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Novel and efficient supramolecular synthesis of pyrroles in the presence of β-cyclodextrin in water

K. Ramesh, K. Karnakar, G. Satish, Y.V.D. Nageswar *

CSIR-Natural Product Chemistry, Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500-007, India

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Abstract

A simple and efficient synthesis of highly substituted pyrroles was achieved in water medium *via* multi-component strategy, using amine, DMAD/DEAD as well as phenacyl bromide catalyzed by β-CD. Utilizing this protocol various pyrrole derivatives were synthesized in good to excellent yields.

Keywords: Amine; DMAD/DEAD; Phenacyl bromide; Water; Recyclability; β-cyclodextrin

Pyrroles are an important class of compounds in organic chemistry, medicinal chemistry, and heterocyclic chemistry [1]. These derivatives are widely used in the synthesis of natural products [2] and drug molecules [3]. Pyrrole and its analogues exhibit varied biological activities such as antibacterial, antiviral, anti-inflammatory, antitumor, and antioxidant [4,5], these are also used in material science [6].

There are numerous drugs such as Atorvastatin, Zomepirac, and Bufotenin containing the pyrrole skeleton as shown in the (Fig. 1). Several methods have been reported for the synthesis of highly substituted pyrroles [7–21]. Recently Lingaiah *et al*. [22] described the synthesis of poly substituted pyrroles by using PEG from aniline, DMAD/DEAD, and phenacyl bromide.

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.

1. Experimental

All the chemicals were purchased from Sigma–Aldrich with purity not less than 99.9%. Analytical thin layer chromatography (TLC) was carried out by using silica gel 60 F254 pre-coated plates. Visualization was accomplished with UV lamp of I_2 stain. All the products were characterized by their NMR and mass spectra. ^{1}H NMR and ^{13}C NMR were recorded on 200 or 300 MHz, in $CDCl_3$, and the chemical shifts were reported in parts per million (ppm, δ) downfield from the tetramethylsilane.

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* Corresponding author.
E-mail address: dryvdnageswar@gmail.com (Y.V.D. Nageswar).

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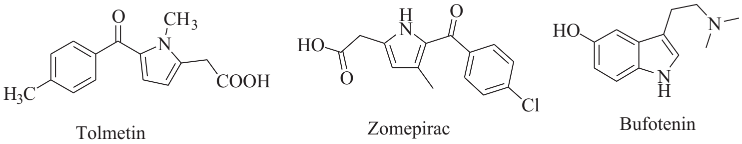


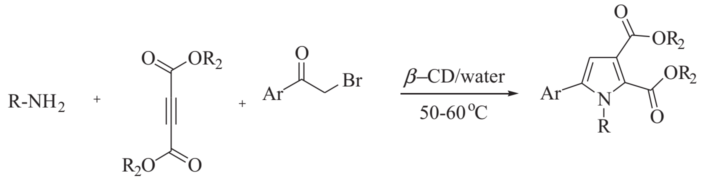
Fig. 1. Some marketed drugs with pyrrole skeleton.

General experimental procedure for the synthesis of pyrroles using β-cyclodextrin (**1a–1o**): β-cyclodextrin (10 mol%) was dissolved in water (15 mL), and to this clear solution, aniline (1.0 mmol) was added, stirred for 15 min, and followed by the addition of dimethyl/diethyl acetylenedicarboxylate (DMAD/DEAD 1.0 mmol) and phenacyl bromide (1.0 mmol). The reaction mixture was heated at 50–60 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to 5 °C and β-cyclodextrin was filtered. The aqueous layer was extracted with ethyl acetate (3 mL × 10 mL). The combined 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 ethyl acetate and hexane (2:8) as eluent. The identity and purity of the product were confirmed by ^{1}H, ^{13}C NMR, and mass spectra.

2. Results and discussion

In continuation of our efforts towards the development of novel environ friendly methodologies [23–33] 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, involving amino compounds, DMAD/DEAD and phenacyl bromide promoted by recyclable β-CD in water (Scheme 1). Presently organic reactions in aqueous phase have attracted the attention of researchers because of the added advantages of water, as an environmentally benign and economically affordable solvent. However, the fundamental problem in performing the reactions in water is that many organic substrates are hydrophobic and are insoluble in water. Cyclodextrins, possessing hydrophobic cavities, are well known supramolecular catalysts, which by reversible formation of host–guest complexes, activate the organic molecules and catalyze the reactions. As part of our ongoing program toward the development of greener chemical approaches for the synthesis of novel reaction intermediates and heterocyclic moieties, we report herein the synthesis of *N*-substituted pyrroles by the reaction of amines, DMAD/DEAD, with phenacyl bromides using β-cyclodextrin, a recyclable supramolecular catalyst, for the first time in aqueous medium.

In this study, a model reaction was conducted by reacting aromatic amines, DMAD/DEAD with phenacyl bromide in water medium at room temperature to obtain the corresponding *N*-substituted pyrrole in low yields (42%). The poor solubility of aniline in water at elevated temperature resulted in the formation of undesired products. When the same reaction was conducted using β-CD at room temperature the product was obtained in moderate yield (61%). However by a controlled experiment using β-CD, as a supramolecular catalyst, at 50–60 °C the product was obtained in excellent yield (88%) (Scheme 1). In general, all the reactions were clean, and the *N*-substituted pyrroles were obtained in excellent yields (80–89%) (Table 2). All the products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectrometry [34]. The catalytic activity of the β-CD was established by the fact that pyrrole formation was not observed in satisfactory yield in the absence of β-cyclodextrin. The evidence for the formation of *N*-aryl substituted pyrrole in the presence of β-CD was supported by ^{1}H NMR studies of inclusion complex between aniline and β-CD [24].



R=Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$ R$_2$ =Me, Et Ar=Ph, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

Scheme 1. Synthesis of highly substituted pyrroles.

Table 1
Recyclability of the catalyst.[a]

Cycles	Yield[b] [%]	Catalyst recovered [%]
Fresh	88	90
1	86	88
2	85	86
3	85	86

[a] Reaction conditions: Aniline (1.0 mmol), DEAD (1.0 mmol), phenacyl bromide (1.0 mmol), β-cyclodextrin (10 mol%), 50–60 °C.
[b] Isolated yield.

Table 2
Synthesis of highly substituted pyrroles (**1a**–**1o**).[a]

Entry	Ar	R	DMAD/DEAD	Product	Yield[b] [%]
1	Ph	Ph	DEAD	**1a**	88
2	Ph	Ph	DMAD	**1b**	89
3	Ph	4-MeC_6H_4	DMAD	**1c**	85
4	Ph	4-MeC_6H_4	DEAD	**1d**	84
5	4-$NO_2C_6H_4$	Ph	DEAD	**1e**	80
6	4-$NO_2C_6H_4$	Ph	DMAD	**1f**	81
7	4-BrC_6H_4	Ph	DEAD	**1g**	85
8	4-BrC_6H_4	Ph	DMAD	**1h**	84
9	4-$NO_2C_6H_4$	4-MeC_6H_4	DEAD	**1i**	83
10	Ph	4-FC_6H_4	DMAD	**1j**	84
11	4-$NO_2C_6H_4$	4-MeC_6H_4	DMAD	**1k**	83
12	4-$NO_2C_6H_4$	4-FC_6H_4	DEAD	**1l**	82
13	4-BrC_6H_4	4-MeC_6H_4	DMAD	**1m**	86
14	4-BrC_6H_4	4-FC_6H_4	DEAD	**1n**	84
15	Ph	NH_4OAc	DMAD	**1o**	82

[a] Reaction conditions: Aniline (1.0 mmol), DMAD/DEAD (1.0 mmol), phenacyl bromide (1.0 mmol), β-cyclodextrin (10 mol%), 50–60 °C.
[b] Isolated yield.

All the reactions were carried out with a catalytic amount (10 mol%) of β-CD in water. In all these reactions β-CD can be recovered and reused. After the reaction, the reaction mass was cooled to room temperature and β-CD was filtered and washed with ice-cold water and dried. The recovered β-CD was further used in the reaction with the same substrates and checked for the yields and catalytic activity of the recovered catalyst (β-CD), as shown in Table 1. It was observed that the yields of *N*-substituted pyrroles diminished slightly after two to three recycles.

In summary, we have developed an eco-friendly method to synthesize substituted pyrroles excellent yields under neutral conditions in one-pot catalyzed by β-cyclodextrin in aqueous medium.

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