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Application of N-methylimidazole for the Synthesis of Dimethyl-{3-methyl-2-[(alkoxycarbonyl) anilino]-2,3-dihydro-1*H*-imidazol-1-yl)}-2-butenedioate Derivatives

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Abstract

A one-pot synthesis ofdimethyl-{3-methyl-2-[(alkoxycarbonyl) anilino]-2,3-dihydro-1H-imidazol-1-yl)}-2-butenedioatesanddimethyl-2-[(alkoxycarbonyl)anilino]-2-butenedioates derivatives via reactions between dimethyl acetylenedicarboxylate,1-methylimidazoleand N-phenylcarbamates is described. The mild reaction condition, simple mixing of the starting materials and good yields exhibit the synthetic advantage of this method.

Keywords: *1-methylimidazole, Phenylcarbamate, 1, 2, 3-functionalized Imidazoles.*

Introduction

Imidazole and derivatives are a class of heterocyclic compounds that contain nitrogen and are currently under intensive focus due to their wide range of applications, because they have many pharmacological properties and play important roles in biochemicalprocesses [1,2]. The potential and wide range of application of the imidazole pharmacophore may be attributed to its hydrogen bond donor-acceptor ability as well as its high affinity for metals. Many of the substituted imidazoles are known as inhibitors of p38 MAP kinase, fungicides, herbicides, plant growth regulators, antibacterial, antitumour, pesticides and therapeutic agents [3-9]. In recent years, alkylated imidazoliums are substantially used in ionic liquids [10] that have been given a new approach to 'Green Chemistry'. The imidazole compounds were also used in photography as photosensitive compound [11]. They also serve as useful building blocks for the synthesis of other classes of compounds. Owing to the wide

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range of pharmacological and biological activities, the synthesis of imidazoles has become an important target in current years. Among them, tri- and tetrasubstituted imidazoles have received much attention recently, and new preparative methods have appeared [12-19].

Here we reported a one-pot and efficient route for the synthesis of 1,2,3-functionalized imidazoles anddimethyl-2-[(alkoxycarbonyl) anilino]-2-butenedioates derivatives via the reaction between 1-methylimidazole **1** dimethyl acetylenedicarboxylate **2** and N-phenylcarbamates3 at room temperature (Figure 1).

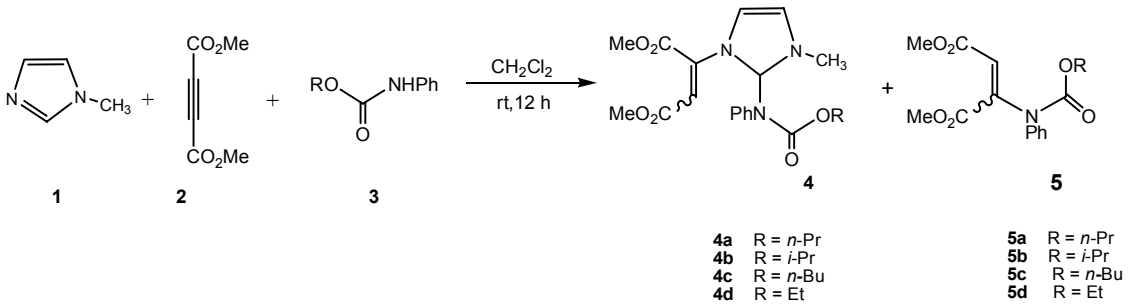

Figure 1. Synthesis of compounds **4** and **5**.

Experimental

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 $CDCl_3$ 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 Nicollet 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. Acetylenic ester and 1-methylimidazole were obtained from Fluka and were used without further purification.

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

To a magnetically stirred mixture of an N-phenylcarbamate **3** (2 mmol) and a dialkyl acetylenedicarboxylate **2** (2 mmol) in CH_2Cl_2 (5 mL), was slowly added 1-methylimidazole1 (2 mmol) and the reaction mixture was stirred for 12 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 adducts.

Results and discussion

The reaction of 1-methylimidazole **1** dialkyl acetylenedicarboxylates2 and N-phenylcarbamates **3** proceeds smoothly at room temperature to produce dimethyl-{3-methyl-2-[(alkoxycarbonyl)anilino]-2,3-dihydro-1*H*-imidazol-1-yl)}-2-butenedioates **4** and dimethyl-2-[(alkoxycarbonyl)anilino]-2-butenedioates **5** derivatives in 80-85 % yield (Figure 1).

The structures of compounds were characterized on the basis of their ^{1}H NMR ^{13}C NMR and IR spectra. The ^{1}H NMR spectrum of **4a** exhibited all expected signals at δ = 0.92, 1.65 and 4.04 ppm for propyl moiety and three singlet peek at δ = 3.58, 3.72 and 3.87 ppm for NMe and two methoxy groups and two singlet at δ = 6.10 and 6.70 ppm along with signals for the phenyl and imidazole at 6.96–7.26 ppm. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the proposed structure.

The 1H NMR spectrum of **5a** displayed five peek at δ = 0.86, 1.53, 4.14, 3.68, 3.77 and 6.12 ppm along with characteristic multiplet signals for the phenyl moiety. The proton-decoupled 13C NMR spectrum of 5a showed signals in agreement with the proposed structure.

A possible mechanism for this reaction is proposed in Figure 2.

The zwitterionic intermediate **6** were produced from the reaction of 1-methylimidazole and dialkyl acetylenedicarboxylate [20] that is subsequently protonated by the N-phenylcarbamates 3 and then attacked by the conjugate base of the carbamate to produce **4** and **5** (Figure 2).

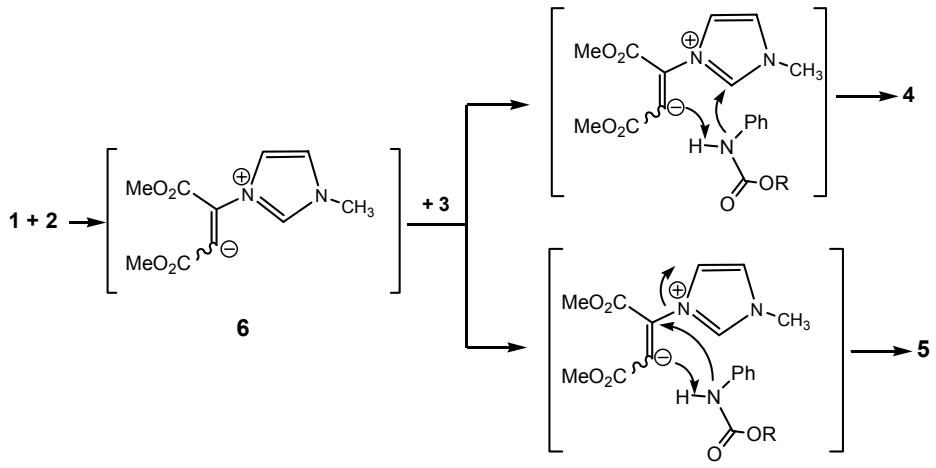

Figure 2. Possible mechanism for the formation of compounds **4** and **5**.

Conclusion

In conclusion we have reported a one-pot and efficientmethod for the synthesis of dimethyl-{3-methyl-2-[(alkoxycarbonyl) anilino]-2,3-dihydro-1*H*-imidazol-1-yl)}-2-butene-dioates anddimethyl-2-

[(alkoxycarbonyl)anilino]-2-butenedioates by reaction of 1-methylimidazole dialkyl acetylenedicarboxylateand *N*-phenylcar bamates at r. t. The advantage of the present procedure is that the reaction is performed at r.t. by simple mixing of the starting materials.

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

Yellow oil yield: 0.40 g (50%). IR (KBr): ν = 1721 (C=O), 1718(C=O), 1706 (C=O), 2989 (CH) cm $^{-1}$. ^{1}H NMR: δ = 0.92 (t,^{3}J = 6.8, CH_3), 1.65 (sixtet,^{3}J = 6.9, CH2), 3.58 (s, NCH_3), 3.72 (s, OCH3), 3.87 (s, OCH3), 4.04 (t,^{3}J = 7.0, CH_2), 6.10 (CH), 6.70 (CH), 6.96–7.26 (m, 8 CH) ppm. ^{13}C NMR: δ = 10.3 (Me), 22.0 (CH_2), 38.7 (NMe), 51.7 (OMe), 52.0 (OMe), 61.0 (OCH_2), 68.2 (CH), 107.7 (CH), 118.6 (CH), 120.6 (2CH), 123.8 (CH), 129.6 (2CH), 137.2 (C), 147.1 (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 $C_{20}H_{25}N_3O_6$ (403.17): calcd. C 59.54, H 6.25%; found C 59.55, H 6.23 %.

*Dimethyl-2-[(propoxycarbonyl)anilino]-2-butenedioates (**5a**)*

Yellow oil yield: 0.23 g (35%). IR (KBr): ν = 1720 (C=O), 1716(C=O), 1696 (C=O), 2985 (CH) cm $^{-1}$. ^{1}H NMR: δ = 0.83 (t,^{3}J = 7.1, CH_3), 1.53 (sixtet,^{3}J = 6.9, CH_2), 3.68 (s, OCH_3), 3.77 (s, OCH_3), 4.14 (t,^{3}J = 7.1, CH_2), 6.12 (CH), 7.26-7.63 (m, 6 CH) ppm. ^{13}C NMR: δ = 10.4 (Me), 22.3 (CH_2), 52.9 (OMe), 53.1 (OMe), 66.8 (OCH_2), 108.0 (CH), 123.3 (2CH), 124.0 (CH), 128.8 (2CH), 140.7 (C), 147.6 (C), 153.5 (C=O), 163.8 (C=O),165.0 (C=O) ppm. EI–MS: *m/z* (%) = 321 (3) [M]+, 178 (12), 144 (40), 43 (100). Anal. for $C_{16}H_{19}NO_6$ (321.12): calcd. C 59.80, H 5.96 %; found C 59.83, H 5.97 %.

*Dimethyl-{3-methyl-2-[(isopropoxycarbonyl) anilino]-2,3-dihydro-1H-imidazol-1-yl)}-2-butenedioates (**4b**)*

Yellow oil yield: 0.42 g (52 %). IR (KBr): ν = 1725 (C=O), 1705 (C=O), 2983 (CH) cm^{-1}. ^{1}H NMR: δ = 1.21 (d,^{3}J = 6.5, CH_3), 1.31 (d,^{3}J = 6.5, CH_3), 3.69 (s, NCH_3), 3.78 (s, OCH_3), 3.88 (s, OCH_3), 4.13 (t,^{3}J = 7.1, CH), 6.10 (CH), 6.64 (CH), 7.00–7.30 (m, 8 CH) ppm. ^{13}C NMR: δ = 21.5 (2Me), 38.5 (NMe), 51.6 (OMe), 52.1 (OMe), 61.5 (OCH_2), 68.6 (CH), 106.9 (CH), 118.1 (CH), 122.0 (2CH), 123.8 (CH), 129.0 (2CH), 137.4 (C), 147.5 (C), 154.0 (C=O), 163.2 (C=O),164.5 (C=O) ppm. EI–MS: *m/z* (%) = 403 (3) [M]+,226 (6), 178 (35),144 (49), 120 (41), 43 (100).Anal. for $C_{20}H_{25}N_3O_6$ (403.17): calcd. C 59.54, H 6.25%; found C 59.55, H 6.24 %.

*Dimethyl-2-[(isopropoxycarbonyl)anilino]-2-butenedioates (**5b**)*

Yellow oil yield: 0.18 g (28 %). IR (KBr): ν = 1724 (C=O), 1699 (C=O), 2987 (CH) cm $^{-1}$. ^{1}H NMR: δ = 1.19 (d,^{3}J = 6.2 CH_3), 1.28 (d,^{3}J = 6.3 CH_3), 3.68 (s, OCH_3), 3.77 (s, OCH_3), 4.14 (t,^{3}J = 6.9, CH_2), 6.12 (CH), 7.24-7.60 (m, 6 CH) ppm. ^{13}C NMR: δ = 21.0 (2Me), 52.9 (OMe), 53.1 (OMe), 66.7 (OCH_2), 108.1 (CH), 123.1 (2CH), 123.9 (CH), 128.9 (2CH), 140.7 (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 $C_{16}H_{19}NO_6$ (321.12): calcd. C 59.80, H 5.96 %; found C 59.83, H 5.97 %.

*Dimethyl-{3-methyl-2-[(butoxycarbonyl) anilino]-2,3-dihydro-1H-imidazol-1-yl)}-2-butenedioates(**4c**)*

Yellow oil yield: 0.45 g (56 %). IR (KBr): ν = 1722 (C=O), 1717(C=O), 1700 (C=O), 2982 (CH) cm $^{-1}$. ^{1}H NMR: δ = 0.95 (t,^{3}J = 7.2, CH_3), 1.52–1.54 (m, CH_2), 1.68–1.71 (m, CH_2), 3.69 (s, NCH_3), 3.78 (s, OCH_3), 3.88 (s, OCH_3), 4.15 (t,^{3}J = 7.0, CH_2), 6.12 (CH), 6.70 (CH), 7.04–7.34 (m, 8 CH) ppm. ^{13}C NMR: δ = 14.1(Me), 22.7 (CH_2), 31.5 (CH_2), 38.5 (NMe), 51.6 (OMe), 52.1 (OMe), 61.3 (OCH_2), 68.3 (CH), 107.2 (CH), 118.6 (CH), 121.6 (2CH), 123.9 (CH), 129.4 (2CH), 137.2 (C), 147.0 (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 $C_{21}H_{27}N_3O_6$ (417.19): calcd. C 60.42, H 6.52 %; found C 60.40, H 6.54 %.

*Dimethyl-2-[(butoxycarbonyl)anilino]-2-butenedioates (**5c**)*

Yellow oil yield: 0.19 g (29 %). IR (KBr): ν = 1728 (C=O), 2981 (CH) cm $^{-1}$. ^{1}H NMR: δ = 0.87 (t,^{3}J = 7.2, CH_3), 1.48–1.51 (m, CH_2), 1.58–1.65 (m, CH_2), 3.68 (s, OCH_3), 3.77 (s, OCH_3), 4.17 (t,^{3}J = 7.1, CH_2), 6.14 (CH), 7.34-7.64 (m, 6 CH) ppm. ^{13}C NMR: δ = 14.0 (Me), 23.0 (CH_2), 31.4 (CH_2), 53.0 (OMe), 53.1 (OMe), 66.7 (OCH_2), 108.0 (CH), 123.1 (2CH), 124.2 (CH), 128.7 (2CH), 139.8 (C) 147.3 (C), 153.7 (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 $C_{17}H_{21}NO_6$ (335.13): calcd. C 60.89, H 6.31 %; found C 60.87, H 6.34 %.

*Dimethyl-{3-methyl-2-[(etoxycarbonyl) anilino]-23-dihydro-1H-imidazol-1-yl)}-2-butene-dioates (**4d**)*

Yellow oil yield: 0.44g (57 %). IR (KBr): ν = 1721 (C=O), 1716(C=O), 1696 (C=O), 2986 (CH) cm $^{-1}$. ^{1}H NMR: δ = 0.81 (t,^{3}J = 6.8, CH_3), 3.68 (s, NCH_3), 3.77 (s, OCH_3), 3.87 (s, OCH_3), 4.13 (q,^{3}J = 7.0, CH_2), 6.10 (CH), 6.62 (CH), 6.96–7.24 (m, 8 CH) ppm. ^{13}C NMR: δ = 13.5 (Me), 37.7 (NMe), 50.6 (OMe), 50.7 (OMe), 60.1 (OCH_2), 67.1 (CH), 106.7 (CH), 118.0 (CH), 122.3 (2CH), 123.0 (CH), 128.0 (2CH), 137.0 (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 $C_{19}H_{23}N_3O_6$

(389.16): calcd. C 58.60, H 5.95 %; found C 58.61, H 5.94 %.

*Dimethyl-2-[(etoxycarbonyl)anilino]-2-butenedioates (**5d**)*

Yellow oil yield: 0.17 g (28 %). IR (KBr): ν = 1732 (C=O), 1710 (C=O),2990 (CH) cm^{-1}. ^1H NMR: δ = 0.84 (t,^3J = 7.1, CH_3), 3.67 (s, OCH_3), 3.76 (s, OCH_3), 4.20 (q,^3J = 7.1, CH_2), 6.12 (CH), 7.25-7.70 (m, 6 CH) ppm. 13C NMR: δ = 13.1 (Me), 51.8 (OMe), 51.9 (OMe), 60.0 (OCH_2), 108.0 (CH), 123.5 (2CH), 124.3 (CH), 129.0 (2CH), 140.7 (C), 146.6 (C), 153.1 (C=O), 162.5 (C=O),164.0 (C=O) ppm. EI–MS: *m/z* (%) = 307 (2)[M]+, 164 (17), 144 (43), 29 (100). Anal. for $C_{15}H_{17}NO_6$ (307.16): calcd. C 58.63, H 5.58 %; found C 58.62, H 5.59 %.

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