Reaction of N-Methylimidazole and Dimethyl Acetylenedicarboxylate in the Presence of N-Phenyl Carbamate under Solvent-free Conditions

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An efficient synthesis of 1,2,3-functionalized imidazoles and dimethyl-2-[(alkoxycarbonyl)anilino]-2-butenedioate derivatives via one-pot reactions between N-methylimidazole, dimethyl acetylenedicarboxylate and N-phenylcarbamates under solvent-free conditions is described. The mild reaction conditions and good yields exhibit the synthetic advantage of this method.

Key words: N-Methylimidazole, Solvent-free, N-Phenylcarbamate 1,2,3-Functionalized Imidazoles

Introduction

Functionalized imidazoles are an important class of heterocyclic compounds in organic chemistry because they are common structural units in a number of natural products and pharmaceuticals and useful building blocks for the construction of various biologically active molecules and functional materials [1 – 3].

Imidazole-based drugs such as Cimetidine, Etomidate and Ketoconazole are currently in clinical use [4]. Imidazole derivatives are used for the synthesis of imidazole-tailored ionic liquids and stable nucleophilic carbenes [5 – 9]. Because of the wide range of pharmacological and biological activities, the synthesis of functionalized imidazoles has become an important target in recent years.

Here we developed an efficient one-pot route for the synthesis of 1,2,3-functionalized imidazoles and dimethyl-2-[(alkoxycarbonyl)anilino]-2-butenedioate derivatives via the reaction between N-methylimidazole (1), dimethyl acetylenedicarboxylate (2) and N-phenylcarbamates 3 under solvent-free conditions at room temperature to produce dimethyl-3-methyl-2-[(alkoxycarbonyl)anilino]-2,3-dihydro-1H-imidazol-1-yl]-2-butenedioates 4 and dimethyl-2-[(alkoxycarbonyl)anilino]-2-butenedioate derivatives 5 in 80 – 85% yield (Scheme 1).

The structures of the compounds were apparent from the 1H NMR, 13C NMR and IR spectra. The 1H NMR spectrum of 4a exhibited all expected signals at δ = 1.04, 1.68 and 4.10 ppm for the propyl moiety, three singlet peaks at δ = 3.68, 3.77 and 3.87 ppm for NMe and two methoxy groups, a singlet at δ = 6.12 ppm for an olefinic proton, and a singlet at 7.63 ppm for a CH that is bonded to three nitrogens, along with signals for the phenyl and imidazole units at 6.96 – 7.26 ppm. The proton-decoupled 13C NMR spectrum of 4a showed 17 distinct resonances in agreement with the proposed structure.

The stereochemistry of compound 4e has been confirmed by nuclear Overhauser effect (NOE) measurements. Thus, when the olefinic proton signal was irradiated, the signal of the imidazole H-2 was enhanced by about 21%, while both ester-OMe signals showed no significant enhancement. The stereochemistry thus deduced was also assumed for the other derivatives of 4.

The 1H NMR spectrum of 5a displayed five peaks at δ = 1.00, 1.63, 4.14, 3.68, 3.77, and 6.14 ppm along with characteristic multiplet signals for the phenyl moiety. The proton-decoupled 13C NMR spectrum of

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Scheme 1. Synthesis of compounds 4a-f and 5a-f.

Scheme 2. Possible mechanism for the formation of compounds 4 and 5.

5a showed signals in agreement with the proposed structure.

The stereochemistry of compound 5e is confirmed by nuclear Overhauser effect (NOE) measurements. Thus, when the OCH$_2$ protons signal was irradiated, the olefinic protons were enhanced by about 10%, while the OMe proton signal showed no significant enhancement. The stereochemistry thus deduced was also assumed for the other derivatives of 5.

A possible mechanism for this reaction is proposed in Scheme 2. The zwitterionic intermediate 6 produced from the reaction of N-methylimidazole and dialkyl acetylenedicarboxylate is subsequently protonated by an N-phenylcarbamate 3 and then attacked by the conjugate base of the carbamate to produce 4 and 5.

**Conclusion**

In conclusion we have reported a convenient one-pot route for the synthesis of 1,2,3-functionalized imidazoles and dimethyl-2-[(alkoxycarbonyl)anilino]-2-butenedioates by reaction of N-methylimidazole, dialkyl acetylenedicarboxylate and N-phenylcarbamates at solvent-free conditions and at room temperature.

**Experimental**

**General information**

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were obtained with a Bruker FT-500 spectrometer in
CDCl₃, and tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values. The acetylenic ester and N-methylimidazole were obtained from Fluka and were used without further purification.

**General procedure for the preparation of compounds 4a-f and 5a-f**

To a magnetically stirred mixture of an N-phenylcarbamate (2 mmol) and dimethyl acetylenedicarboxylate (2.2 mmol) was slowly added N-methylimidazole (1, 2 mmol), and the reaction mixture was stirred for 5 h at r.t. After completion of the reaction as indicated by TLC, the residue was purified by chromatography over silica gel (Merck 230–400 mesh) using an n-hexane-AcOEt mixture (6:1) as eluant to afford the pure compounds 4 and 5.

*Dimethyl [3-methyl-2-[(propoxycarbonyl)anilino]-2,3-dihydro-1H-imidazol-1-yl]-2-butenedioate (4a)*

Yellow oil; yield: 0.42 g (52%). – IR (KBr): ν = 1725 (C=O), 1705 (C=O), 2987 (CH) cm⁻¹. – 1H NMR: δ = 1.04 (t, 3 H, J = 6.9 Hz, CH₂), 1.68 (sextet, 2 H, J = 6.9 Hz, CH₂), 3.68 (s, 3 H, NCH₃), 3.77 (s, 3 H, OCH₂), 3.87 (s, 3 H, OCH₃), 4.10 (t, 2 H, J = 7.0 Hz, CH₂), 6.12 (s, 1 H, CH), 6.96–7.26 (m, 7 H, CH), 7.63 (s, 1 H, CH) ppm. – 13C NMR: δ = 10.3 (Me), 23.7 (CH₂), 38.7 (NMe), 51.7 (OMe), 52.0 (OMe), 61.1 (OCH₂), 68.2 (CH), 107.7 (CH), 120.6 (CH), 123.7 (2 CH), 124.5 (CH), 128.5 (CH), 129.0 (2 CH), 137.2 (C), 147.0 (C), 154.8 (C=O), 163.3 (C=O), 164.8 (C=O) ppm. – EI-MS: m/z (%): 403 (2) [M⁺]⁺, 226 (5), 178 (40), 144 (54), 120 (42), 43 (100). – Anal. for C₂₀H₂₁N₂O₆ (321.12): calcd. C 59.80, H 5.96, N 4.36; found C 59.83, H 5.97, N 4.32%.

*Dimethyl [3-methyl-2-[(isopropoxycarbonyl)anilino]-2,3-dihydro-1H-imidazol-1-yl]-2-butenedioate (5b)*

Yellow oil; yield: 0.18 g (28%). – IR (KBr): ν = 1724 (C=O), 1699 (C=O), 2987 (CH) cm⁻¹. – 1H NMR: δ = 1.21 (d, 3 H, J = 6.2 Hz, CH₃), 1.30 (d, 3 H, J = 6.3 Hz, CH₃), 3.67 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₂), 4.14–4.17 (heptet, 1 H, J = 7.0 Hz, CH), 6.12 (s, 1 H, CH), 7.24–7.60 (m, 5 H, 5 CH) ppm. – 13C NMR: δ = 21.0 (2 Me), 52.9 (OMe), 53.1 (OMe), 66.7 (OCH₂), 108.1 (CH), 123.1 (2 CH), 123.8 (CH), 128.9 (2 CH), 140.0 (C), 147.6 (C), 153.5 (C=O), 163.8 (C=O), 165.0 (C=O) ppm. – EI-MS: m/z (%): 321 (5) [M⁺]⁺, 178 (15), 144 (54), 43 (100). – Anal. for C₁₄H₁₉N₂O₆ (321.12): calcd. C 59.80, H 5.96, N 4.36; found C 59.83, H 5.97, N 4.32%.

*Dimethyl [3-methyl-2-[(butoxy carbonyl)anilino]-2,3-dihydro-1H-imidazol-1-yl]-2-butenedioate (4c)*

Yellow oil; yield: 0.45 g (56%). – IR (KBr): ν = 1722 (C=O), 1717 (C=O), 1700 (C=O), 2982 (CH) cm⁻¹. – 1H NMR: δ = 0.93 (s, 3 H, J = 7.1 Hz, CH₃), 1.52–1.54 (m, 2 H, CH₂), 1.68–1.71 (m, 2 H, CH₂), 3.69 (s, 3 H, NCH₃), 3.78 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₂), 4.15 (t, 2 H, J = 7.0 Hz, CH₂), 6.12 (s, 1 H, CH), 7.04–7.34 (m, 7 H, 7 CH), 7.61 (s, 1 H, CH) ppm. – 13C NMR: δ = 14.1 (Me), 22.7 (CH₂), 31.5 (CH₂), 38.5 (NMe), 51.6 (OMe), 52.1 (OMe), 61.3 (OCH₂), 68.3 (OCH), 106.7 (CH), 118.0 (CH), 123.0 (2 CH), 123.5 (CH), 127.1 (CH), 128.8 (2 CH), 139.1 (C), 146.0 (C), 153.6 (C=O), 162.8 (C=O), 164.5 (C=O) ppm. – EI-MS: m/z (%): 417 (2) [M⁺]⁺, 226 (7), 192 (39), 144 (53), 120 (41), 57 (100). – Anal. for C₁₇H₂₂N₂O₆ (417.19): calcd. C 60.42, H 6.52, N 10.07; found C 60.40, H 6.54, N 10.05%.
Dimethyl 2-([(butoxycarbonyl)anilino]-2-butenedioate (5c)

Yellow oil; yield: 0.19 g (29%). – IR (KBr): v = 1728 (C=O), 2981 (CH) cm⁻¹. – ¹H NMR: δ = 0.83 (t, 3 H, CH₃), 3.69 (s, 3 H, OCH₃), 6.14 (s, 1 H, CH), 7.38–7.59 (m, 5 H, 5 CH) ppm. – ¹³C NMR: δ = 13.0 (Me), 31.4 (CH₂), 53.0 (OMe), 53.1 (OMe), 66.7 (OCH₂), 108.0 (CH), 123.0 (2 CH), 123.4 (CH), 128.7 (2 CH), 128.9 (2 CH), 138.8 (C), 147.9 (C), 153.8 (C=O), 163.5 (C=O), 165.0 (C=O) ppm. – EI-MS: m/z(%) = 307 (5) [M]⁺, 192 (15), 144 (45), 57 (100). – Anal. for C₁₇H₂₃NO₆ (335.13): calc. C 60.89, H 6.31, N 4.18; found C 60.87, H 6.34, N 4.16%.

Dimethyl [3-methyl-2-[(butoxycarbonyl)anilino]-2,3-dihydro-1H-imidazol-1-yl]-2-butenedioate (4d)

Yellow oil; yield: 0.48 g (58%). – IR (KBr): v = 1726 (C=O), 1718 (C=O), 1706 (C=O), 2984 (CH) cm⁻¹. – ¹H NMR: δ = 1.01 (d, 6 H, 3 J = 6.8 Hz, 2 CH₃), 2.35–2.39 (m, 1 H, CH), 3.69 (s, 3 H, NCH₃), 3.78 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₃), 4.11 (d, 1 H, 3 J = 6.9 Hz, CH₂), 6.12 (s, 1 H, CH), 7.04–7.34 (m, 7 H, 7 CH), 7.65 (s, 1 H, CH) ppm. – ¹³C NMR: δ = 17.7 (Me), 17.9 (Me), 21.7 (CH), 37.1 (NMe), 51.9 (OMe), 52.0 (OMe), 58.5 (OCH₂), 67.1 (CH), 106.7 (CH), 118.0 (CH), 123.0 (2 CH), 123.5 (CH), 127.1 (CH), 128.8 (2 CH), 139.1 (C), 146.0 (C), 154.5 (C=O), 162.5 (C=O), 163.2 (C=O) ppm. – EI-MS: m/z(%) = 417 (5) [M]⁺, 226 (9), 192 (36), 144 (42), 57 (100). – Anal. for C₂₁H₂₇N₃O₆ (417.19): calc. C 60.42, H 6.52, N 10.07; found C 60.41, H 6.53, N 10.09%.

Dimethyl 2-[(isobutoxycarbonyl)anilino]-2-butenedioate (5d)

Yellow oil; yield: 0.18 g (27%). – IR (KBr): v = 1730 (C=O), 2985 (CH) cm⁻¹. – ¹H NMR: δ = 0.99 (d, 6 H, 3 J = 7.2 Hz, 2 CH₃), 2.31–1.34 (m, 1 H, CH), 3.68 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₃), 4.14 (d, 1 H, 3 J = 6.8 Hz, CH₂), 6.14 (s, 1 H, CH), 7.36–7.64 (m, 5 H, 5 CH) ppm. – ¹³C NMR: δ = 18.0 (2 Me), 21.7 (CH), 50.7 (OMe), 51.8 (OMe), 58.6 (OCH₂), 68.80 (CH), 108.0 (CH), 123.0 (2 CH), 123.4 (CH), 128.0 (2 CH), 138.8 (C), 147.9 (C), 156.5 (C=O), 163.2 (C=O), 165.0 (C=O) ppm. – EI-MS: m/z(%) = 335 (2) [M]⁺, 192 (157), 144 (47), 57 (100). – Anal. for C₁₇H₂₉NO₆ (335.13): calc. C 60.89, H 6.31, N 4.18; found C 60.91, H 6.30, N 4.20%.

Dimethyl [3-methyl-2-[(ethoxycarbonyl)anilino]-2,3-dihydro-1H-imidazol-1-yl]-2-butenedioate (5e)

Yellow oil; yield: 0.44 g (57%). – IR (KBr): v = 1721 (C=O), 1716 (C=O), 1696 (C=O), 2986 (CH) cm⁻¹. – ¹H NMR: δ = 1.25 (t, 3 H, 3 J = 6.8 Hz, CH₃), 3.68 (s, 3 H, NCH₃), 3.77 (s, 3 H, OCH₂), 3.87 (q, 2 H, 3 J = 7.0 Hz, CH₂), 6.12 (s, 1 H, CH), 6.98–7.24 (m, 3 H, 7 CH), 7.63 (s, 1 H, CH) ppm. – ¹³C NMR: δ = 13.5 (Me), 37.7 (NMe), 50.6 (OMe), 50.7 (OMe), 60.1 (OCH₂), 67.1 (CH), 106.7 (CH), 118.0 (CH), 122.3 (2 CH), 123.5 (CH), 127.2 (CH), 128.0 (2 CH), 137.5 (C), 146.0 (C), 153.8 (C=O), 162.2 (C=O), 163.7 (C=O) ppm. – EI-MS: m/z(%) = 389 (2) [M]⁺, 226 (8), 164 (41), 144 (52), 120 (40), 29 (100). – Anal. for C₁₉H₂₁N₃O₆ (389.16): calc. C 58.60, H 5.95, N 10.79; found C 58.61, H 5.94, N 10.81%.
59.6 (CH), 68.7 (CH), 108.0 (CH), 123.3 (2 CH), 127.7 (CH),
128.2 (2 CH), 140.0 (C), 147.2 (C), 154.5 (C=O), 163.0
(C=O), 164.7 (C=O) ppm. – EI-MS: m/z(%) = 361 (3)
[M]^+; 218(19), 144 (36), 83 (100). – Anal. for C_{19}H_{23}NO_6
(361.15): calcd. C 63.15, H 6.41, N 3.88; found C 63.13, H
6.43, N 3.86%.

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