Synthesis of alkyl 2-(benzoylamino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoates

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Abstract
A simple synthetic approach to imidazolyl-substituted unsaturated amino acid esters **2** starting from the diaminomaleonitrile derivative **5** is reported. This synthesis involves the formation of the imidazole ring with triethyl orthoformate followed by an oxazolone ring-opening reaction with alcohols.

Keywords: Imidazole, didehydroamino acid ester, oxazolone ring-opening

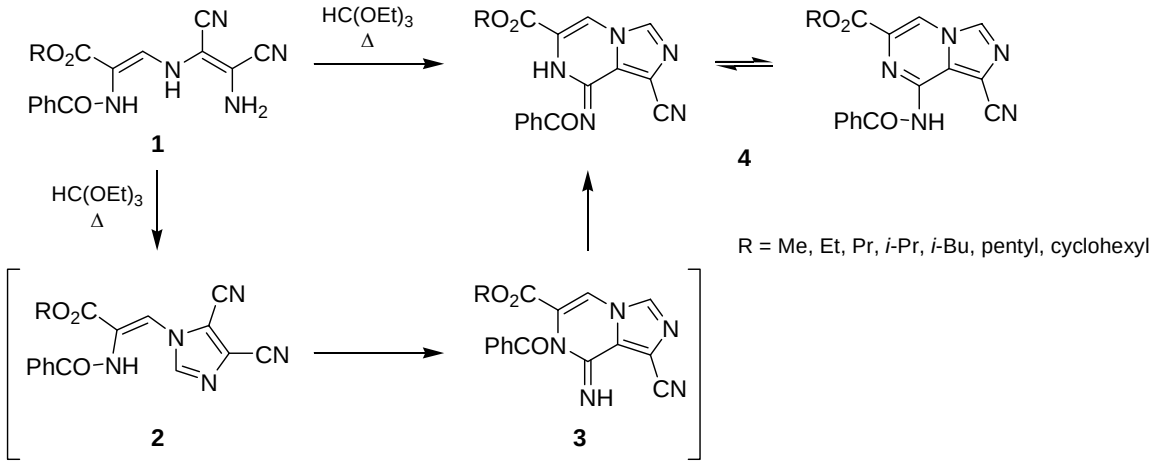
Introduction

Amino acids containing the imidazole moiety and their derivatives represent a well-known group of organic compounds. Beside L-histidine and its derivatives, several structurally related non-proteinogenic amino acids and their derivatives have been the subject of various investigations. Among them are (1*H*-imidazol-1-yl)-substituted amino acid derivatives. For example, 2-amino-3-(1*H*-imidazol-1-yl)propanoic acid and its derivatives have been prepared by the ring-opening reaction of serine β-lactone derivatives with 1-(trimethylsilyl)imidazole[1] or imidazole,[2] or by conjugate addition of imidazole to didehydroalanine derivatives,[3–6] and has been used in studies concerning the design of orally active renine inhibitors.[2] This amino acid has also been synthesized by the condensation of diethyl α-acetamido-α-(dimethylaminomethyl)malonate methiodide with sodium imidazole in liquid ammonia; and the biological activity concerning the ability to support the growth of a histidine-requiring bacterial mutant has been examined.[7] 2-Amino-3-(4-carboxy-1*H*-imidazol-1-yl)propanoic acid prepared by the β-lactone route has been examined as an inhibitor of diaminopimelic acid dehydrogenase from *Bacillus sphaericus* and of diaminopimelic acid epimerase from *Escherichia coli*.[8] (2,4-Dioxoimidazolidin-1-yl)alanine derivatives have been formed via the corresponding ureidoalanine intermediate in the course of investigations of the synthesis of quisqualic acid analogues.[9] 2-Amino-3-(1*H*-imidazol-1-yl)propanoic acid was found to be incorporated into theonellamide F, a bicyclic dodecapeptide

isolated from a marine sponge of the genus *Theonella*, which exhibits antifungal and cytotoxic activities.[10] Its derivatives were synthesized by the β-lactone route.[11] Additionally, the syntheses of ethylene-bridged analogues of arginine have also been reported.[12]

On the other hand, relatively little is known about 1*H*-imidazol-1-yl substituted α,β-didehydroamino acid derivatives. The most frequently investigated derivatives of this type were obtained by the Michael addition of imidazole or protected histidine to *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-toluenesulfonyl)-α,β-didehydro-α-amino acid esters followed by spontaneous detosylation of the Michael products.[13–15]

In the course of our investigations of the use of diaminomaleonitrile in heterocyclic synthesis we reported a new approach to 1,2,3-triazol-1-yl-substituted unsaturated amino acid derivatives.[16] Attempts to prepare structurally similar imidazolyl amino esters **2** by treatment of propenoates **1** with triethyl orthoformate at reflux temperature failed, giving rise to highly functionalized imidazo[1,5-*a*]pyrazines **4**, probably via intermediates **2** and **3** (Scheme 1).[17]



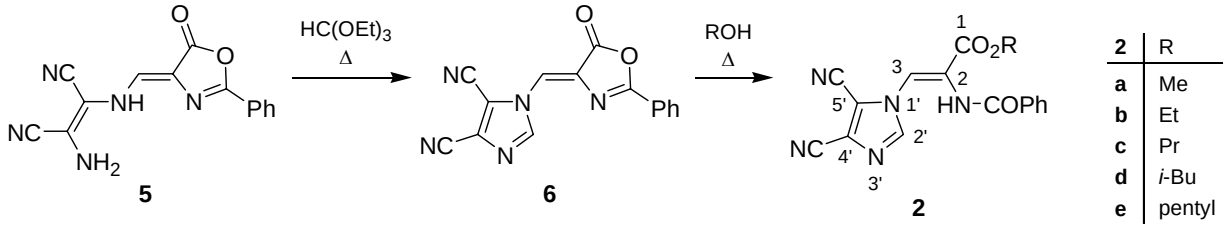
Scheme 1

In order to study the mechanism of the above mentioned formation of **4** and to characterize the imidazole esters **2**, we looked for an alternative method of their preparation. Accordingly, we report here an easy approach to imidazole esters **2** based on the oxazolone ring-opening of the bicyclic compound **6** (Scheme 2).

Results and Discussion

The reaction of the *N*-monosubstituted diaminomaleonitrile derivative **5**[16] with hot triethyl orthoformate afforded 1-(4,5-dihydro-5-oxo-2-phenyl-1,3-oxazol-4-ylidenemethyl)-1*H*-imidazole-4,5-dicarbonitrile **6**. The subsequent careful treatment of this intermediate **6** with a series of alcohols (methyl, ethyl, propyl, isobutyl, and pentyl alcohol) resulted in the opening of the oxazolone ring

affording the corresponding esters **2** in moderate yields. In order to avoid further cyclization of **2** to the imidazo[1,5-*a*]pyrazine system or other side reactions of the multifunctional products **2** and starting compound **6**, all reactions were performed in the absence of acid or base catalyst.



Scheme 2

The structure of products **2** was established on the basis of NMR spectroscopy (^{1}H, ^{13}C, HMBC, HMQC), MS, IR data and elemental analysis. It is worth noting that imidazoles **2** are isomers of imidazo[1,5-*a*]pyrazines **3** and **4** with similar functionalities. The IR spectra of **2** show two absorption bands between 2220–2250 cm^{-1} clearly indicating the presence of two nitrile groups in contrast to the isomeric imidazopyrazines **3** and **4** with only one nitrile group. Differences are also evident in the ^{1}H NMR spectra of isomers **2** and **4**: While imidazopyrazines **4** exhibit two sets of signals of two tautomeric forms (Scheme 1),[17] imidazoles **2** show only one set. HMBC and HMQC spectra were used for the partial assignment of ^{13}C signals of **2e**. The HMBC spectrum of **2e** shows strong correlations between the NH proton and the carbonyl carbon atoms of both the benzoyl and ester groups. The *Z* configuration of the olefinic bond of. compounds **2** was established by the magnitude of the long-range heteronuclear coupling constant between the carbonyl carbon atom and the 3-H proton of **2a** ($^3J_{C–H}$ = 4.0 Hz) measured from the antiphase splitting of cross peaks in the HMBC spectra. A similar value was found in the diaminomaleonitrile derivative **1** (R = propyl) ($^3J_{C–H}$ = 3.0 Hz).[18] Coupling constants of this magnitude are characteristic of the *cis* orientation of the carbonyl group and the 3-H proton of the double bond.[19–21]

In conclusion, we elaborated an easy procedure for the preparation of alkyl 2-(benzoyl-amino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoates **2**. These products can be transformed into the imidazo[1,5-a]pyrazines **4**,[22] and are therefore probable intermediates in the one-pot transformation of **1** into **4**. They may be useful starting compounds for the preparation of new histidine analogues.

Experimental Section

General Procedures. Melting points were determined on a Kofler micro hot stage apparatus. IR spectra were recorded with a Perkin-Elmer 1310 or 727 B spectrophotometer. NMR spectra were recorded with a Bruker AVANCE DPX-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for

^{13}C) in DMSO-d_6 with TMS as an internal standard; coupling constants (J) are given in Hz. MS spectra were obtained from a VG-Analytical AutoSpec Q instrument (70 eV). Elemental analyses were performed on a Perkin-Elmer CHN Analyzer 2400. Compound **5** was prepared as described in the literature.[16] All other compounds were used without purification as obtained from commercial sources.

1-(4,5-Dihydro-5-oxo-2-phenyl-1,3-oxazol-4-ylidenemethyl)-1*H*-imidazole-4,5-dicarbonitrile (6). A mixture of **5** (558 mg, 2 mmol) and triethyl orthoformate (6 mL) was heated at reflux temperature for 2 h. After cooling, the precipitate was filtered off to give **6** (468 mg, 81%) as a pale yellow solid, mp 240–243 °C (acetone). IR (KBr): $\tilde{\nu}$ 3120, 2230, 1800, 1670, 1580, 1550, 1460, 1385, 1370, 1320, 1290, 1225, 1185, 975, 870, 700 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65 (3H, m, 2 H_{Ph}, HC=), 7.79 (1H, m, H_{Ph}), 8.24 (2H, m, H_{Ph}), 9.32 (1H, s, 2-H). Anal. Calcd. for $C_{15}H_7N_5O_2 \cdot 1/3\ H_2O$: C, 61.02; H, 2.62; N, 23.72. Found: C, 61.05; H, 2.57; N, 23.77.

Methyl (*Z*)-2-(benzoylamino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoate (2a). A mixture of **6** (1.16 g, 4 mmol) and methyl alcohol (50 mL) was heated at reflux temperature for 6 h. After cooling, the precipitate was filtered off and washed with a small amount of methyl alcohol to give **2a** (0.545 g, 42%) as a white solid, mp 163–165 °C (methyl alcohol). IR (KBr): $\tilde{\nu}$ 3230, 3110, 2250, 2230, 1715, 1650, 1475, 1435, 1365, 1335, 1285, 1215, 970, 850, 750, 735 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.81 (3H, s, CH_3), 7.58 (4H, m, 3 H_{Ph}, H-3), 7.84 (2H, m, H_{Ph}), 8.56 (1H, s, H-2'), 10.38 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 53.9 (CH_3), 108.9 (CN), 112.9 (CN), 113.3 (5'-C), 120.7 (3-C), 122.7 (4'-C), 128.8 (2,6-C_{Ph}), 129.0 (2-C), 129.4 (3,5-C_{Ph}), 133.3 (4-C_{Ph}), 133.3 (1-C_{Ph}), 144.0 (2'-C), 164.1 (1-C), 166.7 (CONH). MS (EI): *m/z* (%) 321 (9) [M^+]. Anal. Calcd. for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.95; H, 3.38; N, 21.92.

Ethyl (*Z*)-2-(benzoylamino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoate (2b). A mixture of **6** (867 mg, 3 mmol) and ethyl alcohol (30 mL) was heated at reflux temperature for 4.5 h. After cooling, the precipitate was filtered off and washed with a small amount of ethyl alcohol to give **2b** (721 mg, 71%) as a white solid, mp 170–172 °C (ethyl alcohol). IR (KBr): $\tilde{\nu}$ 3220, 3100, 2240, 2220, 1710, 1640, 1470, 1430, 1360, 1330, 1280, 1210, 970, 850, 750, 735 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (3H, t, J =7.0 Hz, CH_3), 4.27 (2H, q, J = 7.0 Hz, CH_2), 7.53 (3H, m, 2 H_{Ph}, 3-H), 7.63 (1H, m, H_{Ph}), 7.83 (2H, m, H_{Ph}), 8.56 (1H, s, 2'-H), 10.36 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 13.9, 61.9, 108.0, 112.0, 112.3, 119.5, 121.7, 127.8, 128.4, 128.5, 132.4, 132.5, 143.1, 162.6, 165.8. MS (EI): *m/z*, (%) 335 (13) [M^+]. Anal. Calcd. for $C_{17}H_{13}N_5O_3$: C, 60.89; H, 3.91; N, 20.89. Found: C, 60.55; H, 3.91; N, 20.48.

Propyl (*Z*)-2-(benzoylamino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoate (2c). A mixture of **6** (1.16 g, 4 mmol) and propyl alcohol (50 mL) was heated at reflux temperature for 1.5 h. After cooling, the precipitate was filtered off and washed with a small amount of ethyl alcohol to give **2c** (815 mg, 58 %) as a white solid, mp 150–152 °C (propyl alcohol). IR (KBr): $\tilde{\nu}$ 3250, 3110, 2970, 2250, 2230, 1720, 1680, 1650, 1500, 1480, 1315, 1295, 1220, 740 cm^{-1}. ^{1}H NMR (300

MHz, DMSO-d_6): δ 0.90 (3H, t, J = 7.4 Hz, CH_3), 1.65 (2H, m, CH_2), 4.18 (2H, t, J = 6.6 Hz, CH_2), 7.53 (3H, m, 2 H_{Ph}, 3-H), 7.62 (1H, m, Ph), 7.83 (m, 2H, H_{Ph}), 8.57 (1H, s, 2'-H), 10.37 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 10.2, 21.4, 67.3, 108.0, 112.0, 112.4, 119.6, 121.7, 127.8, 128.4, 128.5, 132.4, 132.5, 143.1, 162.8, 165.9. MS (EI): *m/z* (%) 349 (37) [M^+]. Anal. Calcd. for $C_{18}H_{15}N_5O_3$: C, 61.89; H, 4.33; N, 20.05. Found: C, 61.66; H, 4.37; N, 20.05.

Isobutyl (*Z*)-2-(benzoylamino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoate (2d). A mixture of **6** (1.16 g, 4 mmol) and isobutyl alcohol (50 mL) was heated at reflux temperature for 3 h. After cooling, the precipitate was filtered off and washed with a small amount of ethyl alcohol to give **2d** (570 mg, 39%) as a white solid, mp 154–156 °C (isobutyl alcohol). IR (KBr): $\tilde{\nu}$ 3250, 2950, 2230, 2220, 1710, 1655, 1640, 1490, 1465, 1370, 1285, 1205, 970, 730 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.90 (6H, d, J = 6.8 Hz, 2 CH_3), 1.93 (1H, m, CH), 4.02 (2H, d, J = 6.4 Hz, CH_2), 7.57 (4H, m, 3 H_{Ph}, 3-H), 7.84 (2H, m, H_{Ph}), 8.58 (1H, s, 2'-H), 10.38 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.7, 27.2, 71.5, 108.0, 112.0, 112.4, 119.7, 121.7, 127.8, 128.4, 128.5, 132.4, 132.5, 143.2, 162.7, 166.0. MS (EI): *m/z* (%) 363 (7) [M^+]. Anal. Calcd. for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found: C, 62.68; H, 4.86; N, 19.25.

Pentyl (*Z*)-2-(benzoylamino)-3-(4,5-dicyano-1*H*-imidazol-1-yl)propenoate (2e). A mixture of **6** (868 mg, 3 mmol) and pentyl alcohol (5 mL) was heated at reflux temperature for 18 min. After cooling, the precipitate was filtered off and washed with a small amount of methyl alcohol to give **2e** (354 mg, 31%) as a white solid, mp 139–140 °C (ethyl alcohol). IR (KBr): $\tilde{\nu}$ 3220, 3100, 2940, 2920, 2230, 2220, 1710, 1650, 1470, 1330, 1300, 1210, 960, 680 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81 (3H, t, J = 7.1 Hz, CH_3), 1.28 (4H, m, 2 CH_2), 1.62 (2H, m, CH_2), 4.21 (2H, t, J = 6.6 Hz, CH_2), 7.53 (3H, m, 2 H_{Ph}, 3-H), 7.63 (1H, m, H_{Ph}), 7.83 (2H, m, H_{Ph}), 8.57 (1H, s, 2'-H), 10.37 (1H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 13.7 (CH_3), 21.6 (CH_2), 27.4 (CH_2), 27.6 (CH_2), 65.8 (CH_2), 108.0 (CN), 112.0 (CN), 112.4 (5'-C), 119.5 (3-C), 121.7 (4'-C), 127.8 (2,6-C_{Ph}), 128.5 (2-C, 3,5-C_{Ph}), 132.4 (4-C_{Ph}), 132.5 (1-C_{Ph}), 143.1 (2'-C), 162.8 (1-C), 165.9 (CONH). MS (EI): *m/z* (%) 377 (10) [M^+]. Anal. Calcd. for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.73; H, 5.08; N, 18.61.

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