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

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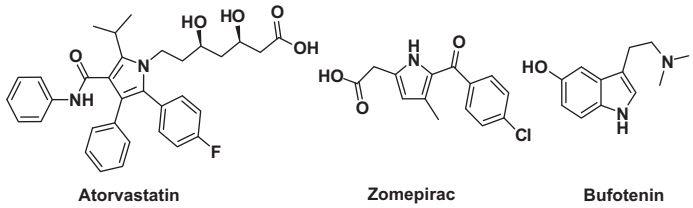
ABSTRACT

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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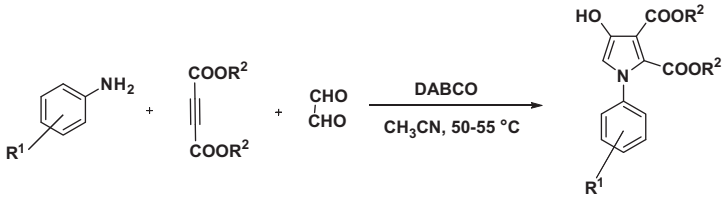
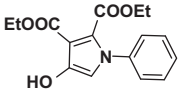
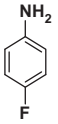
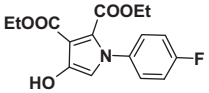
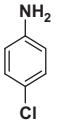
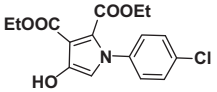
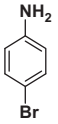
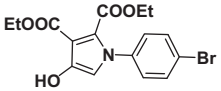
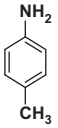
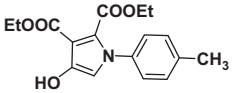
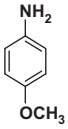
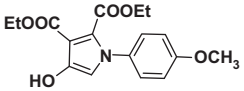
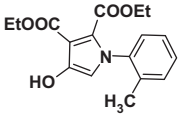
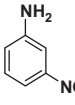
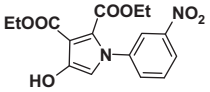
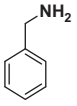
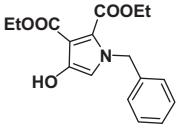
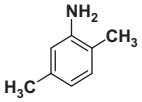
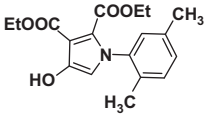
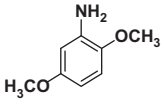
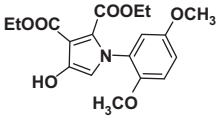


R^1 = -H, -F, -Cl, -Br, $-NO_2$, $-CH_3$, $-OCH_3$, $-CH(CH_3)_2$. R^2 = -Et, -Me

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