100°C for 15 h. The results in Table 3.3 indicated that changing the base from KOH to NaOH or CsOH led to lower yields of the desired 2-arylpyrrole. Therefore, we selected KOH as a base for converting CaC_2 into pyrrole via the Trofimov-type reaction.

Table 3.3 Effect of bases



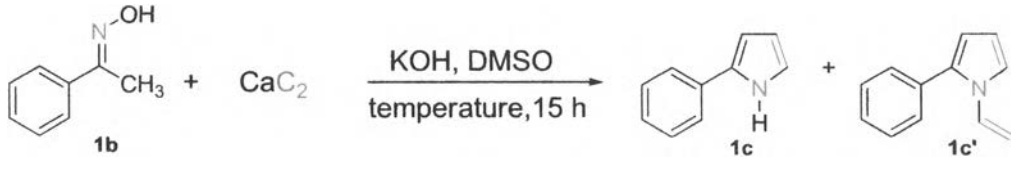
entry	base (1.5 equiv)	yield 1c(%)[a]	yield 1c'(%)[a]
1	KOH	58	3
2	NaOH	44	0
3	CsOH	48	0

[a]Isolated yield

3) *Temperature of reaction*

Base on the above study, we selected DMSO as solvent and KOH as a base and performed the reaction from 100°C to 120°C in order to convert the remaining oxime **1b** in the reaction mixture hoping for the higher yield of product **1c**. The results in Table 3.4 demonstrated that increasing the temperature resulted in lower yields of the desired pyrrole even though the starting material oxime **1b** was completely consumed. We hypothesized that 2-arylpyrrole might decompose at the temperature beyond 120°C due to its unstable nature of pyrrole. Moreover, the vinylation product **1c'** increased up to 9%. Although, we changed the type of base from KOH to NaOH and CsOH (Table 3.4, entries 5-6), but these condition gave 2-phenylpyrrole **(1c)** only in 43-44% yields. Therefore, controlling reaction temperature is a very important factor to obtain the optimal yield.

Table 3.4 Effect of temperature



entry	base (1.5 equiv)	temperature (°C)	yield 1c(%)[a]	yield 1c'(%)[a]
1	KOH	100	58	3
2	NaOH	100	44	0
3	CsOH	100	48	0
4	KOH	120	44	9
5	NaOH	120	43	5
6	CsOH	120	44	7

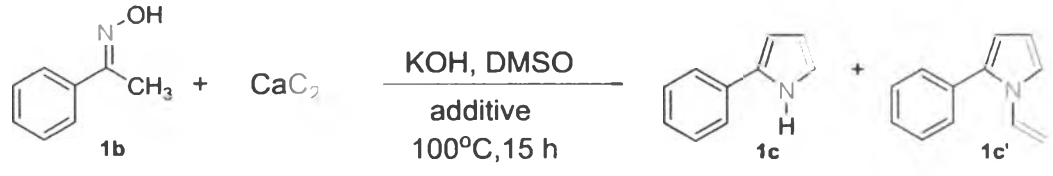
[a]Isolated yield

4) *Effects of additives and the amount of CaC_2 and KOH*

Based on the previous investigation, the reaction was found to be sensitive to temperature which should not exceed 100°C; we therefore, used a phase transfer catalyst such 18-crown-6 and tetrabutylammonium hydrogen sulfate (TBASH) to promote the solubility of KOH in DMSO. 3 mol% of 18-crown-6 or TBASH was added

to the CaC_2 reaction and the results were shown in Table 3.5 (entries 2, 3). In case of 18-crown-6, the higher yield of pyrrole **1c** was obtained in 65% yield along with 2-phenylvinylpyrrole **(1c')** in 8% yield. On the other hand, TBASH failed to increase the reaction efficiency and only 38% yield of 2-phenylpyrrole **1c** was isolated. Furthermore, we varied the equivalent of calcium carbide and potassium hydroxide in entries 4-6 but those experiments failed to improve the reaction yield. In conclusion, 6 equiv of CaC_2, 1.5 equiv of KOH, in DMSO as solvent and the 18-crown-6 as the phase transfer catalyst are the optimized condition as presented in Table 3.5, entry 2.

Table 3.5 Effect of additive and amount of CaC_2 and base



entry	CaC_2 (equiv)	additive (3 mol%)	base (equiv)	yield 1c(%)[a]	yield 1c'(%)[a]
1	6.0	-	KOH (1.5 equiv)	58	3
2	6.0	18-crown-6	KOH (1.5 equiv)	65	8
3	6.0	TBASH[b]	KOH (1.5 equiv)	38	4
4	6.0	18-crown-6	KOH (1.0 equiv)	40	6
5	4.0	18-crown-6	KOH (1.5 equiv)	12	0
6	10.0	18-crown-6	KOH (3.0 equiv)	32	12

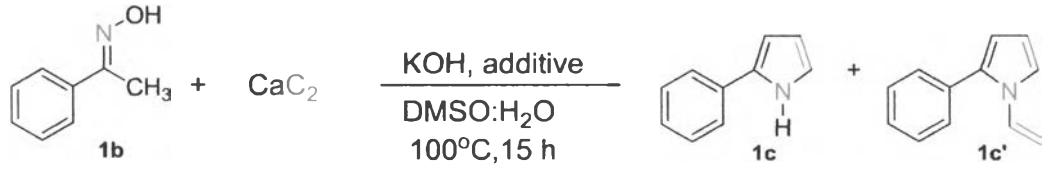
[a]Isolated yield, [b]TBASH = tetrabutylammonium hydrogen sulfate

5) Effects of water

A conventional way to synthesize pyrrole compounds involved the Trofimov reaction, requiring acetylene gas as a starting material. However, in this work CaC_2 was used as starting material to generate acetylene gas through hydrolysis of calcium carbide. Therefore, the amount of water must be investigated in order to control the rate of CaC_2 hydrolysis. In this section, the reactions were then performed using various amount of water in DMSO and the results were presented in Table 3.6. For

entries 1 and 2, the reactions were carried out in the absence of 18-crown-6 using DMSO/water in 50:1 and 50:5 ratios as solvent, respectively. The results showed that the reaction yield dropped to 60% and 32% yields respectively, confirming the necessity of the 18-crown-6 in order to improve the solubility of base in solvent. It was confirmed that 50:1 of DMSO/water is enough for driving the reaction to completion, but the excess amount of water resulted in a lower yield, perhaps due to the fast generation of acetylene gas. When 18-crown-6 was added, the desired product **(1c)** was obtained in 73% yield (Table 3.6, entry 3). Thus, this reaction condition was selected as the optimal condition for this system. We would like to note that the presence of water suppressed the formation of the over-vinylated product **1c'** in all cases. However, the proper explanation remains unknown.

Table 3.6 Effect of water[a]



entry	additive (3 mol%)	DMSO : water (mL)	yield 1c(%)[b]	yield 1c'(%)[b]
1	-	50 : 1	60	0
2	-	50 : 5	32	0
3	18-crown-6	50 : 1	73	0

[a]General condition: 100 mg of acetophenone oxime, 6 equiv of CaC_2, 1.5 equiv of KOH and 10 mL of the mixture of solvent was stirred in a sealed tube at 100°C for 15 h, [b]Isolated yield,

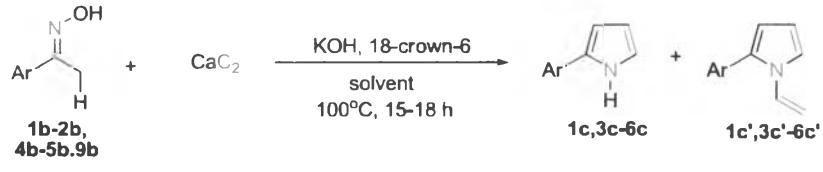
3.2.2 Screening functional groups on the aryl oximes

With the optimal condition in hand, we intended to demonstrate the effectiveness of our method for a panel of oximes carrying various functional groups. In this section, the oxime starting materials were divided into 4 groups as shown in Table 3.7-3.11. All reactions were subjected to CaC_2 under two optimized conditions. Condition A employed pure DMSO as solvent and condition B employed DMSO/water (50:1) as solvent.

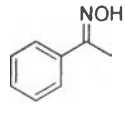
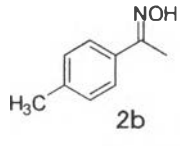
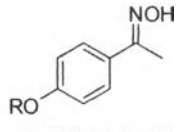
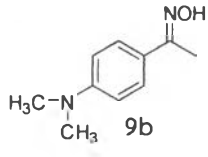
1) Oximes carrying electron-donating groups

The aryl oximes bearing methyl **(2b)**, methoxy **(4b)**, butoxy **(5b)**, *N,N*-dimethylamine **(9b)** were subjected to the optimized condition A and B and the results were presented in Table 3.7. In general condition B showed the better efficiency, giving the pyrrole **1c, 3c–6c** in higher yields and also better selectivity. Arylpyrrole **1c, 3c-6c** were obtained in a range of 26-65% yields under condition A while, condition B gave the desired product in between 32-73% yields (Table 3.7, entries 1-4). Also using condition B the over-vinylated product **1c', 3c'-6c'** were less than 10% yields.

Table 3.7 Substrates scope: oximes carrying electron donating group



1b-2b, 4b-5b.9b — **1c,3c-6c** — **1c',3c'-6c'**

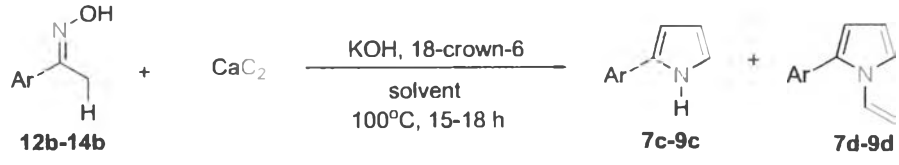
entry	Oxime	product	condition[a]	yield(%)[b]
1	 **1b**	**1c/1c'**	A	65/8
			B	73/0
2	 **2b**	**3c/3c'**	A	26/7
			B	46/0
3	 R= Methyl; **4b** R = Butyl; **5b**	**4c/4c'**	A	35/10
			B	51/5
		5c/5c'	A	34/2
			B	49/0
4	 **9b**	**6c/6c'**	A	32/9
			B	48/6

[a]Condition: (A) a mixture of aryl oxime (1 equiv), CaC_2 (6 equiv), KOH (1.5 equiv), 18-crown-6 (3mol%) was stirred in 10 mL of DMSO at 100°C for 15 h; (B) same as (A) expect solvent used DMSO/water (50:1). [b]Isolated yield

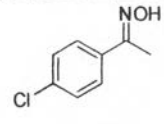
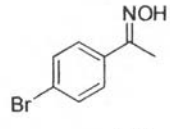
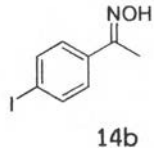
2) Oximes carrying halogenated benzene

The purpose of this study was to synthesize halogenated pyrroles **7c-9c**. Such product can be applied for further functionalization to some more complicated pyrroles. We found that chloride substituted oxime **(12b)** can be converted to 2-arylpyrrole **(7c)** in 51% yield under condition B (Table 3.8, entry 1) and this substrate is the most compatible halide with our reaction condition. Other halide substrates such as bromide **(8c)** and iodide **(9c)** gave poorer yields in 26% and 3%, respectively, under condition A (Table 3.8, entries 2, 3).

Table 3.8 Substract scope : oximes carrying halides group.



12b-14b 7c-9c 7d-9d

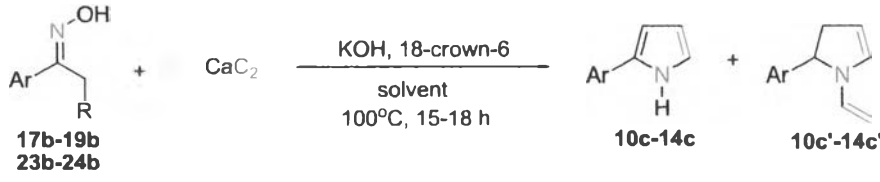
entry	Oxime	product	Condition[a]	yield(%)[b]
1	 12b	7c/7c'	A	38/0
			B	51/0
2	 13b	8c/8c'	A	26/0
			B	32/0
3	 14b	9c/9c'	A	3/0
			B	12/0

[a]Condition: (A) a mixture of aryl oxime (1 equiv), CaC_2 (6 equiv), KOH (1.5 equiv), 18-crown-6 (3mol%) was stirred in 10 mL of DMSO at 100°C for 15 h; (B) same as (A) expect solvent used DMSO/water (50:1). [b]Isolated yield

3) Oximes carrying polyaromatic groups

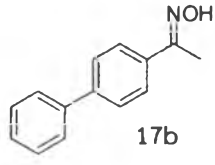
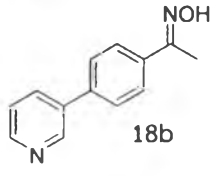
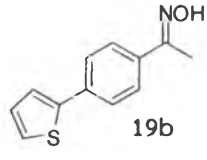
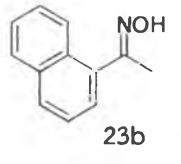
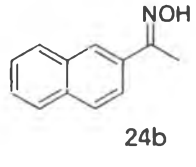
In this section, we planned to synthesize polyaromatic substituted arylpyrroles. These compounds could be applied for the synthesis of high by conjugated BODIPY dye. Therefore, the oximes **17b-19b, 23b, 24b** were reacted with CaC_2 under condition A and B and the results were summarized in Table 3.9. We found that phenyl **(17b)** and pyridine **(18b)** substituted oximes gave 88% and 59% yield, respectively, under condition B (Table 3.9, entries 1, 2). In case of the thiophene substituted oxime **(19b)**, only 19% yield of **12c** could be obtained under condition B (Table 3.8, entry 3). This is perhaps due to the instability of the thiophene functional group. For the synthesis of pyrrole with polyaromatic substitution such as naphthalene (Table 3.9, entry 4-5) at alpha **(23b)** and beta **(24b)** position, we found that the compound **23b** gave slightly higher yield than oxime **24b**. This can be explained by the steric hindrance of oxime **24b**.

Table 3.9 Substrate scope: oximes carrying of polyaromatic group



17b-19b
23b-24b

10c-14c **10c'-14c'**

entry	Oxime	product	condition[a]	yield(%)[b]
1	 17b	**10c/10c'**	A	60/0
			B	88/0
2	 18b	**11c/11c'**	A	42/6
			B	59/2
3	 19b	**12c/12c'**	A	12//0
			B	19/0
4	 23b	**13c/13c'**	A	24/31
			B	27/2
5	 24b	**14c/14c'**	A	24/1
			B	30/0

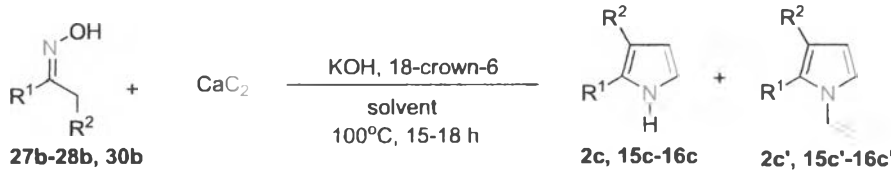
[a]Condition: (A) a mixture of aryl oxime (1 equiv), CaC_2 (6 equiv), KOH (1.5 equiv), 18-crown-6 (3mol%) was stirred in 10 mL of DMSO at 100°C for 15 h; (B) same as (A) expect solvent used DMSO/water (50:1). [b]Isolated yield

4) Oximes carrying elongated alkyl chain

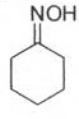
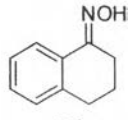
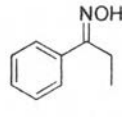
Previously, oximes derived from aryl methyl ketones are suitable for the Trofimov-type reaction with CaC_2. In this section, we intended to synthesize some disubstituted pyrroles at position 2 and 3. Therefore, a variety of oximes derived from cyclohexanone **(27b)**, 1-cyclohexenylethanone oxime **(28b)** and propiophenone oxime **(30b)** were tested using our optimized condition A and B. In case of the oxime derived from cyclohexanone **(27a)** the *N*-vinyl by-product was

isolated as a sole product in 50-52% yield without the desired arylpyrrole **15c**. This result might be governed by the strong nucleophilic property of pyrrole **15c** from the alkyl substituent. On the other hand, oxime **28b** and **30b** were reacted with CaC_2 and produced the desired pyrrole product in 27% and 33% yield, respectively, under condition B.

Table 3.10 Substrate scope: oximes carrying elongation alkyl chain



27b-28b, 30b — 2c, 15c-16c — 2c', 15c'-16c'

entry	Oxime	product	condition[a]	yield(%)[b]
1	 27b	**15c/15c'**	A	0/50
			B	0/52
2	 28b	**16c/16c'**	A	22/0[c]
			B	27/0[c]
3	 30 b	**2c/2c'**	A	22/11
			B	33/8

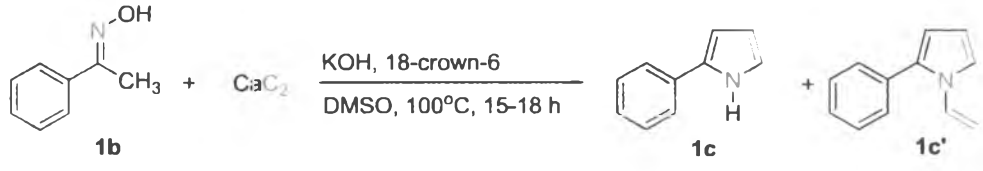
[a]Condition: (A) a mixture of aryl oxime (1 equiv), CaC_2 (6 equiv), KOH (1.5 equiv), 18-crown-6 (3mol%) was stirred in 10 mL of DMSO at 100°C for 15 h; (B) same as (A) expect solvent used DMSO/water (50:1). [b]Isolated yield

3.2.3 Scale-up for the synthesis of 2-phenylpyrrole

With the optimized condition in hand, our next goal is to scale up from milligram to the multi-gram scale. Therefore, the effect of concentration and amount of acetophenone oxime **(1b)** were investigated as shown in Table 3.11. Previously, for a 100-mg scale of acetophenone oxime **(1b)**, a sealed tube was used to run the reaction and we isolated the 2-phenylpyrrole **(1c)** in 65% yield (Table 3.11, entry 1). When we increased the scale up to 2 grams of oxime **1b** under the same concentration, the pressure reactor equipped with mechanic stir (600 mL size) was used to give the desired 2-phenylpyrrole **(1c)** 45% yield (Table 3.11, entry 2). In order to reduce the amount of solvent for industrial application, we needed to

increase the reaction concentration from 0.074 mM to 0.15 mM. The result showed that the yield of product **1c** dropped down to 38% yield as shown in Table 3.11, entry 3. We believed that the decrease in product yield in the multi-gram scale reaction was caused by the poor stirring and the leakage of acetylene gas during the course of reaction.

Table 3.11 Effect of reaction concentration



1b **1c** **1c'**

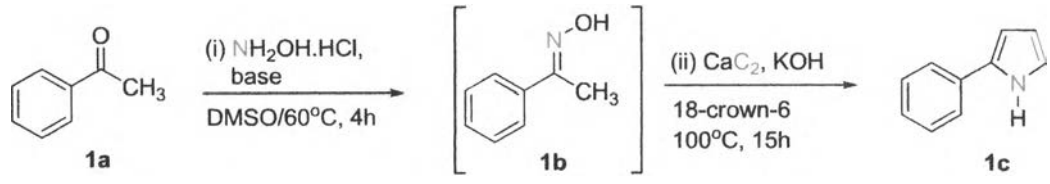
entry	oxime **1b** (mmol/g)	concentration (mM/mL)	yield[a] **1c** (%)	yield[a] **1c'** (%)
1	0.74/0.1	0.074/10	65	3
2	14.8/2.0	0.074/200	45	6
3	14.8/2.0	0.15/100	38	7
4[b]	14.8/2.0	0.074/200	50	2

[a]Isolated yield, [b]Used (50:1) DMSO/water as the solvent

3.2.4 One-pot synthesis of 2-phenylpyrrole

Finally, in order to develop our Trofimov-type reaction into a more practical use for routine laboratory work, we attempted to synthesize the 2-phenylpyrrole **(1c)** directly from commercially available acetophenone **(1a)** in a one-pot fashion. The additional step of this work is the oxime formation. Therefore, we needed to seek suitable and efficient bases for the first step. Four difference bases were used for the formation of oxime. The reaction was monitored by TLC and upon the completion of the reaction, CaC_2 were added according to the optimized condition to produce the desired pyrrloe **1c** (Table 3.12). Among 4 bases, $NaHCO_3$ gave the best result giving the pyrrole **1c** in 56% yield (Table 3.12, entry 1).

Table 3.12 Effect of base for preparation acetophenone oxime



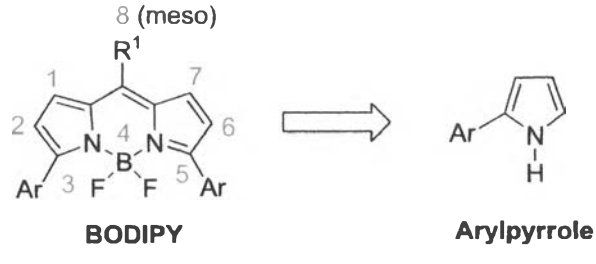
Entry	base[a]	yield[b] 1c (%)
1	$NaHCO_3$	56
2	Pyridine	0
3	KO^tBu	25
4	KOH	22
5[c]	$NaHCO_3$	43

[a]Base in first step, [b]Isolated yield, [c] Added H_2O in second step

3.3 Application of 2-phenylpyrrole for the synthesis of red BODIPY dye

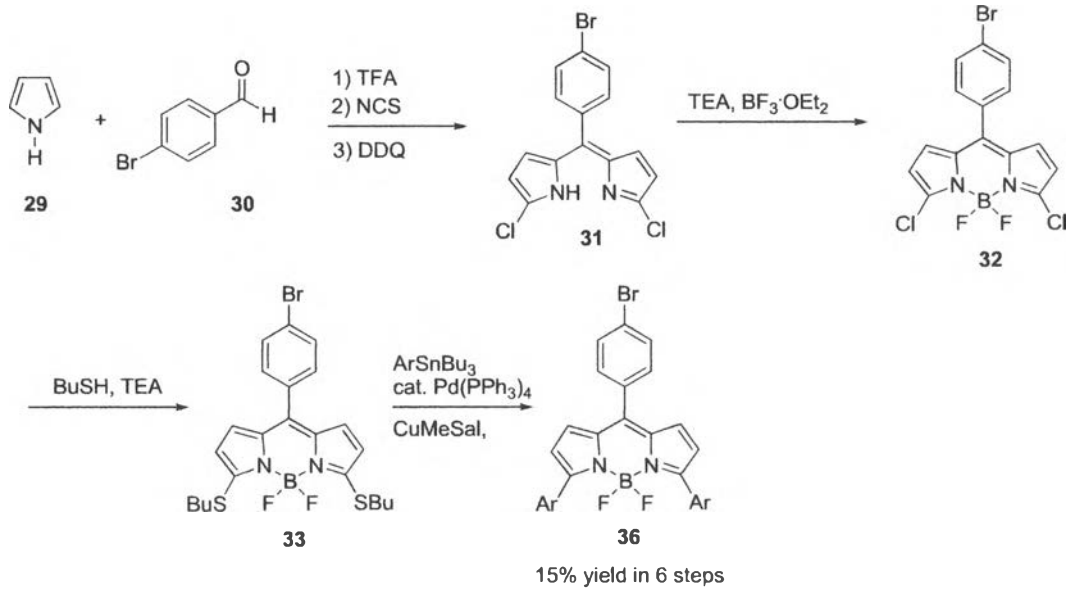
3.3.1 Synthesis of red BODIPY dye

4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) has many advantages such as narrow bandwidth, long wavelength emission and high intensities [26, 27]. Normally, BODIPY derivatives that have 3-, 5-aryl substitution positions (Scheme 3.22) are important because the fluorescence maxima of BODIPY strongly depends on the structure of the aryl group [28]. Halogenation and organometallic coupling reactions were used to produce these compounds. Moreover, 3-, 5- aryl BODIPY was synthesized in a multi-step fashion in low yields.



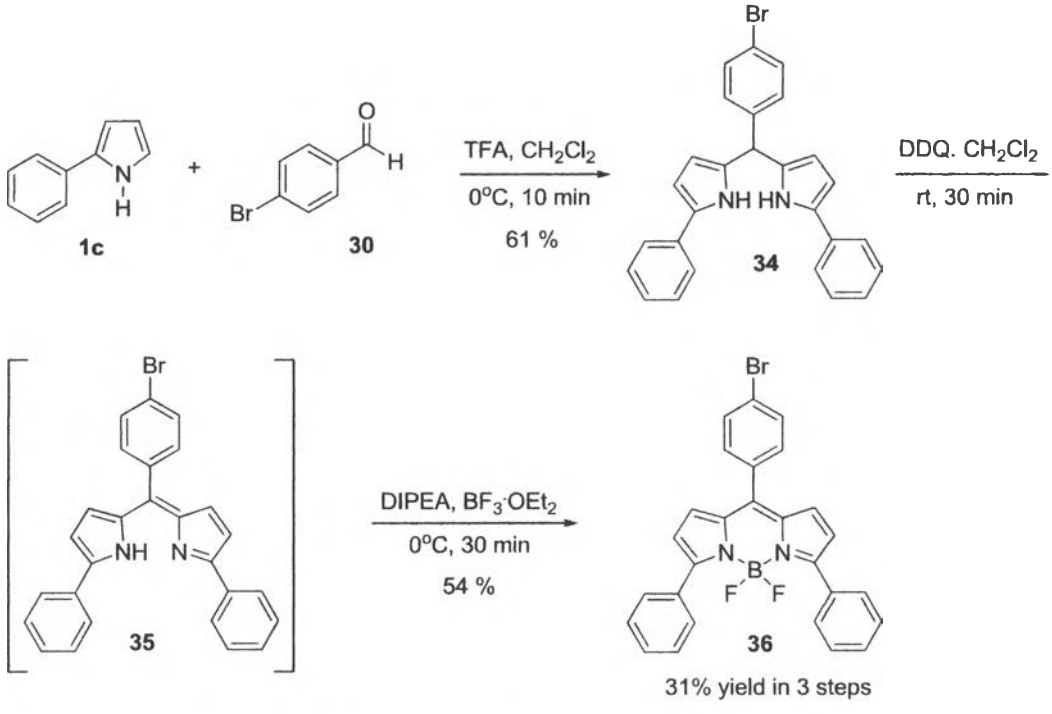
Scheme 3.5 Retrosynthesis of aryl BODIPY

For example, Burgess and co-workers [29, 30] used six steps for the synthesis of 3-, 5-phenyl BODIPY and gave the desired product in 15% overall yield.



Scheme 3.6 Burgess's method for the synthesis of BODIPY (**36**)

In this work, we used 2-phenylpyrrole as starting material for the synthesis of BODIPY D (Scheme 3.6). Notably, we synthesized 2-phenylpyrrole **(1c)** via a two-step synthesis following Table 3.6, entry 3 in 73% yield. Then, addition reaction between 2-phenylpyrrole **(1c)** and 4-bromobenzaldehyde **(30)** gave dipyrrole **(34)**. After that, BODIPY **34** was synthesized in 2 steps via oxidation and complexation to generate the desired BODIPY product in 31% overall yield.



Scheme 3.7 Our method for the synthesis of BODIPY **36**

3.3.1 Photophysical properties of BODIPY 36

Most of commercial BODIPY dyes show the blue to green emission. However, the red fluorescence has become popular for fluorescence tracking lately because it is noninvasive and minimizes the unwanted background. In our case, our BODIPY containing an extra phenyl group appears as red in CH_2Cl_2 solution (as shown in Figure 3.2). The compound was shown to process the maximum absorption at 550 nm and strong emission at 600 nm corresponding to bright orange color under blacklight.

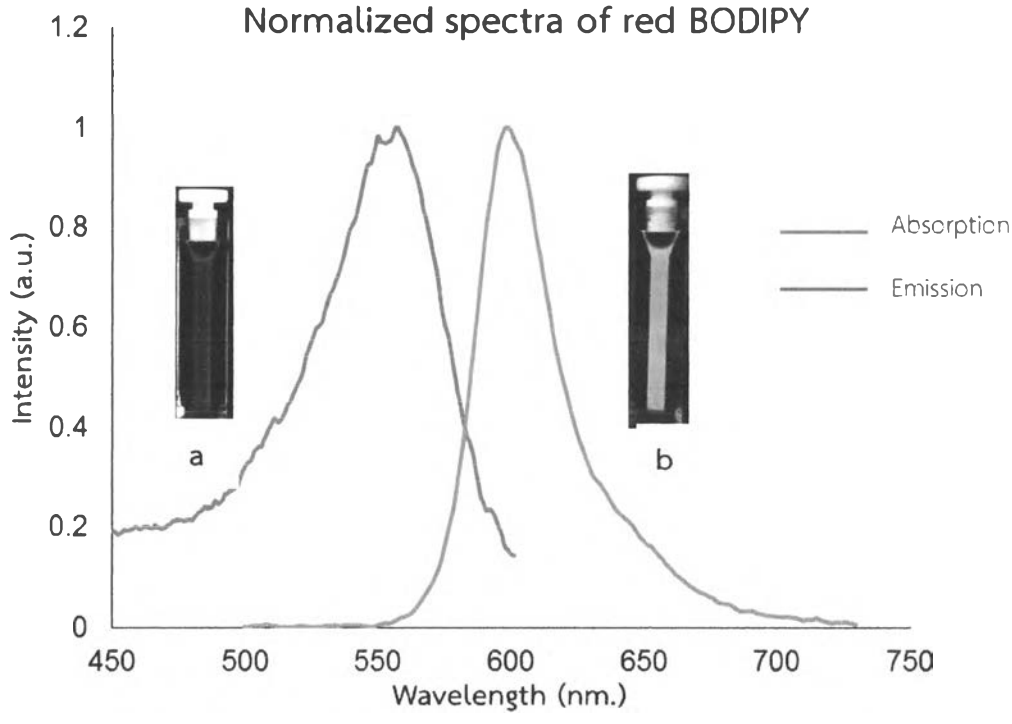


Figure 3.2 Normalized spectra of a) BODIPY **36** in CH_2Cl_2 solution b) BODIPY solution under blacklight.