Synthesis of unsaturated amidine derivatives by three component reaction of alkyl isocyanides, dialkyl acetylenedicarboxylates and pyrrole or indole

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The reactive intermediate generated by the reaction of alkyl isocyanides and dialkyl acetylenedicarboxylates was trapped by pyrrole or indole to produce unsaturated amidine derivatives in good yields.

Keywords: isocyanides, acetylenic esters, amidines, pyrrole, indole

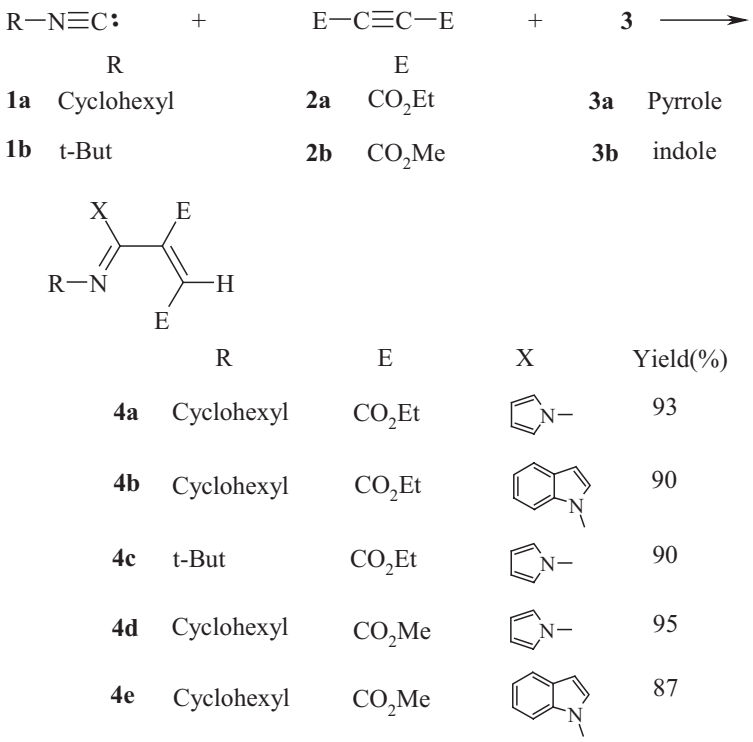
Isocyanides, by virtue of their carbenoid character, react readily with most common multiple bonds.[1-3] The reaction of isocyanides with carbon–carbon triple bonds tends to occur in a stepwise manner initiated by formation of a zwitterionic intermediate whose ultimate fate appears to be dictated by the nature of the original triple-bonded substrate.[4] These reactions are of interest for the synthesis of functionalised heterocyclic ring systems.[5] The reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of different electrophiles, in order to trap the zwitterionic intermediate, has been well documented.[6-9] In the presence of alcohols, ketenimine and unsaturated iminoesters were obtained as main products.[7] The products of the reaction between isocyanides and dimethyl acetylenedicarboxylate in the presence of naphthols and phenols are respectively benzochromene[8] and chromene[9] derivatives, formed via ketenimine intermediates. Other reports exist of the reaction of isocyanides with acetylenic esters in the presence of organic NH-acids; all produce ketenimines as intermediate or final products.[10] Syntheses of unsaturated amidines have been already reported in Pd-catalysed three component reactions using isocyanides.[11]

The reaction between isocyanides and dialkyl acetylenedicarboxylates, in the presence of NH-acid, pyrrole, indole and carbazole has been reported to afford unsaturated amidines.[12] Here we report the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of pyrrole or indole as NH-acids, to yield new unsaturated amidines as the only products in fairly good yields.

The reaction of cyclohexyl isocyanide with diethyl acetylenedicarboxylate in the presence of pyrrole afforded diethyl 2-(cyclohexyliminopyrrol-1-ylmethyl) but-2-enedioate **4a** in 93 % yield (Scheme 1).

On the basis of the well established chemistry of isocyanides[1-5] it is reasonable to assume that compound **4a** results from an initial addition of the cyclohexyl isocyanide to diethyl acetylenedicarboxylate and subsequent protonation of the 1: 1 adduct by pyrrole (Scheme 2). Then, the positively charged ion **5** is attacked by the conjugate anion of pyrrole **6** to yield product **4a**.

Structure **4a** was assigned to the isolated product on the basis of its elemental analysis and IR, ^{1}H NMR, ^{13}C NMR, HETCOR, and mass spectral data. The mass spectrum of **4a**



Scheme 1

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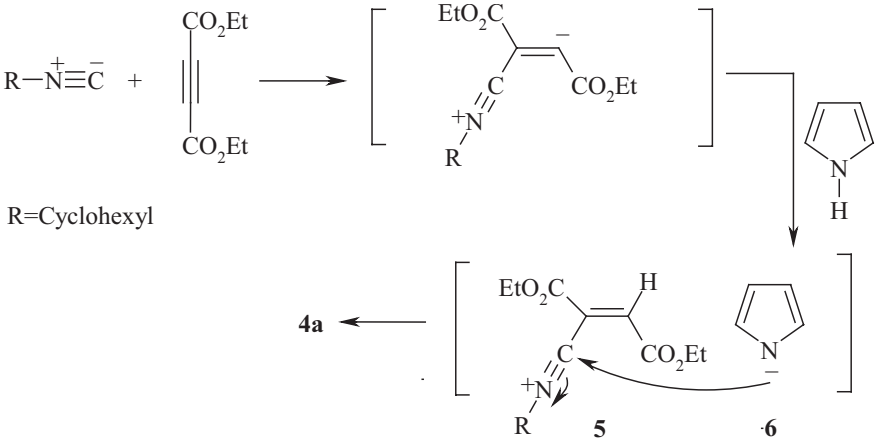


Scheme 2

exhibits a molecular ion peak at *m/z* 346, consistent with a 1: 1: 1 adduct of **1a**, **2a**, and **3a**. The ^{1}H NMR spectrum of **4a** displays two triplets for methyl protons at δ = 0.9 and 1.1 ppm, multiplets for cyclohexyl methylene protons at 1.1–1.6 ppm, two multiplets for methylene protons of ethyl groups at 3.9 and 4.1 ppm, and a multiplet for the methine proton of the cyclohexyl group at 2.9 ppm. The hydrogens of the pyrrole moiety appear as triplets at δ = 6.0 and 6.9. A singlet is observed at 7.0 ppm for an olefinic proton. The chemical shift of the olefinic proton is consistent with the *Z*-geometry of the carbon–carbon double bond.[13a]

A significant feature of the ^{1}H NMR spectrum of **4a** in $CDCl_3$ at room temperature (25 °C) is the methylenes of ethyl groups which appear as multiplets instead of quartets. Decreasing the temperature to –45 °C, the methylene protons exhibit three multiplets at 3.9, 4.1, and 4.3 ppm with integrals in 2: 1: 1 ratio. The ^{1}H NMR spectrum of **4a** at –45 °C also shows a fairly broad signal for the cyclohexyl methine proton, and broad singlets are also observed for the pyrrole protons. The signals of the cyclohexyl methylene protons are also completely broadened at –45 °C. At + 50 °C two sharp triplets at 6.1 and 7.1 ppm are observed in the ^{1}H NMR spectrum of **4a** for the pyrrole hydrogens. The ethyl methylene protons appear still as multiplets. The ^{13}C NMR spectrum of **4a** at + 50 °C shows 15 sharp signals, consistent with the proposed structure. This behaviour of the NMR spectra of **4a** arises from restricted rotation around the carbon–carbon single bond (Scheme 3). This causes the molecule to become chairal and consequently the ethyl methylene hydrogens and cyclohexyl methylenes become diastereotopic. Similar restriction of rotation about sp^2–sp^2 carbon–carbon single bond is well established for other sterically congested butadiene derivatives.[13b]

Rotation of pyrrole ring around the N–C single bond is also restricted at low temperatures, resulting in broadening of the signals related to this residue in ^{1}H NMR spectra.

When the pyrrole ring is replaced by indole, in **4b**, broadening of signals in both ^{13}C NMR and ^{1}H NMR spectra is observed even at room temperature, showing that rotation related to the larger indole moiety is still more restricted. The broadening of signals is also observed when the cyclohexyl group is replaced by *t*-butyl, in **4c**, showing that the observed behaviour does not arise from ring inversion.

In conclusion, the three-component reaction between alkyl isocyanides, dialkyl acetylenedicarboxylates and pyrrole or indole furnishes a simple one-pot route to substituted unsaturated amidines. The reaction is performed under neutral conditions, without any activation or modification of the reactants.

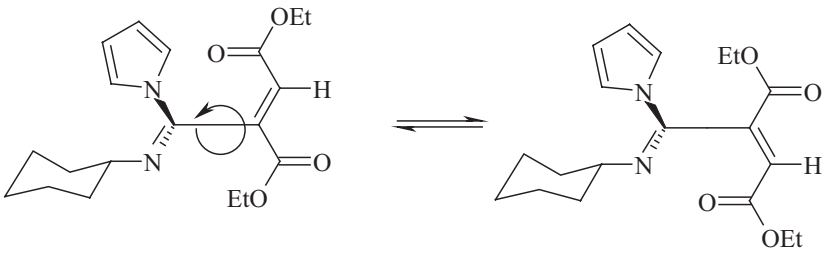
Experimental

Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser at the Islamic Azad University. E.I. mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometre operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometre. ^{1}H, and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometre at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C NMR spectra were obtained of solutions in $CDCl_3$ using TMS as internal standard. Column chromatography was performed with Merck silica gel 60, 230–400 mesh. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Typical procedure for the 1: 1: 1 condensation reaction

To a magnetically stirred solution of a mixture of pyrrole (**3a**, 0.14 g, 2 mmol) and cyclohexyl isocyanide (**1a**, 0.17 g, 2 mmol) in dichloromethane (10 ml) was added dropwise diethyl acetylenedicarboxylate (**2a**, 0.34 g, 2 mmol) in dichloromethane (5 ml) at room temperature over 10 min. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product.

Diethyl 2-[(cyclohexylimino)(pyrrol-1-yl)methyl]-but-2-enedioate (**4a**): Yellow oil (0.64 g, 93 %). IR: ν_{max} 1719 (2 C=O), 1664 cm^{-1} (C = N). ^{1}H NMR: δ 0.90 (3H, t, ^3J = 7.1 Hz, CH_3), 1.11 (3H, t, ^3J = 7.1 Hz, CH_3), 1.11–1.62 (10H, m, 5 CH_2 of cyclohexyl), 2.94 (1H, m, CH of cyclohexyl), 3.90 (2H, m, OCH_2), 4.12 (2H, m, OCH_2), 6.03 (2H, t, ^3J = 2.1 Hz, 2 CH of pyrrole), 6.94 (2H, t,



Scheme 3

^3J = 2.1 Hz, 2 CH of pyrrole), 7.05 (1H, s, olefinic CH). ^{13}C NMR: δ 13.6 and 14.0 (2 CH_3), 24.2, 25.6, 33.4 (5 CH_2 of cyclohexyl), 59.9, 61.7, and 62.6 (2 OCH_2 and N–CH), 110.6, 118.5 (4 CH of pyrrole), 133.1 (CH), 137.1 (C), 144.26 (C = N), 163.2 and 163.3 (2 CO). MS: *m/z* (%) 346 ($M^{+\cdot}$, 35). Anal. Calcd for $C_{19}H_{26}N_2O_4$ (346.42): C, 65.87; H, 7.56; N, 8.09. Found: C, 65.7; H, 7.6; N, 8.1 %.

Diethyl 2-[(cyclohexylimino)(indol-1-yl)methyl]but-2-enedioate (**4b**): Yellow oil (0.71 g, 90 %). IR: ν_{max} 1726 (2 C=O), 1660 cm^{-1} (C = N). ^{1}H NMR: δ 0.91 (3H, t, ^3J = 7.1 Hz, CH_3), 1.33 (3H, t, ^3J = 7.2 Hz, CH_3), 1.42–1.91 (10H, m, 5 CH_2 of cyclohexyl), 3.20 (1H, m, CH of cyclohexyl), 4.15 (2H, m, OCH_2), 4.34 (2H, m, OCH_2), 6.55 (1H, d ^3J = 5.8 Hz, CH of indole), 7.15–7.62 (5H, m, 4 CH of indole and olefinic CH), 8.62 (1H broad m, CH of indole). ^{13}C NMR: δ 12.4, 13.0 (2 CH_3), 23.2, 24.7, and 32.9 (5 CH_2 of cyclohexyl, broad signals), 59.0 (CH of cyclohexyl), 60.7, and 61.7 (2 OCH_2), 104.5, 115.2, 119.4, 120.9, 122.4, and 124.5 (6 CH, broad signals), 129.3, 134.6 (2 C), 131.7 (broad, CH), 136.1 (broad, C), 144.1 (broad, C = N), 162.3 and 162.4 (2 CO). MS: *m/z* (%) 396 ($M^{+\cdot}$, 27). Anal. Calcd for $C_{23}H_{28}N_2O_4$ (396.48): C, 69.67; H, 7.12; N, 7.07. Found: C, 69.6; H, 7.0; N, 7.1 %.

Diethyl 2-[(t-butylimino)(pyrrol-1-yl)methyl]but-2-enedioate (**4c**): Yellow oil (0.58 g, 90 %). IR: ν_{max} 1725 (2 C=O), 1668 cm^{-1} (C = N). ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 0.93 (3H, t, ^3J = 7.2 Hz, CH_3), 1.01 (3H, t, ^3J = 7.2 Hz, CH_3), 1.20 (9H, s, 3 CH_3), 3.94 (2H, m, OCH_2), 4.15 (2H, m, OCH_2), 6.04 (2H, t, ^3J = 2.2 Hz, 2 CH of pyrrole), 6.93 (3H, m, 2 CH of pyrrole and olefinic CH). ^{13}C NMR: δ 13.7 and 13.9 (2 CH_3), 30.7 (3 CH_3 of *t*-Bu), 45.9 (C of *t*-Bu), 61.7 and 62.6 (2 OCH_2), 110.2, 118.4 (4 CH of pyrrole), 132.8 (olefinic CH), 139.9 (C), 144.3 (C = N), 163.4 and 163.8 (2 CO). MS: *m/z* (%) 320 ($M^{+\cdot}$, 16). Anal. Calcd for $C_{17}H_{24}N_2O_4$ (320.38): C, 63.73; H, 7.55; N, 8.74. Found: C, 63.7; H, 7.6; N, 8.8 %.

Dimethyl 2-[(cyclohexylimino)(pyrrol-1-yl)methyl]but-2-enedioate (**4d**): Yellow oil (0.61 g, 95 %). IR: ν_{max} 1728 (broad, 2 C=O), 1665 cm^{-1} (C = N). ^{1}H NMR: δ 1.31–1.81 (10H, m, 5 CH_2 of cyclohexyl), 3.22 (1H, m, CH of cyclohexyl), 3.65 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.24 (2H, t, ^3J = 2.1 Hz, 2 CH of pyrrole), 7.14 (2H, broad s, 2 CH of pyrrole), 7.23 (1H, s, olefinic CH). ^{13}C NMR: δ 23.2, 24.5, 32.2, and 32.4 (broad signals, 5 CH_2 of cyclohexyl), 51.5 and 52.5 (2 OCH_3), 59.1 (CH of cyclohexyl), 110.0, 117.6 (4 CH of pyrrole), 131.9 (olefinic CH), 135.9 (C), 144.5 (C = N), 162.4 and 162.5 (2 CO). MS: *m/z* (%) 318 (M^+, 16). Anal. Calcd for $C_{17}H_{22}N_2O_4$ (318.38): C, 64.13; H, 6.97; N, 8.80. Found: C, 64.2; H, 7.1; N, 8.8 %

Dimethyl 2-[(cyclohexylimino)(indol-1-yl)methyl]but-2-enedioate (**4e**): Yellow oil (0.64 g, 87 %). IR: ν_{max} 1726 and 1728 (broad, 2 C=O), 1662 cm^{-1} (C = N). ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.32–1.80 (10H, m, 5 CH_2 of cyclohexyl), 3.21 (1H, m, CH of cyclohexyl), 3.63 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.53 (1H, d, ^3J = 5.8 Hz, CH of indole), 7.15–7.73 (5H, broad m, 4 CH of indole and olefinic CH), 8.62 (1H broad, CH of indole). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 24.2, 25.7, 33.7, and 34.0 (broad signals, 5 CH_2 of cyclohexyl), 52.6 and 53.5 (2 OCH_3), 60.2 (CH of cyclohexyl), 105.6, 116.2, 120.6, 122.0, 123.6, and 125.4 (6 CH, broad signals), 130.4, 135.7 (2 C), 132.5 (broad, CH), 137.1 (broad, C), 143.6 (broad, C = N), 163.6 and 163.9 (2 CO). MS: *m/z* (%) 368 ($M^{+\cdot}$, 16). Anal. Calcd for $C_{21}H_{24}N_2O_4$ (368.43): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.3; H, 6.6; N, 7.5 %.

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