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DABCO-promoted three-component reaction between amines, dialkyl acetylenedicarboxylates, and glyoxal

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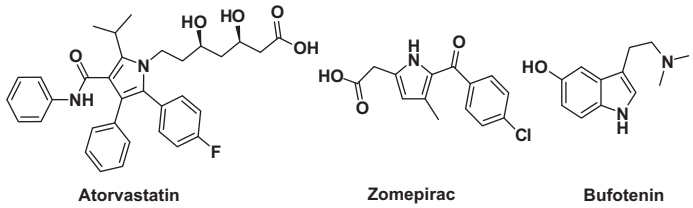
ABSTRACT

A simple and efficient three-component protocol for the synthesis of highly substituted pyrroles has been developed by using amines, DEAD/DMAD, and glyoxal, with the formation of products in good to excellent yields.

Pyrroles play a crucial role in the context of synthetic organic chemistry, hetero cyclic chemistry, as well as medicinal chemistry.[1] Their derivatives are used as important intermediates in the preparation of drug molecules, as well as natural products. These have been given special emphasis due to a wide variety of medicinal and biological properties associated with them[2] (Fig. 1). Several methods are developed for the synthesis of pyrroles such as Knorr reaction[3] which involves the reaction between α-aminoketones derived from α-haloketones, ammonia and β-ketoesters; and Paal–Knorr condensation reaction.[4–14] However Paal–Knorr reaction, a prominent condensation strategy, between γ-ketones and primary amines gained importance for the synthesis of pyrroles.

Liang and co-workers[15] developed a methodology for the synthesis of pyrrole derivatives by the oxidative cyclization of β-enamino ketones and alkynoates using CuI in the presence of oxygen. Yu and co-workers[16] demonstrated an efficient method for the synthesis of polysubstituted pyrroles via the coupling of phenyliodonium ylides and enamine esters using $BF_3{\cdot}Et_2O$. Shi and co-workers[17] used a low-valent Titanium reagent ($TiCl_4$) to access polysubstituted pyrroles using a highly regioselective three-component reaction. Jia and co-workers[18] reported a silver acetate-catalyzed reaction between aldehydes and amines for the preparation of 3,4-disubstituted pyrroles in a one-pot condensation strategy under mild conditions. Ngwerume and Camp[19] described a concise synthesis of highly substituted pyrroles via intermolecular addition of oximes to activated alkynes and subsequent thermal rearrangement of in situ generated *O*-vinyl oximes to form pyrroles via nucleophilic catalysis. Recently, Liu and co-workers[20a] described an efficient method for the synthesis of polysubstituted pyrroles via [4C+1N] cyclization of 4-acetylenic ketones with primary amines using $FeCl_3$. M. A. Abbasinejad et al.[20b] reported the synthesis of highly functionalized pyrroles by using amines, dialkylacetylenedicarboxylates, and aryl glyoxals



Atorvastatin Zomepirac Bufotenin

Figure 1. Biologically active molecules with pyrrole as core skeleton.

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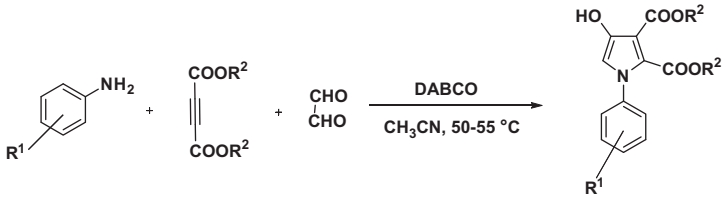


R^1 = -H, -F, -Cl, -Br, $-NO_2$, $-CH_3$, $-OCH_3$, $-CH(CH_3)_2$. R^2 = -Et, -Me

Scheme 1.

Table 1
Synthesis of highly substituted pyrroles using DABCO as catalyst[a]

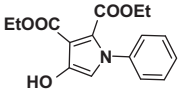
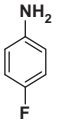
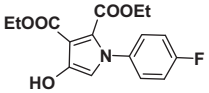
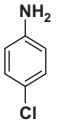
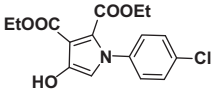
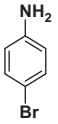
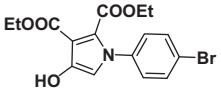
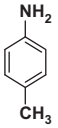
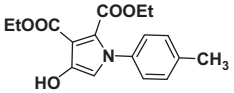
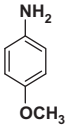
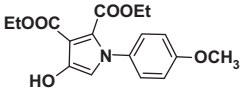
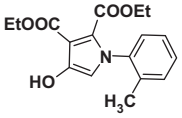
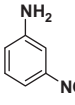
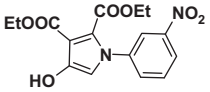
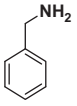
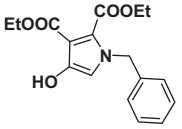
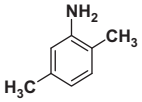
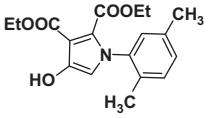
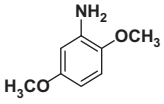
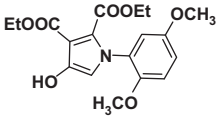
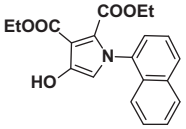
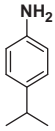
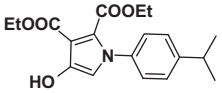
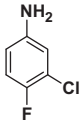
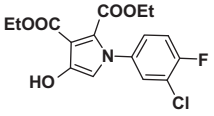
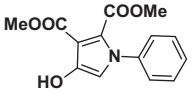
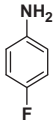
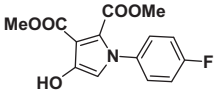
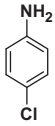
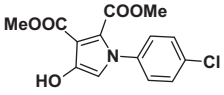
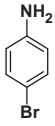
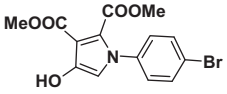
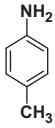
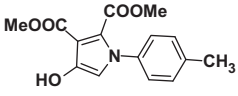
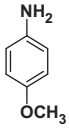
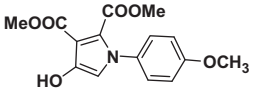
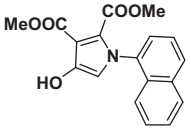
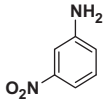
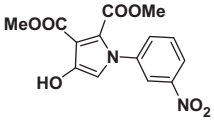
Entry	Amine	DEAD/DMAD	Product	Yield[b] (%)
1				91
2				89
3				88
4				88
5				92
6				93
7				91
8				75
9				77
10				90
11				91

Table 1 (*continued*)

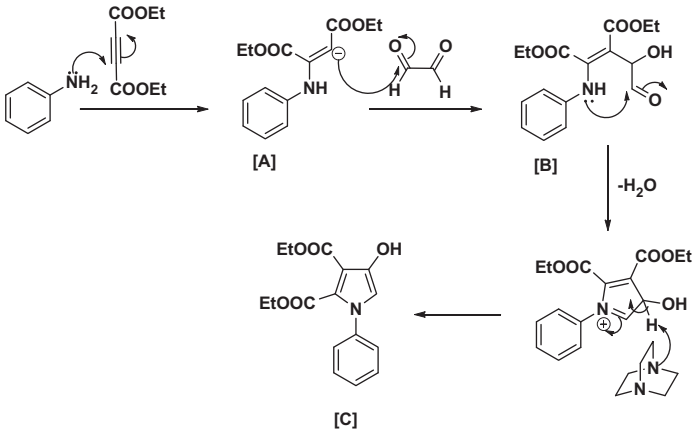
Entry	Amine	DEAD/DMAD	Product	Yield[b] (%)
12				89
13				88
14				86
15				89
16				86
17				85
18				86
19				86
20				89
21				86
22				75

[a] Reaction conditions: amine (1.0 mmol), DEAD/DMAD (1.0 mmol), glyoxal (1.5 mmol), catalyst (0.7 mol %), acetonitrile (10 mL).
[b] Isolated yield.

promoted by Ph_3P in CH_2Cl_2 at rt. Maiti et al.[21] have recently developed a straightforward synthesis of polysubstituted pyrroles using $FeCl_3$ as a catalyst under refluxing conditions.

However, the above mentioned methods suffer from one or more disadvantages such as the use of hazardous organic solvents, expensive moisture-sensitive catalysts, tedious workup conditions, longer reaction times, and large volume of catalyst loadings which in turn result in the generation and release of huge burden of metal wastes into the environment.

Organic chemical synthesis involving multi-component reaction strategies has great value, as the target molecules are often obtained in a single step rather than multiple steps, minimizing the elaborate work-up procedures and environmental pollution. In continuation of our efforts towards the development of novel environmentally friendly methodologies[22] which include the synthesis of heterocyclic compounds, herein, we report a mild and efficient one-pot protocol for the synthesis of highly substituted pyrrole derivatives for the first time by a three-component reaction involv-



Scheme 2. Plausible mechanistic pathway for the synthesis of highly substituted pyrroles using DABCO.

Table 2
Screening of DABCO-catalyzed synthesis of diethyl 4-hydroxy-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate[a]

Entry	Catalyst	Solvent	Time (h)	*T* (°C)	Yield[b] (%)
1	—	CH_3CN	3	80	—
2	DABCO	CH_3CN	3	rt	58
3	DABCO	CH_3CN	3	50–55	91
4	—	Toluene	4	100	—
5	DABCO	Toluene	4	rt	45
6	DABCO	Toluene	4	60	50
7	DABCO	Ethanol	5	60	48

[a] Reaction conditions: amine (1.0 mmol), DEAD (1.0 mmol), glyoxal (1.5 mmol), catalyst (0.7 mol %), solvent (10 mL).
[b] Isolated yield.

ing amine, DEAD/DMAD, and glyoxal using DABCO as a catalyst (Scheme 1).

In our initial studies towards the development of this methodology, aniline (1.0 mmol) was reacted with DEAD (1.0 mmol) and glyoxal (1.5 mmol) in acetonitrile and found that no reaction occurred instead, the starting materials were recovered. It was observed that the same reaction proceeded efficiently when DABCO was used as a catalyst in acetonitrile at room temperature yielding the corresponding substituted pyrrole in 58% yield after 3 h. When the same reaction was attempted in acetonitrile at 50–55 °C the reaction proceeded to completion within 3 h and yielded the corresponding pyrrole derivative in 91% yield.[23, 24] While evaluating the influence of different solvent systems for DABCO-catalyzed synthesis of substituted pyrroles, a few solvents were screened such as toluene, ethanol, and acetonitrile, and among them acetonitrile appeared to be a better choice (Table 2).

To expand the scope of this novel methodology, several diversely substituted anilines having electron-donating as well as electron-withdrawing groups were reacted with glyoxal and DMAD/DEAD in the presence of DABCO resulting in good yields in fast reaction times. It was observed that aromatic amines bearing electron-donating groups resulted in higher yields of the products compared to amines with electron-withdrawing groups. The experimental results are included in Table 1. All the products were characterized by ^1H, ^{13}C NMR, IR, and mass spectra.

The plausible mechanism for the synthesis of highly substituted pyrroles in the presence of DABCO involves the nucleophilic addition of amine with DEAD leading to the formation of intermediate [A], this enamine part on reaction with glyoxal gives another intermediate [B], which undergoes condensation process followed by proton abstraction by DABCO leading to the desired product [C] (Scheme 2).

In conclusion, we have developed a convenient one-pot synthesis of highly substituted pyrroles catalyzed by DABCO in excellent yields. This method involves mild reaction conditions and cleaner reaction profiles.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.100.

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23. *General experimental procedure for the synthesis of highly substituted pyrrole derivatives*: To a stirred solution of acetonitrile (10 mL), amine (1.0 mmol) and DABCO (0.7 mol %) were added and stirred for 10 min. To this DEAD/DMAD (1.0 mmol) followed by glyoxal (1.5 mmol) were added, after which the reaction mixture was heated at 50–55 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to room temperature and the solvent was removed. The crude residue was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with water, saturated brine solution, and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethylacetate and hexanes (0.2:9.8) as eluent to give the corresponding substituted pyrrole derivative in (75–93%) yield. The identity and purity of the product was confirmed by ^1H, ^{13}C NMR, and mass spectra.
24. *Data for the representative examples of synthesized compounds*: Diethyl 4-hydroxy-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate: (Table 1, entry1): yellow liquid; IR(KBr); 3290, 2929, 1780, 1680, 1572, 1452, 1378, 1205, 1151, 1102, 935, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ = 9.67 (s, 1H, -OH), 7.25 (t, 2H, *J* = 8.3 Hz), 7.06 (t, 1H, *J* = 7.3 Hz), 6.91 (d, 2H, *J* = 7.7 Hz), 5.34 (s, 1H), 4.22–4.09 (m, 4H), 1.32–1.25 (m, 6H); ^{13}C NMR (75 MHz $CDCl_3$, TMS) δ = 164.3, 158.9, 140.2, 128.4, 125.3, 123.5, 122.1, 111.9, 58.9, 14.8; Mass (ESI-MS): *m*/*z* 326 $(M+Na)^+$. Anal. calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.29; H, 5.62; N, 4.58.