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An efficient synthesis of functionalized pyrroles from *N*-protected amino acid by microwave irradiation

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Abstract: We report the microwave-assisted rapid synthesis of dialkyl 2-alkyl-5-aryl-1H-pyrrole-3,4-dicarboxylates in good yields from reaction of N-aroyl *alpha*-amino acids and dialkyl acetylendicarboxylates in the presence of anhydride acetic as a dehydrating agent.

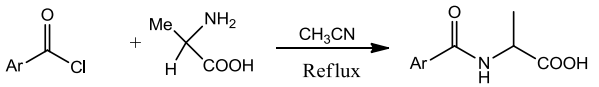
Keywords: Microwave-assisted, Dialkyl acetylendicarboxylate, N-Aroyl *α*-amino acid, Acetic anhydride, Dehydrating agent.

Introduction

Pyrroles are an important class of compounds with different biological activities [1].

The pyrrole moiety is found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B_{12}. Pyrroles are also present in various bioactive drug molecules such as atorvastatin, anti-inflammatory and antitumor agents, and *immunosuppressants* [2].

Many methods for the synthesis of diversely substituted pyrroles have been developed [3]. Pyrroles are synthesized *via* conjugate addition reactions [4], reductive couplings [5], aza-wittig reactions [6], the Paal-Knorr reaction [7] and 1,3-dipolar cycloaddition of azomethine ylides and alkynes [8]. Among of them, 1, 3-dipolar cycloaddition is an efficient reaction carried out with simple building blocks. N-aroyl amino acids, prepared from reaction aroyl chlorides with *a*-amino acids, are readily available reagents with a wide variety of functional groups. As part of our current studies on the development of new routes in approach to the synthesis of heterocyclic compounds [9-12], we describe an efficient synthesis of functionalized pyrroles **5** from reaction of N-aroyl amino acids **3** and dimethyl acetylenedicarboxylate (DMAD) or dimethyl acetylenedicarboxylate (DEAD) **4** in the presence of acetic anhydride under microwave condition. N-aroyl amino acids **3** were prepared from reaction of aroyl chlorides with *α*-amino acids (Scheme **1**).



1	Ar
a	Ph
b	4-ClC_6H_4

2

3	Ar	Yield (%)
a	Ph	95
b	4-ClC_6H_4	93

Scheme 1: Synthesis of *N*-protected *a*-amino acid **3**:

This facile method can be used to synthesis highly substituted pyrroles, containing two substituents from the amino acid, and two from the alkyne (Scheme **2**).

Results and discussion

This research was done in two steps. First, N-aroyl amino acids **3** were prepared from reaction of aroyl chlorides with *a*-amino acids. Second, the reaction of compounds **3a-b** with dialkyl acetylenedicarboxylates **4** in the presence of anhydride acetic produced pyrroles **5** under microwave radiation, and was completed within 5 minutes. ^{1}H and ^{13}C NMR spectra of the products clearly indicated the formation of dialkyl 2-

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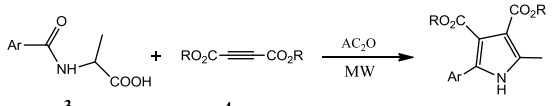
methyl-5-aryl-1H-pyrrole-3,4-dicarboxylate **5** (Scheme **2**).

The structures of compounds **3a** and **3b** were confirmed by E_A, IR, and ^{1}H NMR. The structures of compounds **5a-5d** were also deduced from their IR, ^{1}H NMR, and ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. For example, the mass spectrum of **5a** displayed a molecular ion peak at *m/z* 273 and more important, an ion peak at *m/z* 241 indicated that MeOH has been lost and thus the presence of CO_2Me group in the structure was confirmed. The most important absorption band in IR spectrum is due to the NH stretching frequency of pyrrole. Absorption bands at 1658 and 1628 cm^{-1} are due to the two carbonyl groups. The ^{1}H NMR spectrum of **5a** in $CDCl_3$ showed a singlet for methyl pyrrole ring (δ = 2.12), two singlets for OMe groups and a singlet for NH (δ = 8.40) proton, along with characteristic signals phenyl group. The ^{13}C NMR spectrum of **5a** in $CDCl_3$ showed 13 distinct signals in agreement with the proposed structure that characteristic carbons of pyrrole and phenyl rings resonances at 118.8-134.1 ppm. Partial assignments of these resonances are given in section experimental. Moreover, the carbonyl resonances of **5a** appeared at 161.5, 162.3 ppm.



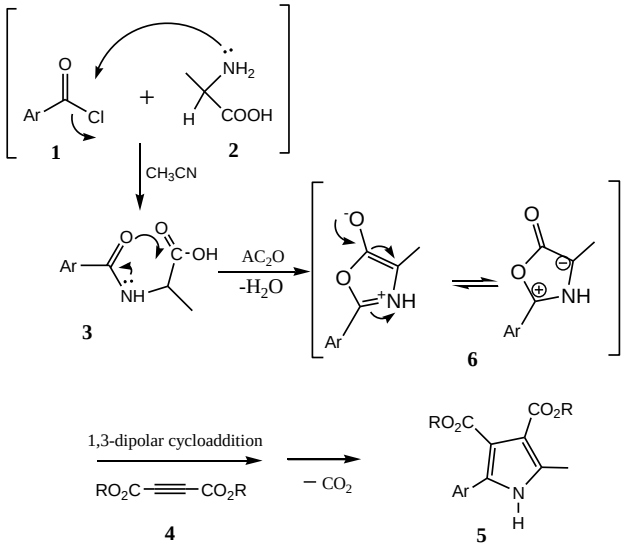
5	Ar	R	Yield %
a	C_6H_5	Me	86
b	p-ClC_6H_4	Me	90
c	C_6H_5	Et	85
d	p-ClC_6H_4	Et	83

Scheme 2: Synthesis of tetrasubstituted pyrroles **5** by microwave irradiation.

A tentative mechanism for this transformation is proposed in Scheme **3**. Presumably, N- aroyl amino acid, formed by the initial reaction of an amino acid and aroyl chloride, undergoes ring-closure in the presence of anhydride acetic, as a water-removing agent, to produce azomethine ylide **6**. The cycloaddition reaction of the ylide **6** with a dialkyl acetylenedicarboxylate and then removing CO_2 led to highly functionalized pyrroles **5a-5d.**

Conclusion

In conclusion, we reported an efficient method for the synthesis of four-substituted pyrroles. The advantages of our work are as follows: (1) this microwave-assisted catalytic synthesis is facile and rapid, (2) work up procedure is easy and gives pure target compounds, (3) four functional groups are on the product, which are capable to convert to other functional groups.



Scheme 3: Proposed mechanism for the formation of compounds **5**.

Experimental

Benzoyl chloride, p-chlorobenzoyl chloride, alanine, valine, anhydride acetic and dialkyl acetylene dicarboxylates were obtained from fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus; IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra: *Bruker DRX-300 AVANCE* instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ in ppm, *J* in Hz; EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in *m*/*z*. The results agreed favorably with the calculated values.

*General procedure for the preparation of compounds **3:***

A mixture of aroyl chloride **1** (1mmol) and α-amino acid **2** (1 mmol) was stirred in 2 ml of acetonitrile for 4 h under reflux. Then, the solvent was removed under reduced pressure. The residue was purified by recrystallization from a mixture of AcOEt/n-Hexane (1:3) and was used in the next step.

Acid equivalents (E_A) were calculated by titration of **3a** and **3b** with sodium hydroxide solution in the presence of phenolphthalein.

Spectroscopic data for compounds 3a-c:

2-(Benzamido)propanoic acid (3a):

White powder, mp 137-138 ºC, E_A= 193.5; $C_{10}H_{11}NO_3$ yield: 0.37 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3331, 2490-3100 (COOH), 1718, 1633, 1531, 1280, 1153 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (3 H, d, ^3J 7.0, Me), 5.05 (1 H, quintet, ^3J 7.0, CH), 6.79 (1 H, s, NH), 7.58 (2 H, t, ^3J 7.3, 2 CH), 7.68 (1 H, t, ^3J 7.3, CH), 7.89 (2 H, d, ^3J 7.3, 2 CH), 11.27 (1 H, br s, COOH).

2-(4-Chlorobenzamido)propanoic acid (3b):

White powder, m.p. 165-167 ºC, E_A= 227.6; $C_{10}H_{10}ClNO_3$ yield: 0.43 g (96%). IR (KBr) (ν_{max}/cm^{-1}): 3259, 2750-3200 (COOH), 1715, 1639, 1280, 1082 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (3 H, d, J = 7 Hz, Me), 4.83 (1 H, q, J = 7 Hz, CH), 6.63 (1 H, s, NH), 7.77 (2 H, d, J = 8.5 Hz, 2 CH), 8.04 (2 H, d, J = 8.5 Hz, 2 CH), 10.91 (1H, br s, COOH) ppm.

*General procedure for the preparation of compounds **5:***

N-Aroyl amino acid **3** (1 mmol) and alkyne **4** (1 mmol) were placed in a microwave reaction tube. Acetic anhydride (3 mL) was added. The reaction mixture was irradiated at 120 ºC for 5 min. Water was added and the product was extracted by ethyl acetate. After evaporating of solvent, the crude product was purified by flash chromatography.

*Spectroscopic data for compounds **5a-d**:*

*Dimethyl2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (**5a**):*

Pale yellow oil, yield: 0.23 g (86%). IR (KBr) (ν_{max}/cm^{-1}): 3310, 1658, 1628, 1213, 1190, 856 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.12 (3 H, s, Me), 3.83 (3 H, s, OMe), 3.92 (3 H, s, OMe), 7.34-7.62 (5 H, m, 5 CH), 8.40 (1 H, br-s, NH) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 13.3 (Me), 52.8 (OMe), 54.1 (OMe), 118.8 (C), 120.7 (C), 128.3 (CH), 128.7 (2 CH), 129.5 (2 CH), 130.2 (C), 132.3 (C), 134.1 (C), 161.5 (C=O), 162.3 (C=O). $C_{15}H_{15}NO_4$, EI-MS: *m/z (%)* = 273 (M+, 66), 242 (76), 241 (100), 212 (22), 183 (47), 155 (75), 77 (20).

Dimethyl 2-(4-chlorophenyl)-5-methyl-1H-pyrrole-3,4-dicarboxylate (**5b**):

Pale yellow oil, yield: 0.27 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3290, 1720, 1690, 1457, 1230, 1132 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.53 (3 H, s, Me), 3.81 (3 H, s, OMe), 3.83 (3 H, s, OMe), 7.37 (2 H, d, ^3J = 8.8 Hz, 2 CH), 7.43 (2 H, d, ^3J = 8.8 Hz, 2 CH), 8.23 (1 H, br-s, NH) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 13.8 (Me), 52.2 (OMe), 53.2 (OMe), 120.9 (C), 122.4 (C), 126.2 (C), 126.9 (2 CH), 127.8 (2 CH), 130.2 (C), 132.2 (C), 133.1 (C), 163.8 (C=O), 164.1 (C=O). $C_{15}H_{14}ClNO_4$, EI-MS: *m/z (%)* = 309 (M+2, 16), 307 (46), 277 (34), 275 (100), 246 (23), 217 (41), 189 (35), 111 (23).

*Diethyl 2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (**5c**):*

Pale yellow oil, yield: 0.25 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 3288, 1708, 1455, 1287, 1215cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (3 H, t, ^3J = 7.2 Hz, Me), 1.36 (3 H, t, ^3J = 7.2 Hz, Me), 2.54 (3 H, s, Me), 4.30 (2 H, q, ^3J = 7.2 Hz, OMe), 4.31 (2 H, q, ^3J = 7.2 Hz, OMe), 7.34-7.51 (5 H, m, 5 CH), 8.39 (1 H, br-s, NH) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 13.9 (Me), 14.1 (Me), 17.4 (Me), 60.5 (OCH_2), 62.0 (OCH_2), 119.9 (C), 121.4 (C), 127.8 (CH), 128.1 (2 CH), 128.8 (2 CH), 130.1 (C), 132.9 (C), 134.1 (C), 162.8 (C=O), 163.1 (C=O). $C_{17}H_{19}NO_4$, EI-MS: *m/z (%)* = 301 (M+, 57), 255 (100), 227 (64), 226 (70), 183 (45), 153 (28), 155 (42), 77 (26).

*Diethyl 2-(4-chlorophenyl)-5-methyl-1H-pyrrole-3,4-dicarboxylate (**5d**):*

Pale yellow oil, yield: 0.28 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 3231, 1698, 1628, 1223, 1199, 856 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (3 H, t, ^3J = 7.0 Hz, Me), 1.36 (3 H, t, ^3J = 7.0 Hz, Me), 2.54 (3 H, s, Me), 4.29 (2 H, q, ^3J = 7.0 Hz, OMe), 4.31 (2 H, q, ^3J = 7.0 Hz, OMe), 7.34 (2 H, d, ^3J = 6.5 Hz, 2 CH), 7.38 (2 H, d, ^3J = 6.5 Hz, 2 CH), 8.30 (1 H, br-s, NH) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 14.1 (Me), 14.3 (Me), 19.1 (Me), 60.0 (OCH_2), 61.1 (OCH_2), 123.1 (C), 125.4 (C), 128.4 (C), 128.8 (2 CH), 128.9 (2 CH), 130.9 (C), 133.9 (C), 135.1 (C), 161.8 (C=O), 162.8 (C=O). $C_{17}H_{18}ClNO_4$, EI-MS: *m/z (%)* = 337 (M+2, 19), 335 (48), 291 (31), 289 (100), 261 (56), 260 (62), 189 (37), 111 (19).

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