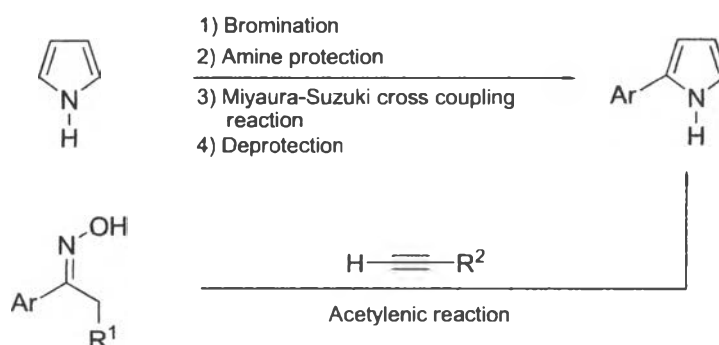


CHAPTER I

INTRODUCTION

1.1 Introduction

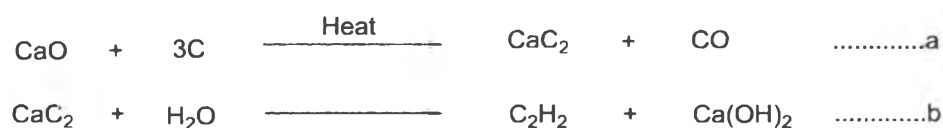
Pyrrole series are of great importance for their biological properties, and have found many applications in pharmaceutical, medicine and technology, especially aryl- and hetero aryl-substituted pyrroles. There are many methods to install an aryl group onto the pyrrole ring such as the metal catalyzed cross-coupling reactions between pyrrole and aryl halide [1] but this method required expensive and hazardous metal catalysts and multiple-step synthesis (Scheme 1.1) which has been reported in many literatures. In addition, this process is not popular and less possible to be applied for the industrial scale synthesis. Currently, there are also many researches trying to develop pyrrole synthesis by the use of more economical starting materials. Due to the simplicity and efficiency of the Trofimov reaction, it become the most powerful method to synthesize pyrrole from an inexpensive starting material acetylene gas or protected acetylene with oxime under superbase condition as shown in Scheme 1.1. Historically, Trofimov reaction utilized terminal acetylene, normally obtained from protected acetylene, as an alkyne source and acetylene gas has also been used [2]. This gas is appreciably more economical than other acetylene sources for the synthesis of arylpyrrole because acetylene gas is less expensive than other protected acetylene. However, the use of acetylene gas requires some complicated instrument set-up and the gas itself is flammable. Nowadays, researchers are seeking a new triple bond source to replace the acetylene gas. Recently, a number of reports indicated the low production cost of calcium carbide, which can be utilized as the alkyne surrogate in the preparation of polyynes [3] carbon spheres [4], aryl triazole [5], diarylethynes [6] and derivatives of acetylene [7-9] for its easy handling and low cost. Thus, we are interested in developing some new synthetic methods for 2-arylpyrrole using calcium carbide as acetylene source via the Trofimov-type reaction which has not been reported in any literature.



Scheme 1.1 Conventional route for the synthesis of 2-arylpyrrole.

1.2 Introduction to calcium carbide

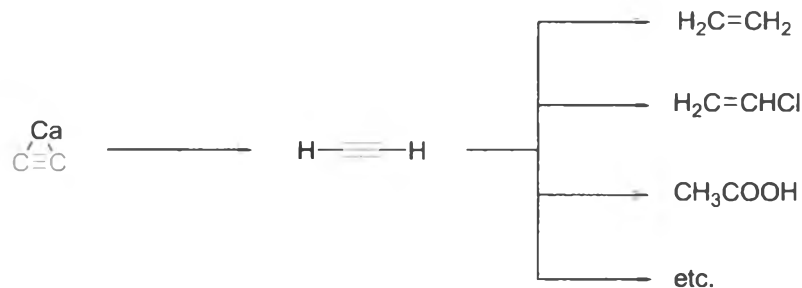
In 1862, calcium carbide (CaC_2) was discovered by Friedrich Wöhler [10]. It is produced industrially by reacting lime (CaO) with coke- it is obtained as metallurgical grade in petroleum refining -in an electric furnace at 2000-2300°C. This forward reaction to calcium carbide required the temperature to reach at least 1600°C; below this temperature, the reaction will reverse from right to left (Scheme 1.2, a). When calcium carbide reacted with water, the reaction is highly exothermic and produced acetylene gas along with calcium hydroxide (Ca(OH)_2) (Scheme 1.2, b). Normally, the carbide coal producing flammable gas generally contains around 80% by weight of calcium carbide and the rest are other products such as hydrogen sulfide and phosphine impurities in the acetylene [10]. Nowadays, acetylene has been generated from calcium carbide, and it has served as the primary chemical feedstock in organic synthesis [11] as well as in chemical industries such as manufacturing of vinyl chloride monomer and calcium cyanamide [10]. This is largely because calcium carbide is more cost-efficient and safer than the direct use of acetylene gas.



Scheme 1.2 Process of (a) calcium carbide, (b) acetylene gas.

Acetylene gas is the first element of value-added chemical chain to make core basic chemicals in industries such as manufacturing ethylene, vinyl chloride monomer, acetic acid and etc. [10] as shown in Scheme 1.3. In contrast, this flammable gas should be stored in storage cylinders which pose certain risks and high costs of maintenance. Thus, the direct use of calcium carbide was investigated for the primary chemical feedstock in organic synthesis [11] and chemical industry

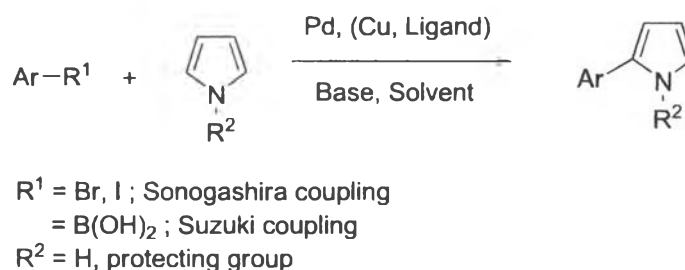
because calcium carbide is more cost-efficient and safer than using acetylene gas directly.



Scheme 1.3 Traditional way for synthesis of value-added compounds.

1.3 Introduction to 2-arylpyrrole

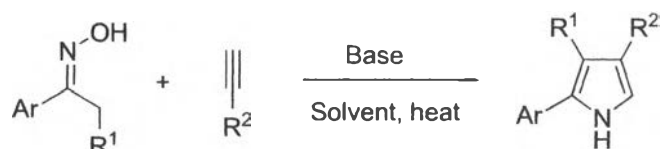
2-Arylpyrrole is one of the pyrrole derivatives which is an important core of medicinal compounds, natural products, insecticides and fluorescence dyes [12]. Thus, many researchers are interested in devising new and efficient synthetic methods. As a result, the numbers of reports on the new way to prepare this type of compounds incessantly grow. Generally, the methods to synthesize substituted pyrroles could be summarized into two strategies. The first one involves coupling reactions of the pyrrole ring with halides [12-22]. A number of different sets of reagents and catalysts have been developed. For example, both the Cu-Pd Sonogashira and B-Pd Suzuki cross coupling reactions are popular (Scheme 1.4). However, these reactions require relatively expensive Pd catalysts as well as *N*-protected pyrroles both of which render the first strategy less economical and desirable.



Scheme 1.4 General method of metallic cross coupling.

The other strategy for the synthesis of 2-arylpyrroles is the reaction of oximes with terminal alkynes under basic conditions, the so-called Trofimov pyrrole synthesis which was discovered in 1970s (Scheme 1.5). However, these reaction conditions gave low yields and low regioselectivity [2]. After that, the Trofimov reaction has been studied to improve the yields and selectivity. The efforts included

the development of suitable catalysts. Importantly, this method has been successfully used for the one-pot direct transformation of ketone to 2-arylpyrrole [23].

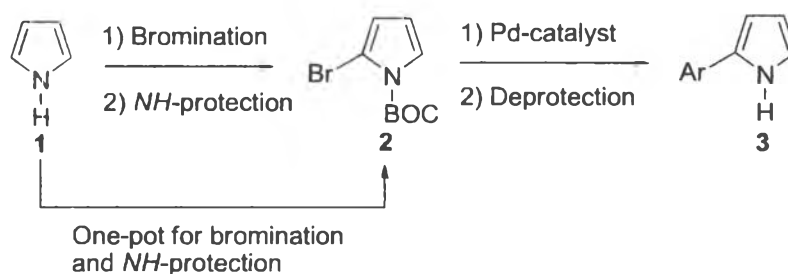


Scheme 1.5 General method of the Trofimov reaction.

1.4 Literature reviews

1.4.1 Synthesis of 2-arylpyrrole via metal-catalyzed cross-coupling

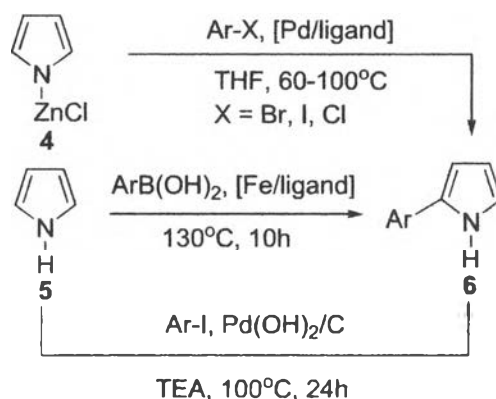
In 1999, Burgess and co-workers [14] synthesized 5 different 2-arylpyrroles as starting materials for the synthesis of boron dipyrrole metheme (BODIPY) via Suzuki cross-coupling reaction of *N*-*tert*-butoxycarbonyl-4-bromopyrrole with arylboronic acids (Scheme 1.6). Bromination and *NH*-protection gave the protected pyrrole (**2**) in 93-99% yields. Suzuki reactions followed by deprotection of the BOC-protecting group gave 2-arylpyrrole (**3**) in 65-98% yields. In addition, Lee [17] reported new aryl substituents of the 2-arylpyrrole for the synthesis of aryl-BODIPY dyes, in 2008. Bromination and *NH*-protection were performed in one step using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in AIBN. In the following step, *N*-BOC pyrrole reacted with a variety of aryl boronic acids via Suzuki cross-coupling reaction. After that, the *N*-BOC group was deprotected, giving the 2-arylpyrrole (**3**) in 45-95% yields as shown in Scheme 1.6. However, these two methods have some disadvantages such as the required of several steps for one transformation and expensive catalysts.



Scheme 1.6 *NH*-protection/ C–Br activation of pyrrole for the synthesis of 2-arylpyrrole (**3**).

In 2004, Sadighi and co-workers [12] developed some Pd-catalysts for the conversion of pyrrolylzinc chloride (**4**) to 2-arylpyrrole (Scheme 1.7). The method was compatible with a variety of aryl halides, including aryl chlorides and some very

sterically hindered arylbromides. The arylation process gave the pyrrole products in 48-93% yields depending on initial conditions. After that, in 2010, Yu and co-workers [18] modified a new catalyst for the Suzuki coupling reaction for the *ortho*-arylation of pyrrole and pyridine. This work used a novel Fe-catalyst and studied types of ligand and found that the Fe-catalyzed 2-arylation of pyrrole with arylboronic acids as shown in Scheme 1.7, gave the products in moderate to good yields (26-84%). In the same year, Jafarpour and co-workers [20] demonstrated Pd-catalyzed direct arylation of inactivated free *NH*-pyrrole (Scheme 1.7). Aryl iodides were coupled with free *NH*-pyrrole by using Pd(OH)₂/C via Heck reaction. Ten C-2 arylation of free *NH*-pyrroles were synthesized in 27% to 80% yields.

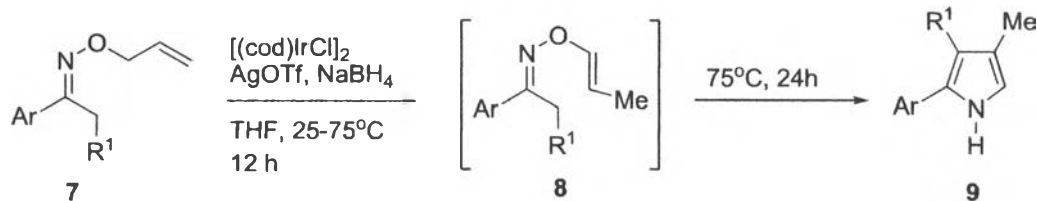


Scheme 1.7 Free *NH*-pyrrole/C-H activation of pyrrole for the synthesis of 2-arylpyrrole (**6**).

1.4.2 Synthesis of 2-arylpyrrole using protected acetylene

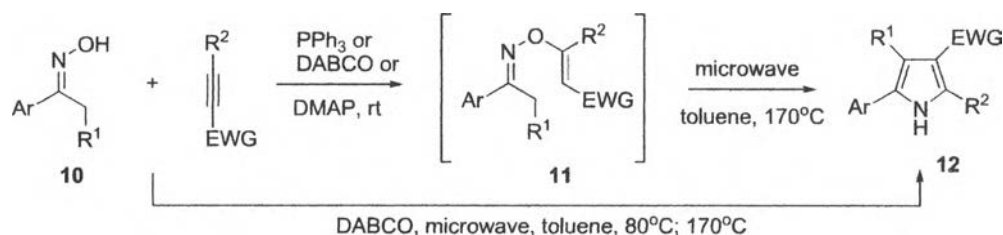
Protected acetylene has been generally utilized for the synthesis of 2-arylpyrroles in laboratory. The two-step synthesis gave the products in moderate to good yields. However, limited of this process is the difficulty and inconvenient in the deprotection step of the *N*-protected 2-arylpyrrole.

In 2010, Anderson and co-workers [18] tried to solve some limitations of the Trofimov reaction involving the regioisomeric mixture of products. In this research the *O*-allyl oximes (**7**) were converted to the corresponding *O*-vinyl oximes (**8**) via iridium-catalyzed isomerization reaction (Scheme 1.8); subsequent cyclization/[3,3]-sigmatropic rearrangement of *O*-vinyl oximes (**8**) gave the pyrrole (**9**).



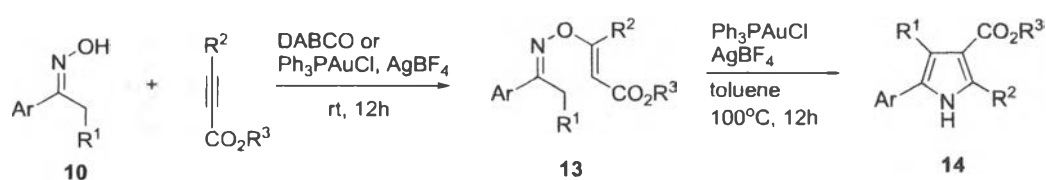
Scheme 1.8 Synthesis of pyrroles via rearrangement of *O*-allyl oximes.

In the same year, Camp and co-workers [21] obtained vinyl oximes (**11**) from the addition of oximes (**10**) via the use of a nucleophilic catalyst. In addition, rearrangements of vinyloximes (**11**) were successfully performed using microwave irradiation to yield the corresponding 2-arylpyrrole (**12**) as shown in Scheme 1.9. Importantly, one-pot pyrrole synthesis was also developed (Scheme 1.9).



Scheme 1.9 Synthesis of pyrroles via thermal rearrangement of oximes.

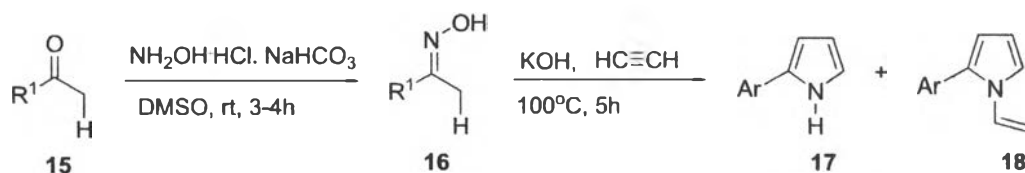
In 2011, the same research group developed the use of a gold catalyst for the synthesis of pyrrole from vinyloximes (**13**) [22]. In addition, pyrroles (**14**) were obtained via the one-pot gold catalyzed reactions of activated alkynes and oximes (**10**) (Scheme 1.10). However, the reaction yields were only slightly improved.



Scheme 1.10 Synthesis of pyrroles using a gold-catalyst.

1.4.3 Synthesis of 2-arylpyrrole using acetylene gas

In 2005, Mikhaleva and co-workers [2] developed a one-pot synthesis of 2-arylpyrrole (**17**) and 2-aryl-*N*-vinylpyrrole (**18**) from aryl ketone (**15**) and acetylene gas. The condition was based on the Trofimov reaction as shown in Scheme 1.11. Eight substrates were tested and the corresponding desired pyrrole products were synthesized in 12-72% yield as evaluated by GLC or NMR.



Scheme 1.11 One-pot synthesis of 2-arylpyrrole via Trofimov reaction.

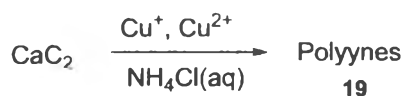
In 2012, the same research group modified the one-pot synthesis for 2-arylpyrrole (**17**) [24] to improve the reaction yields. This work successfully increased yields to 73-74%. Thus, the important techniques are to decrease the concentration of KOH and reaction time, as well as increase the concentration of oximes (**16**) and reaction temperature up to 135-150°C. Importantly, DMSO was distilled before dilution of the residue with water.

In conclusion, most of the reported 2-arylpyrrole synthesis required some expensive transition metals for the coupling reactions. Therefore, the non-metal process for pyrrole synthesis remains a challenge and it is our main goal to develop such method.

1.4.3 The uses of calcium carbide in organic synthesis

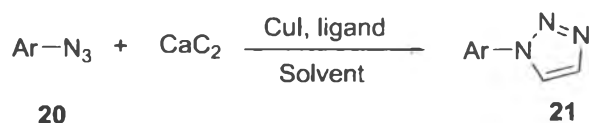
Calcium carbide is a primary chemical feedstock to generate acetylene gas for the synthesis of small acetylenic molecules. Calcium carbide is 500 times cheaper and safer than acetylene gas. Its use also requires much simpler experimental set up. In contrast, only a few reports indicated the use of calcium carbide as starting material or acetylene source for organic synthesis.

In 2005, Cataldo [3] reported a new method for the synthesis of polyynes (**19**) from calcium carbide. Hydrolysis of calcium carbide in ammonium chloride solution (Scheme 1.12) was used to improve efficiency of the new method.



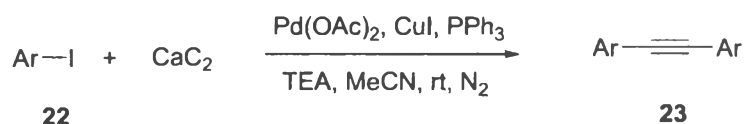
Scheme 1.12 Synthesis of polyynes (**19**) from calcium carbide.

In 2009, Kuang and co-workers [5] successfully synthesized aryltriazoles (**21**) via Click chemistry using calcium carbide as shown in Scheme 1.13. Water and acetonitrile were used as a mixed solvent system for this reaction and copper(II) was used as the catalyst. In this reaction nitrogen and the desired product (**21**) was obtained in 70-90% yields.



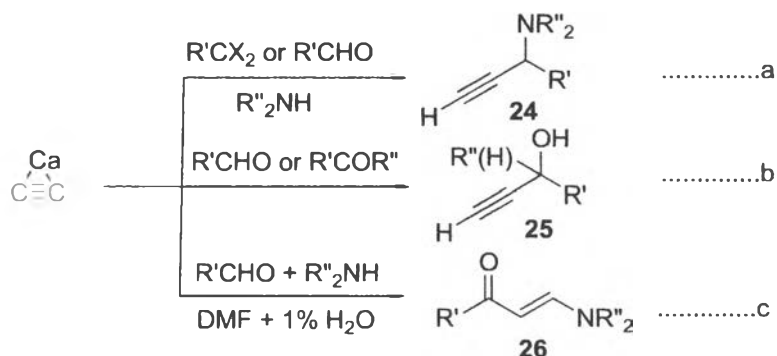
Scheme 1.13 The use of calcium carbide for the synthesis of aryltriazoles (21) via Click reaction.

In 2011, Chuentragool and co-workers [6] synthesized diarylethyne (23) via Sonogashira coupling between aryl iodide (22) and calcium carbide instead of acetylene gas as shown in Scheme 1.14. They also optimized the condition for this reaction as well.



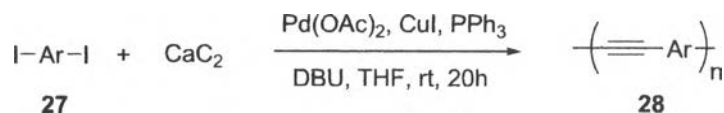
Scheme 1.14 Synthesis of diarylethyne (23) from calcium carbide.

In 2012, Zhang and co-workers [7] studied the use of calcium carbide instead of acetylene gas for the coupling reactions to yield the propargyl amine derivatives (24) from three main building blocks alkyne, aldehyde, amine and haloalkane as shown in Scheme 1.15, a. Moreover, they successfully studied the one-pot synthesis using copper(II) iodide as catalyst. In 2013, this research group reported the synthesis of propargyl alcohols (25) from calcium carbide with aldehyde or ketone compounds [8] as shown in Scheme 1.15, b. Importantly, the reaction was metal-free and took place under very mild conditions. In addition, this research team successfully modified a simple method for the synthesis of enaminone compounds (26) using acetylide ion from calcium carbide as a bridge to link electrophile and nucleophiles [9] (Scheme 1.15, c).



Scheme 1.15 The use of calcium carbide for the synthesis of (a) propargyl amines (24), (b) propargyl alcohols (25) and (c) enaminones (26).

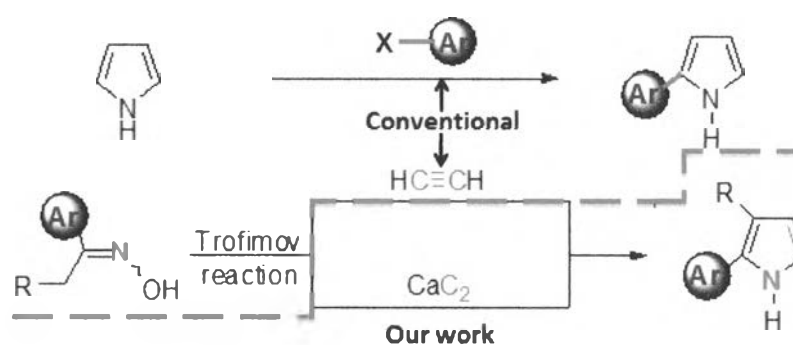
Recently, in 2014 Thavornsinn and co-workers [25] developed a new way for the synthesis of poly(*p*-phenyleneethynylene)s (PPEs) from calcium carbide as shown in Scheme 1.16. The yield of a variety of PPE (**28**) was high (71-93%) and the degree of polymerization was between 36 and 128.



Scheme 1.16 Synthesis of PPEs (**28**) from calcium carbide.

1.5 Objective of this research

According to the reviews above, calcium carbide was used as a nucleophile for acetylenic compounds. However, there has been no report that calcium carbide can also be used as an electrophile or applied for the synthesis of 2-arylpyrroles. The advantages of using calcium carbide in a reaction are its relatively low price and purification easy handling. Thus, this research strives to use calcium carbide as a source of triple bond in the synthesis of 2-arylpyrroles via the Trofimov-type reaction as shown in Scheme 1.17. This work has focused on optimizing the reaction conditions based on the effect of solvents, bases, additives, temperature, and amount of calcium carbide as well as the effect of water. Furthermore, multi-gram scale and one-pot synthesis were studied in order to adapt this methodology to chemical industry.



Scheme 1.17 Different routes entailing the three methods for the synthesis of 2-arylpyrroles.