Synthesis of unsaturated amidines by three component reaction of alkylisocyanides, dialkyl acetylenedicarboxylates, and aromatic amides

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The reactive intermediate generated by the reaction of alkyl isocyanides and dialkyl acetylenedicarboxylates was trapped by aromatic amides to produce unsaturated amidine derivatives in good yield.

Keywords: alkylisocyanides, acetylenic esters, amidines, aromatic amides, 1,4-dihydrobenzoquinoline

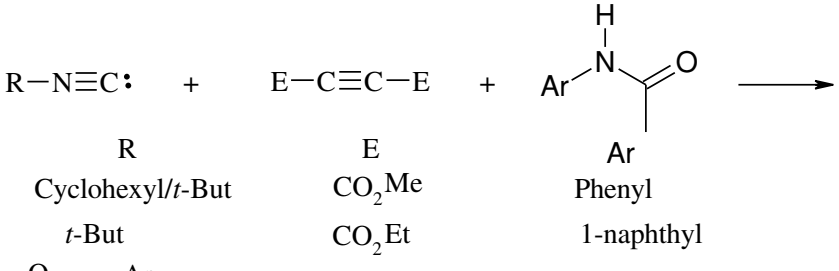
Isocyanides by virtue of their carbenic character, react readily with most common multiple bonds.[1-3] The reaction of isocyanides with carbon–carbon triple bonds occur in a stepwise manner involving a zwitterionic intermediate whose ultimate fate appears to be dictated by the nature of the original 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 has been carried out in the presence of different electrophiles, in order to trap the zwitterionic intermediate.[6-9] In the presence of alcohols, ketenimine and unsaturated iminoesters were obtained as the main products.[7] The reaction between isocyanides and dimethyl acetylenedicarboxylate in the presence of naphthols and phenols respectively yields benzochromene[8] and chromene[9] derivatives. Here we report the reaction between alkyl isocyanides and dialkylacetylenedicarboxylates in the presence of aromatic amides such as acetanilide and 1-naphthyacetamide. This condensation reaction produces the unsaturated amidines **1–3** in fairly good yield (Scheme 1).

Surprisingly, 1-naphthylacetamide reacts with dimethyl acetylenedicarboxylate and cyclohexylisocyanide to afford dimethyl 1-acetyl-2-cyclohexylamino-1,4-dihydro-benzo[h] quinoline-3,4-dicarboxylate **4** (Scheme 2).

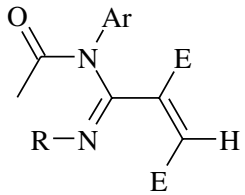
The structures of compounds **1–4** were deduced from their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H NMR spectrum of **1** exhibited five single sharp lines readily recognised as arising from *t*-butyl (δ = 1.0), methyl (δ = 2.1), methoxy (δ = 3.6 and 3.8), and olefinic (δ = 6.3) protons, along with multiplets (δ = 6.8–7.3) for aromatic protons. The ^{13}C NMR spectrum of **1** showed 15 distinct resonances in agreement with the proposed structure.

The formation of compound **1** can be rationalised as shown in Scheme 3. The reaction starts with nucleophilic attack of *t*-butyl isocyanide on dimethyl acetylenedicarboxylate and subsequent protonation by acetanilide. The addition of conjugate anion of acetanilide on the positively charged intermediate **5** affords product **1**.

^{1}H and ^{13}C NMR spectra of compound **4** are consistent with the presence of two conformations at room temperature. ^{1}H NMR spectrum of **4** exhibited four single lines arises from methyl (δ = 2.1), methoxy (δ = 3.7 and 3.9), and methine (δ = 5.1) protons of major conformer. A single line observed at δ = 6.9 which arises from NH proton disappeared on addition of D_2O to the solution of **4**. The corresponding signals for minor isomer appear at δ = 2.4 (methyl protons), 3.6 and 3.8 (methoxy protons), 5.3 (methane proton), and 6.8



	R	E	Ar
	Cyclohexyl/*t*-But	CO_2Me	Phenyl
	t-But	CO_2Et	1-naphthyl



	R	E	Ar	Yield(%)
1	*t*-But	CO_2CH_3	Phenyl	93
2	Cyclohexyl	CO_2CH_3	Phenyl	90
3	*t*-But	CO_2Et	1-naphthyl	90

Scheme 2

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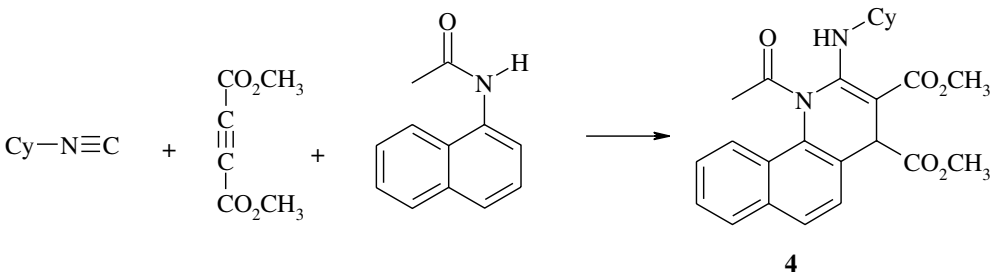
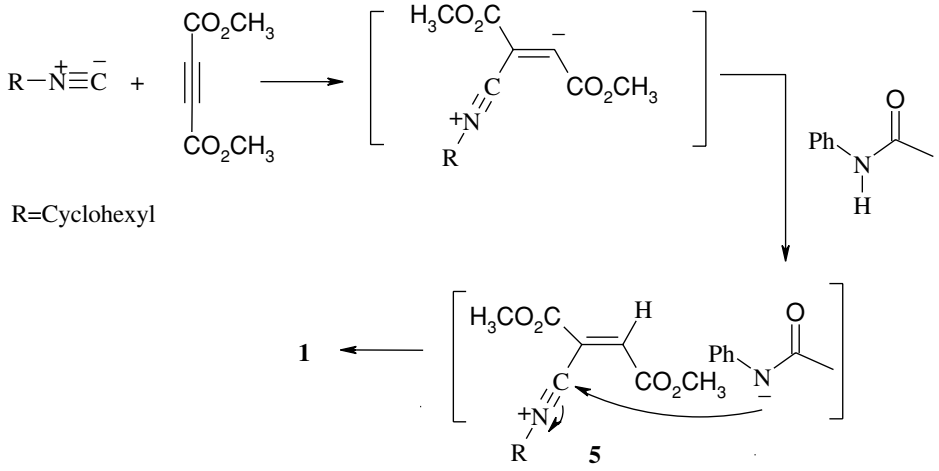


4

Scheme 2



R=Cyclohexyl

Scheme 3

(NH proton). The ^{1}H NMR spectrum of compound **4** at 50 °C shows the broadening of some signals and the coalescence of signals related to the methine proton of cyclohexyl moiety. This shows the presence of different conformers which probably arise from restricted rotation around the amide C–N bond. The ^{13}C NMR spectrum of compound **4** shows 25 distinct signals for each conformer in agreement with the proposed structure. The IR spectrum of **4** shows an absorption band at ν = 3350 cm^{-1} for NH stretching.

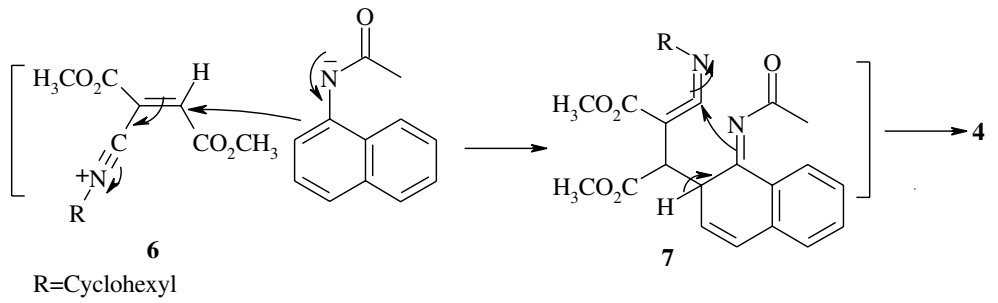
A plausible mechanism for formation of **4** is proposed in Scheme 4. The Michael addition of conjugate anion of NH-acid on cation **6** leads to keteneimine **7** which cyclises to product **4**.

These reactions provide simple entries to the synthesis of 1-acetyl-2-cyclohexylamino-1,4-dihydro-benzo[h]quinoline-3,4-dicarboxylate and unsaturated amidine derivatives of potential synthetic interest.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, and ^{13}C NMR spectra were recorded on Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ using TMS as an 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.

Dimethyl 2-[acetylphenylamino-tert-butyliminomethyl]-but-2-ene dicarboxylate (**1**): To a magnetically stirred solution of acetanilide (0.28 g, 2 mmol) and *t*-butyl isocyanide (0.17 g, 2 mmol) in dichloromethane (10 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.28 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 as a yellow oil, (0.33 g, 93%). IR (KBr) (ν_{max}/cm^{-1}): 1738 (C=O ester), 1668 (C=O, amide). Anal. Calcd for $C_{19}H_{24}N_2O_5$ (360.40): C, 63.32; H, 6.71; N, 7.77. Found: C, 63.1; H, 6.7; N, 7.6%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.0 (9 H, s, 3 CH_3), 2.1 (3 H, s, CH_3), 3.6, and 3.8 (6 H, 2 s, 2 OCH_3), 6.3 (1 H, s, CH), 6.8–7.3 (5 H, m, C_6H_5). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 24.71 (CH_3), 27.10 (3 CH_3), 52.03 and 52.25 (2 OCH_3),



R=Cyclohexyl

Scheme 4

58.55 (C-N) 102.54, 124.44, 126.27, and 128.511 (5 CH and C of phenyl), 145.50 (C=N), 149.35 and 150.56 (2 C, olefinic), 163.18, 165.31, 168.32 (2 CO ester and CO amide). MS, *m/z* (%): 360 ($M^{+\cdot}$, 35).

Dimethyl 2-[acetylphenylamino-cyclohexyliminomethyl]-but-2-ene dicarboxylate (**2**): Yellow oil, (0.35 g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 1726 (C=O ester), 1672 (C=O, amide). Anal. Calcd for $C_{21}H_{26}N_2O_5$ (386.44): C, 65.27; H, 6.78; N, 7.25. Found: C, 65.3; H, 6.7; N, 7.4%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.0–1.5 (10 H, m, 5 CH_2 of cyclohexyl), 1.9 (3 H, s, CH_3), 2.9 (1 H, m, CH of cyclohexyl), 3.7, and 3.8 (6 H, 2 s, 2 OCH_3), 6.7 (1 H, s, CH), 7.2–7.4 (5 H, m, C_6H_5). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 23.73 (CH_3), 25.04, 25.68, 33.11 (3 CH_2), 52.13 and 52.29 (2 OCH_3), 58.57 (C–N), 124.54, 126.44, 126.87, and 128.57 (5 CH and C of phenyl), 140.50 (C=N), 141.00 and 147.66 (2 C, olefinic), 164.14, 164.88, 171.81 (2 CO ester and CO amide). MS, *m/z* (%): 386 ($M^{+\cdot}$, 35).

Dieethyl 2-[(1-naphthyl)-phenyl-amino-tert-butyliminomethyl]-but-2-ene dicarboxylate (**3**): Yellow powder, m.p. = 132–133 °C, (0.39 g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 1727 (C=O ester), 1668 (C=O, amide). Anal. Calcd for $C_{25}H_{30}N_2O_5$ (438.52): C, 68.47; H, 6.90; N, 6.39. Found: C, 68.3; H, 6.7; N, 6.4%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.1 (9 H, 3 CH_3), 1.4 (3 H, t $^3J_{HH}$=7Hz, CH_3), 1.5 (3 H, t $^3J_{HH}$=7Hz, CH_3), 2.3 (3 H, s, CH_3), 4.4 (2 H, m, OCH_2), 4.5 (2 H, m, OCH_2), 6.5 (1 H, s, CH), 6.9–8.2 (7 H, 7 CH of naphthyl). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 14.45, 14.48, and 25.86 (3 CH_3), 28.39 (3 CH_3 of *t*-butyl), 60.02, 62.14, and 62.39 (2 OCH_2 and C–N), 114.77, 124.38, 125.65, 126.12, 126.88, 127.10, 128.05, 128.34, 129.51, 134.53 (7 CH and 3 C of naphthyl), 142.03 (C=N), 150.28 and 151.41 (2 C, olefinic), 164.41, 166.02, 169.57.81 (2 CO ester and CO amide). MS, *m/z* (%): 438 (M^+, 35).

Dimethyl 1-acetyl-2-cyclohexylamino-1,4-dihydro-benzo[h]quinoline-3,4-dicarboxylate (**4**): White powder, m.p. 142–144 °C, (0.41 g, 95%). IR (KBr) (ν_{max}/cm^{-1}): 3300 (N–H), 1733 (C=O ester), 1673 (C=O, amide). Anal. Calcd for $C_{25}H_{28}N_2O_5$ (436.50): C, 68.79; H, 6.47; N, 6.42. Found: C, 68.6; H, 6.5; N, 6.5%. NMR data for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.1–2.3 (10 H, m, 5 CH_2 of cyclohexyl), 2.1 (3 H, s, CH_3), 3.7, and 3.9 (6 H, 2 s, 2 OCH_3), 4.5 (1 H, m, CH of cyclohexyl), 5.1 (1 H, s, CH), 6.9 (1 H, s, NH), 7.3–7.9 (6 H, m, 6 CH of naphthyl). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 22.84 (CH_3), 25.91, 25.98, 26.26, 29.70 (5 CH_2), 33.91 (CH), 46.45 and 52.01 (2 OCH_3), 55.91 (C–N), 97.58 (C), 113.92, 119.95, 122.62, 124.24, 126.81, 127.14, 127.37, 129.05, 131.37, 134.50, (6 CH and 4 C of naphthyl), 144.43 (C), 166.66, 171.27, 173.38 (2 CO ester and CO amide). NMR data for minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.1–2.3 (10 H, m, 5 CH_2 of cyclohexyl), 2.4 (3 H, s, CH_3), 3.6, and 3.8 (6 H, 2 s, 2 OCH_3), 4.4 (1 H, m, CH of cyclohexyl), 5.3 (1 H, s, CH), 6.8 (1 H, s, NH), 7.3–7.9 (6 H, m, 6 CH of naphthyl). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 22.89 (CH_3), 25.87, 25.94, 26.26, 29.94 (5 CH_2), 32.28 (CH), 46.60 and 52.17 (2 OCH_3), 56.95 (C–N), 95.86 (C), 113.01, 120.11, 122.57, 124.66, 126.87, 127.24, 127.41, 129.22, 131.58, 134.53, (6 CH and 4 C of naphthyl), 144.55 (C), 166.66, 170.57, 173.14 (2 CO ester and CO amide). MS, *m/z* (%): 436 ($M^{+\cdot}$, 35).

Received 18 August 2005; accepted 13 October 2005
Paper 05/3444

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