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Microwave - Assisted Catalyst- Free Synthesis of Tetrasubstituted Pyrroles Using Dialkyl Acetylenedicarboxylates and Monophenacylanilines

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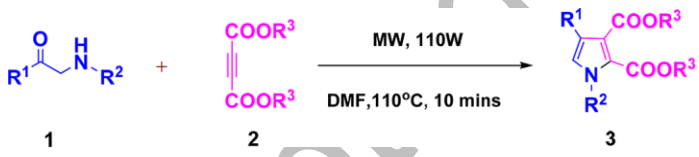
Abstract

An efficient catalyst free microwave assisted synthesis of tetrasubtituted pyrroles using dialkyl acetylenedicarboxylates and substituted monophenacylanilines has been developed. Axial chirality has been noticed in some *N*-(α-naphthyl/2-isopropylphenyl)-2,3-dicarbethoxy-4-arylpyrroles, but not with *N*-aryl-2,3-dicarbethoxy-4-(α-naphthyl)pyrrole.



1 2 3

KEYWORDS: Diethylacetylene dicarboxylate; Polysubtituted pyrrole; Microwave synthesis; Axial chirality

INTRODUCTION

Pyrrole nucleus can be found in many natural bioactive molecules,[1] synthetic pharmaceuticals[2] and functional materials[3] with varied applications. Several polysubstituted pyrroles, in particular, are effective as anti-bacterial,[4] anti-convulsant,[5] anti-cancer,[6] anti-oxidant,[7] anti-tumour[8] and anti-inflammatory[9] agents. It must be

pointed out that pyrrole skelton has been found as a subunit in heme, chlorophyll, bile pigments and vitamin B12 apart from alkaloids derived from marine sources. Some popular pyrrole containing drugs are shown in Figure 1. Pyrrole derivatives have also been widely used as organic conducting materials.[10]

The pyrrole unit can be generated from routes proposed by Knorr,[11] Paal–Knorr,[12] and Hantzsch[13] and the other strategies include the transition metal mediated cyclisation,[14] reductive coupling,[15] isocyanide based reactions,[16] rearrangement reaction[17] and cycloaddition methods.[18] The present investigation reports the synthesis of the polysubstituted pyrroles, dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylates. Though there are many reports for the synthesis of the dialkyl 1,5-diaryl-*1H*-pyrrole-2,3-dicarboxylate,[19] only a few reports describe the route for its regioisomer, dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylate. Abbasinejad *et al* first reported a two-step strategy involving triphenylphosphine catalyzed cyclisation of α-aminoketones with dialkyl acetylenedicarboxylates followed by chromium trioxide oxidation.[20] Ardakani *et al* reported triphenylphosphine promoted condensation reaction between dialkyl acetylenedicarboxylates and 1-aryl-2-(arylamino)-2-hydroxyethanones.[21] A direct four-component coupling reaction of aldehydes, amines, dialkyl acetylenedicarboxylates, and nitromethane using iodine as a catalyst has been reported[22a] and also an iron(III) chloride catalysed three-component reaction of primary amines, dialkyl acetylenedicarboxylates and β-nitrostyrene reported by Ghabraie et al.[22b] Very recently, Jeong *et al* reported one-pot four component, reaction of amines, aldehydes, dialkyl

acetylenedicarboxylates and nitroalkanes using silica supported ceric ammonium nitrate as a heterogeneous catalyst.[22c] Liu *et al* reported a gold-catalyzed cascade hydroamination/cyclization reaction of α-amino ketones with alkynes.[23] These protocols involve (i) tedious task of removing the triphenylphosphine oxide or (ii) prefunctionalisation of the monophenacylaniline part or (iii) more steps to reach the desired product or (iv) long reaction time or (v) cascade hydroamination/cyclization reaction where expensive gold has been used as the catalyst. To overcome these shortcomings and exploiting the advantages of microwaves in modern synthetic organic chemistry, the present scheme for pyrrole synthesis has been proposed in continuation of our work[24] on the development of useful synthetic methodologies for the construction of heterocycles. A microwave assisted catalyst free efficient synthesis of dialkyl 1,4-diaryl-1*H*-pyrrole-2,3-dicarboxylates from α-amino ketones with dialkyl acetylenedicarboxylates has been achieved (Scheme 1).

RESULTS AND DISCUSSION

We started our investigation with **1a** as the model substrate and treated that with DEAD in THF without catalyst at room temperature. It must be admitted that a related reaction has been reported involving acidic reagent with limited substrate scope after isolating the intermediate.[25a] Our strategy involves no acidic reagent, no isolation of the intermediate and a wide substrate scope. Similar work yielding 2-trifluormethyl substituted pyrrole has been reported very recently.[25b] After 16 hrs, **3a** was formed in 50% yield (Table 1, entry 1) with 25% of starting material, the remaining being unrecognizable mass. Increasing the reaction time had no impact on the yield of **3a**. Carrying out the reaction in acetic acid

also did not enhance the yield as expected, but resulted in additional by-products as evidenced by TLC. However, when the reaction was carried out in DMF under reflux without any catalyst, the reaction got completed within 6 hrs (Table 1, entry 2) with 62% yield of **3a**. When we investigated the reaction by applying microwave with varying MW power, temperature and the solvents (Table 1, entries 3-9), we found that **3a** was obtained in good yield with DMF in 110W at 110^{o}C (Table 1, entry 9) in 10 minutes. Increasing the reaction time beyond 10 minutes did not improve the yield, rather a slight decrease in the yield has been observed as evidenced by TLC. The yield was relatively good with solvents like ethanol, acetonitrile and water (Table 1, entries 13-15), but it was relatively poor with the other solvents such as toluene, 1,4 dioxane and 1,2 DCE (Table 1, entries 10-12). The one pot reaction of all three compounds, as reported in the previous literature,[19] resulted in diethyl 1,5-diphenyl-*1H*-pyrrole-2,3-dicarboxylate. Here the reaction of aniline with the diethyl acetylenedicarboxylate was preferred over the formation of monophenacylaniline. The initial reaction between aniline to phenacyl bromide followed by the addition of DEAD could afford the desired product. When we attempted the one pot synthesis through the addition of aniline to phenacyl bromide under MW for 1 min at 110^{o}C followed by the addition of DEAD, it resulted in lower yield of the dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylate. This may be due to the initial formation of α,α'-amino ketones preventing the formation of the pyrrole. After optimization we investigated the scope of the reaction and it worked well with variety of α-aminoketones and different acetylene esters (Table 2). The structures of the products **3** has been unambiguously assigned by spectral and analytical data, and that of **3d** has been confirmed by single crystal X-ray analysis as well [Figure. 2].[26] A closely related

methodology employing gold catalyst has reported the synthesis of similar skeleton,[23] whereas the present work uses no catalyst generating a library of eighteen compounds.

It is pertinent to note that this cyclisation occurred successfully with both electron withdrawing as well as electron donating groups in the aryl ring (Table 2). Presence of electron withdrawing groups on the carbonyl attached phenyl ring and the electron donating groups on the aniline ring of the monophenacylaniline promoted the formation of product enhancing the yield of the desired product (Table 2, compounds **3d**, **3e**, **3i** and **3q**). All the other monophenacylaniline derivatives differing from the aforementioned combination of electron withdrawing and donating groups afforded moderate yield (Table 2). Based on the observed results, a plausible mechanism is proposed (Scheme 2). Initially the reaction of α-amino ketones with electron deficient alkynes afforded the enamine intermediate **A**. Then the nucleophilic attack of the enamine to the carbonyl group afforded intermediate **B** followed by the elimination of water provided the desired product **3**.

One out of the two sets of methylene hydrogens in **3j, 3l** and **3p** are found to be diastereotopic indicating that chirality has arisen due to the restricted rotation around N-(α-naphthyl/N-(2-isopropylphenyl) bond in these cases. In the case of **3i**, the diasterotopic behavior has been felt with the isopropyl methyls as well, both in the ^{1}H and ^{13}C NMR spectra. It must be noted that when a simple methyl is present in the 2-position of the *N*-phenyl ring, no chirality has been noticed.[22c] It is also interesting to note that the presence

of α-naphthyl group in the 4th position of the pyrrole (**3o**) has not raised any chiral characteristics.

CONCLUSION

In summary, we have developed a microwave assisted synthesis of dimethyl 1,4-diphenyl-*1H*-pyrrole-2,3-dicarboxylates, the main advantage of this method being that it is catalyst free with shorter reaction time resulting in good to excellent yield. Another interesting feature is the realisation of axial chirality in *N*-(α-naphthyl/2-isopropylphenyl)-2,3-dicarbethoxy-4-arylpyrroles, but not in *N*-aryl-2,3-dicarbethoxy-4-(α-naphthyl)pyrrole.

EXPERIMENTAL SECTION

All solvents were purchased from commercial sources and used without further purification. The melting points were measured in open capillary tubes and are uncorrected. A CEM Discover microwave synthesizer (Model No: 908010) operating at 180/264 V and 50/60 Hz with microwave power maximum level of 300 W and microwave frequency of 2455 MHz was employed for the microwave-assisted experiments. Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (*J* values) are reported in Hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quatret), sept (septet), m (multiplet). ^{13}C NMR spectra were routinely run

with broadband decoupling. Elemental analyses were performed on a Perkin Elmer 2400Series II Elemental CHNS analyzer.

General Procedure for the Synthesis of Dimethyl 1,4-Diphenyl-1*H*-Pyrrole-2,3-Dicarboxylate 3

A mixture of substituted monophenacylaniline **1** (1 mmol), dialkyl acetylenedicarboxylate **2** (1.1 mmol) in DMF (1 mL) was sealed and subjected to microwave irradiation programmed at 110 °C and 110 W for 10 minutes. The completion of the reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuum. Crude product was purified by column chromatography using petroleum ether − ethyl acetate (5: 95) as the eluent to get **3**.

Selected Spectral Data For Diethyl 4-(4-Chlorophenyl)-1-(P-Tolyl)-*1H*-Pyrrole-2,3-Dicarboxylate (3d) are Given Below

Yellow solid; mp 97 – 100 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.27 – 7.21 (m, 4H), 6.94 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 159.9, 138.5, 136.8, 132.9, 131.8, 129.4, 129.1, 128.6, 125.8, 125.5, 123.9, 123.5, 121.2, 61.3, 60.9, 21.1, 14.0, 13.9. Anal. Calcd for $C_{23}H_{22}ClNO_4$: C, 67.07; H, 5.38; N, 3.40 %. Found: C, 67.09; H, 5.33; N, 3.43 %. ESI-MS m/z calcd $[M+H]^+$ 412.12, found 412.11.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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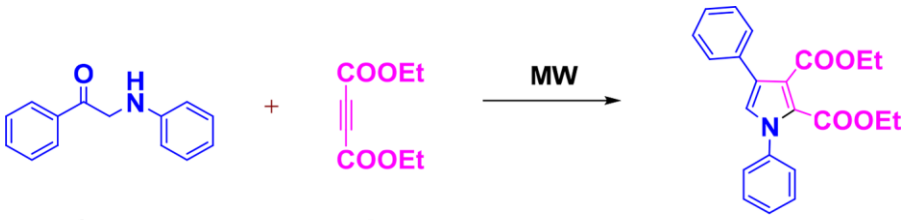
[26] CCDC number for **3d**: 14336.

Table 1. Optimization of the reaction conditions[a]

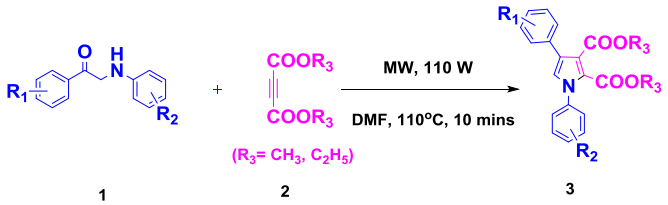


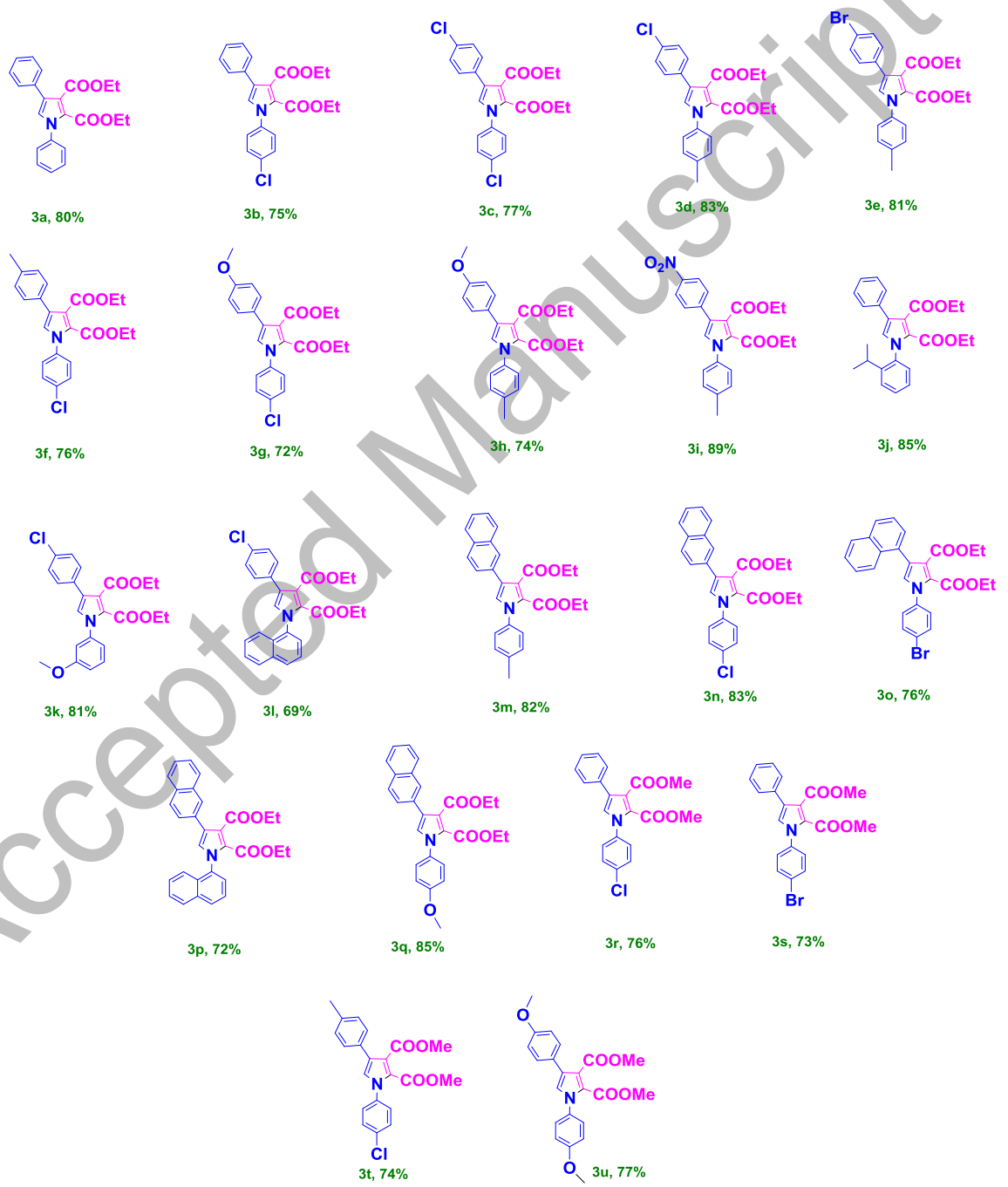
1a 2 3a

Entry	Solvent	Temp (^{o}C)	MW (Watt)	Time (mins)	Yield[c] of 3(%)
1	[b]THF	-	-	960	50
2	[d]DMF	140	-	360	62
3	THF	100	100	10	56
4	EtOH	100	120	10	55
5	MeCN	100	110	10	53
6	DMF	110	120	10	68
7	Water	120	100	10	62
8	Toluene	120	110	10	52
9	DMF	110	110	10	80
10	Toluene	110	110	10	48
11	1,4 Dioxane	110	110	10	45
12	1,2 DCE	110	110	10	37
13	MeCN	110	110	10	60
14	EtOH	110	110	10	58
15	Water	110	110	10	65

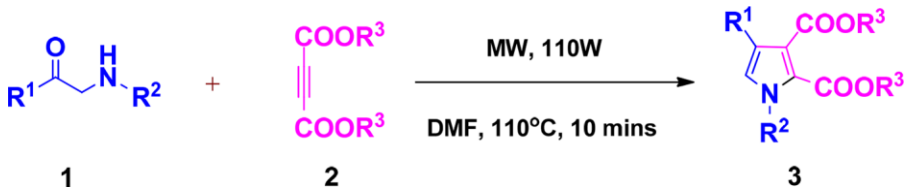
[a]Reaction conditions: **1a** (1mmol), **2** (1.1 mmol), solvent (1 ml) for 10 min. [b]Reaction at room temperature. [c]Isolated yield. [d]Reaction at reflux condition.

Table 2. Synthesised compounds (**3a-3u**)





Scheme 1. Synthesis of 1,2,3,4-tetrasubstituted pyrroles



1 2 3

Scheme 2. A plausible mechanism for the formation of 3

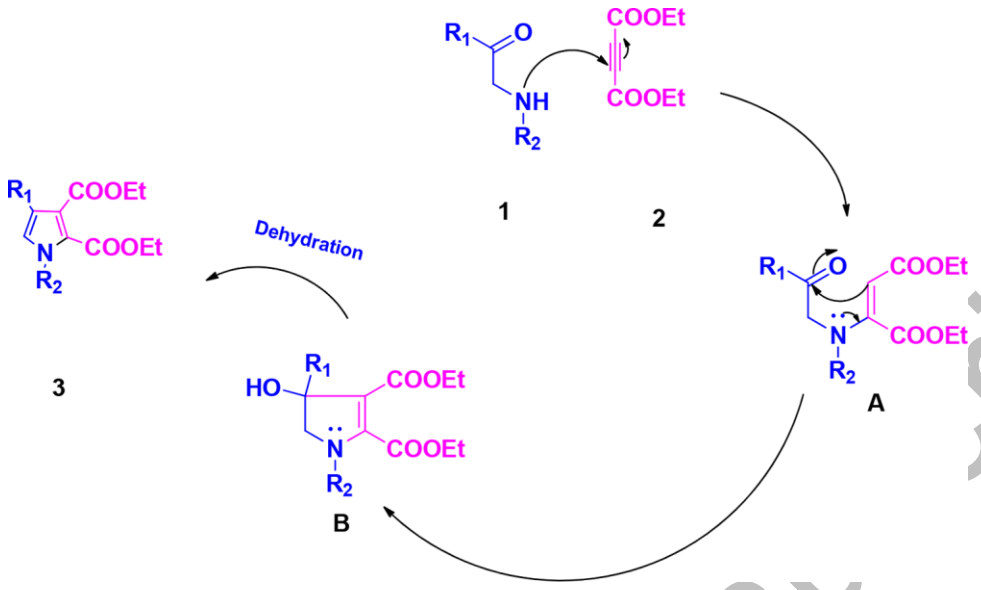


Figure 1. Examples of pyrrole derived drugs

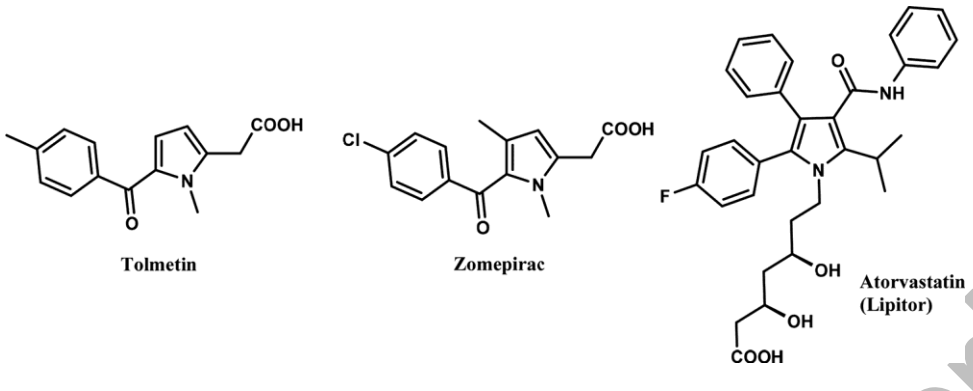


Figure 2. Crystal structure of **3d**