RECYCLABLE, GRAPHITE-CATALYZED, FOUR-COMPONENT SYNTHESIS OF FUNCTIONALIZED PYRROLES

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GRAPHICAL ABSTRACT

Abstract A facile, convenient, and multicomponent coupling strategy for the synthesis of highly functionalized pyrroles is developed using graphite as a catalyst, but devoid of moisture-sensitive metal catalysts and corrosive acidic reagents. This method involves four-component coupling reactions of ethyl acetoacetate compound or diethyl acetylene dicarboxylate, amines, aromatic aldehydes, and nitromethane without an inert atmosphere. This approach provides easy access to highly substituted pyrroles in good yields via one-pot tandem reaction. The method is very simple, straightforward, and environmentally friendly compared to the existing methods.

Keywords Carbon catalyst; graphite; multicomponent reaction; Paal–Knorr synthesis; pyrroles

INTRODUCTION

Pyrrrole is one of the most important heterocyclic compounds, with increasing importance in medicinal chemistry and organic synthesis. Pyrrrole is an important class of structural unit frequently found in many natural products that have biologically and pharmaceutically active compounds. It has been widely used as antitumor, anti-inflammatory, antibacterial, antioxidant and
antifungal agent. Consequently, an enormous number of synthetic methodologies have been developed for the construction of pyrroles. The classical methods for pyrroles synthesis are as follows: (i) the Hantzsch reaction, which provides pyrroles from the reaction of α-chloromethyl ketones with β-ketoesters and ammonia; (ii) the Knorr reaction, which assembles pyrroles by the reaction between α-amino ketones derived from α-haloketones, ammonia, and β-ketoesters; and (iii) the Paal–Knorr reaction, one of the most common approaches in which γ-diketone is converted into pyrroles by the reaction with primary amines in the presence of various promoting agents. Although these methods are very useful for the synthesis of pyrrole derivatives, the classical reactions involved have major drawbacks such as availability of the starting materials, multistep synthetic operations, functional group compatibility, regiospecificity, and harsh reaction conditions, which limit their easy operation. To overcome these limitations, various new efficient strategies such as multicomponent coupling reactions have recently been introduced.

Reddy and coworkers reported the palladium-catalyzed synthesis of functionalized pyrroles as potential phosphodiesterase (PDE) inhibitors. According to Ghabraie et al., pyrroles can be obtained from Michael reaction of β-enamino ketones or esters and nitromethane followed by cyclization. Very recently, Guan et al. reported the synthesis of pyrrole from enamino esters and nitroolefins (Scheme 1). Moreover, in this method it is a prerequisite to prepare nitroalkenes from aldehydes, nitromethane, and β-enamino carbonyl derivatives. Maiti et al. reported a four-component coupling reaction to synthesize functionalized pyrroles catalyzed by FeCl$_3$ employing ethyl acetoacetate, aromatic aldehyde, amines, and nitromethane. Very recently Khan et al. have reported a four-component coupling reaction for the syntheses of functionalized pyrroles by NiCl$_2$ · 6H$_2$O. Over the past few years graphite has been considered to be an effective, alternative, and promising Lewis acid catalyst, and has received much attention because of its low price sustainability, ready availability, lack of toxicity, easy handling, and environmentally friendly properties. However, to the best of our knowledge there are no methods published for the synthesis of graphite-catalyzed pyrroles. In continuation of our work on the development of synthetic methodologies, we perceived that graphite might be useful as a Lewis acid catalyst for the synthesis of highly substituted pyrroles. Herein we propose a simple and useful synthetic
protocol for the synthesis of tetra-substituted pyrroles employing graphite as a catalyst through one-pot, four-component condensation reaction of aromatic aldehyde, aromatic amine, ethyl acetoacetate, and nitromethane as shown in Scheme 2.

RESULTS AND DISCUSSION

To explore the scope and optimal conditions (Table 1), graphite-catalyzed synthesis of pyrrole 1c was selected as a model. The reaction of aniline 1a, aldehyde 1b, ethyl acetoacetate and nitromethane at 90–100 °C in the presence of different solvents and different concentrations of catalyst are summarized in Table 1. Increasing the amount of graphite from 5 mol% to 20 mol% had a positive effect on the catalytic activity (Table 1, entries 7–10). However, the enhancement of graphite beyond 20 mol% did not give a significant increase in the yield of pyrrole. Similarly, increase the amount of catalyst gave a decrease in the reaction time, but with no significant increase in the yield of pyrrole (Table 1, entries 11 and 12). Next, we examined the effect of the solvents. The reaction did not proceed to completion in dichloromethane, ethanol, or water, but in tetrahydrofuran (THF), dimethylformamide (DMF), and toluene it gave poor yield. Interestingly, when nitro methane was used as reactant as we observed better yield. Here nitromethane’s dual nature acts as reactant as well as solvent. It was observed that diverse functional groups played significant roles in achieving the product yields. Aldehydes with electron-withdrawing groups reacted well with aromatic amines and gave the better yield (Table 2, entries 13–16). In this protocol, even aliphatic cyclic amines generated products in moderate amounts. Graphite accelerated this reaction and gave good yield of product (Table 2, entries 1–13). When studied in diethyl acetylene dicarboxylate, the reaction also gave good yield of product (Table 3, entries 14–16). The experimental procedure involved in this reaction was very simple and straightforward. A mixture of ethyl acetoacetate aromatic amine (1.5 mmol), aromatic aldehyde (1 mmol), nitromethane, and graphite was heated to reflux for 4–6 h.

| Entry | Solvent   | Catalyst (mol %) | Reaction time (h) | Yield (%)b |
|-------|-----------|------------------|-------------------|------------|
| 1     | CH₂Cl₂    | 5                | 24                | No product |
| 2     | Ethanol   | 5                | 24                | No product |
| 3     | H₂O       | 5                | 24                | No product |
| 4     | THF       | 5                | 20                | 30         |
| 5     | Toluene   | 5                | 16                | 30         |
| 6     | DMF       | 5                | 16                | 30         |
| 7     | CH₃NO₂    | 5                | 12                | 20         |
| 8     | CH₃NO₂    | 10               | 10                | 30         |
| 9     | CH₃NO₂    | 15               | 10                | 50         |
| 10    | CH₃NO₂    | 20               | 6                 | 88         |
| 11    | CH₃NO₂    | 30               | 4                 | 80         |
| 12    | CH₃NO₂    | 40               | 4                 | 80         |

a All reaction were carried out using aldehyde (1 mmol), amine (1.5 mmol), ethyl acetoacetate (1 mmol), and (Table 1, entries 1–6) nitromethane (3 mmol) and (Table 1, entries 7–12) nitromethane (1.5 ml).
b Yield obtained after column chromatography.
Table 2. Graphite-mediated synthesis of functionalized pyrroles with various substrates

| Entry | R_1 | R_2 | Product | Reaction time (h) | Yield % |
|-------|-----|-----|---------|------------------|---------|
| 1     | Ph  | Benzo[d][1,3]dioxole | 1c       | 5                | 65      |
| 2     | 4-OMeBn | 4-Acetyl Ph | 2c       | 4                | 73      |
| 3     | 4-Me Bn   | 4-Acetyl Ph   | 3c       | 4                | 68      |
| 4     | 4-Et Ph   | Benzo[d][1,3]dioxole | 4c       | 5                | 70      |
| 5     | 4-t-Bu Bn | Ph            | 5c       | 4                | 67      |
| 6     | 4-F Ph    | Benzo[d][1,3]dioxole | 6c       | 5                | 70      |
| 7     | 4-Cl Bn   | 4-Acetyl Ph   | 7c       | 4                | 70      |
| 8     | Ph-O-CHF_2 | Ph         | 8c       | 4                | 67      |
| 9     | 4-CF_3 Bn | Ph            | 9c       | 4                | 66      |
| 10    | C_6H_5   | 3-Ome Ph     | 10c      | 6                | 60      |
| 11    | C_6H_5CH_2 | 3-Ome Ph   | 11c      | 6                | 65      |
| 12    | C_7H_13CH_2 | 3-Ome Ph | 12c      | 6                | 67      |
| 13    | 4-Cl Ph   | 4-Cl Ph      | 13c      | 6                | 88      |
| 14    | Bn        | 4-Cl Ph      | 14c      | 6                | 80      |
| 15    | 3-Ome Bn  | 4-Cl Ph      | 15c      | 6                | 83      |
| 16    | 2-F Bn    | 4-Cl Ph      | 16c      | 6                | 82      |

*Reaction time 4–6 h.

Purified by column chromatography.

without an inert atmosphere (Scheme 3). When the reaction was completed the product was directly purified by column chromatography. The scope of this reaction was examined with various aromatic amines and the results are summarized in Table 2.

All the compounds were characterized by physical and spectral data. The recyclability of the catalyst was also demonstrated. The reaction mixture was allowed to cool, and the catalyst was recovered by filtration, washed with water, and dried under reduced pressure. The catalyst was reused (Table 3, entries 13 to 16). The reaction proceeded smoothly even after three cycles without any extension of reaction time or any substantial loss of yield (Table 3).

A possible mechanism for the graphite-catalyzed reaction of amine, aldehyde, diethylacetalenecarboxylate, and nitromethane is proposed in Scheme 4. The reaction of amine 1 with diethylacetalenecarboxylate 3 generates β-enaminocarboxylate A and simultaneously nitrostyrene B is obtained by the reaction of aldehydes 2 with nitro methane 4 in one pot in the presence of graphite as Lewis acid catalyst. If β-enaminocarboxylate A and nitrostyrene B undergo Michel reaction to form C followed by intramolecular cyclization to generate intermediate D, which finally undergoes aromatization to form the product E, this could represent a possible tandem synthesis of functionalized pyrroles (Scheme 4).

In conclusion, we have developed a tandem, economical, and one-pot multicomponent synthesis of functionalized pyrroles. This method has several advantages: It is...
inexpensive and environmentally friendly, a wide variety of functional group can survive, and all the components are readily available. A wide variety of substituted pyrroles were synthesized in good yield. This is the first report on functionalized pyrrole synthesis from ethyl acetoacetate utilizing graphite as catalyst. More important is that this method is suitable to library generation, diversity-oriented synthesis, and drug discovery, which make the methodology more attractive for organic synthesis.

**EXPERIMENTAL**

All work relating to analytical thin-layer chromatography (TLC) was performed with E. Merck silica-gel 60F<sub>254</sub> aluminum plates and was visualized with ultraviolet (UV) light. The following mobile phases were employed for TLC: chloroform,
methanol and hexane, and ethyl acetate in different ratios. The instrumental techniques employed for the characterization of the newly synthesized compounds include $^1$H and $^{13}$C NMR and mass spectroscopy. $^1$H and $^{13}$C NMR spectra were recorded on a (400- and 300-MHz) Fourier transform spectrophotometer in CDCl$_3$ or DMSO-d$_6$ solution using tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in parts per million (ppm) relative to TMS. Mass and purity were recorded on a LC–MSD-Trap-XCT.

**Typical Procedure**

Graphite (20 mol%) was added to a solution of benzo[d][1,3]dioxole-5-carbaldehyde (100 mg, 0.666 mmol), aniline (93.03 mg, 1.10 mmol), and ethyl acetoacetate (86 mg, 0.666 mmol) in nitromethane (1.5 ml). The mixture was refluxed at 90–100°C for 5 h (TLC monitoring). The reaction mixture was cooled to room temperature and the graphite was filtered. The filtrate was concentrated under vacuum and the residue was directly purified by column chromatography with ethyl acetate in hexanes as eluent to afford the desired product. The products were further identified by $^1$H NMR, $^{13}$CNMR, and liquid chromatography–mass spectrometry (LCMS), which were all in good agreement with the assigned structures.

**Ethyl-4-(benzo[d][1,3]dioxol-5-yl)-2-methyl-1-phenyl-1H-pyrrole-3-carboxylate (1c)**

Brown semiliquid: 0.152 g (65%); IR (KBr): 1739 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.15–7.29 (m, 5H, ArH), 6.91 (s, 1H, ArH), 6.78–6.87 (d, 2H, ArH, $J$ = 8.0 Hz), 6.62 (s, 1H, ArH), 5.96 (s, 2H, CH$_2$), 4.18 (q, 2H, OCH$_3$, $J$ = 7.5 Hz), 2.40 (s, 3H, CH$_3$), 1.18 (t, 3H, CH$_3$, $J$ = 7.5 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 165.6, 163.0, 161.0, 136.5, 134.9, 129.3, 128.0, 122.3, 120.7, 111.7, 110.1, 107.6, 100.8, 59.5, 14.1, 12.6; MS: $m/z$ = 350.20 [M$^+$ + H], Anal. calcd. for C$_{21}$H$_{19}$NO$_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.02; H, 5.65; N, 3.90.

**Diethyl-1-benzyl-4-(4-chlorophenyl)-1H-pyrrole-2,3-dicarboxylate (14c)**

Brown semiliquid: 0.236 g (80%); IR (KBr): 1756 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.37 (d, 2H, ArH, $J$ = 7.6 Hz), 7.25–7.33 (m, 5H, ArH), 7.17 (d, 2H, ArH, $J$ = 7.2 Hz), 6.91 (s, 1H, ArH), 5.51 (s, 2H, CH$_2$), 4.23 (q, 2H, OCH$_2$, $J$ = 8.0 Hz), 1.25 (t, 3H, CH$_3$), $J$ = 6.8 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 166.4, 160.2, 136.8, 132.8, 131.9, 128.6, 127.5, 126.8, 125.2, 122.2, 121.6, 60.7, 52.4, 14.0; MS: $m/z$ = 412.10 [M$^+$ + H], Anal. calcd. for C$_{23}$H$_{22}$ClNO$_4$: C, 67.02; H, 5.38; N, 3.40. Found: C, 69.97; H, 5.62; N, 3.32.

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SUPPORTING INFORMATION

Complete experimental procedure and relevant LCMS, \(^1\)H NMR, and \(^{13}\)C NMR spectra are available online for all compounds.

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