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Regioselective reactions of N^1-alkyl-N^2-(4-nitrophenyl)ethanediamide and acetylenic esters in the presence of *tert*-butyl isocyanide

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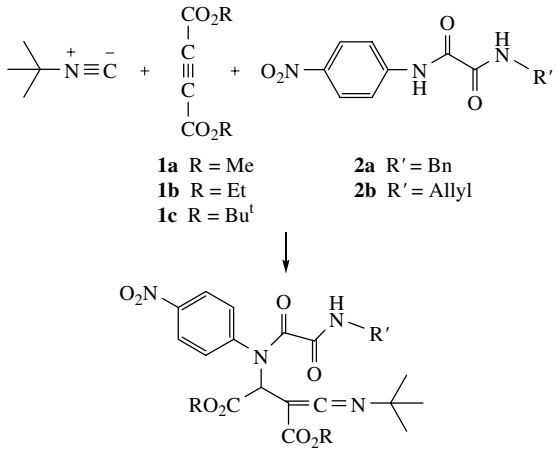
The regioselective reactions of N^1-alkyl-N^2-(4-nitrophenyl)ethanediamide with dialkyl acetylenedicarboxylates in the presence of *tert*-butyl isocyanide lead to dialkyl 2-{[2-(alkylamino)-2-oxoacetyl]-4-nitroanilino}-3-[(*tert*-butylimino)methylene]succinates in good yields.

Multicomponent reactions are of interest to combinatorial chemistry, for example, versatile isocyanide-based Ugi and Passerini reactions.[1–4] In recent years, the synthetic applications of multifunctional heteroallenes have been widely investigated.[5,6] In spite of extensive developments in the chemistry of modified ketenes and isocyanates,[7,8] little attention has been paid to the synthesis of ketenimines.[8–10]

Ketenimines are transient intermediates in many interconversions, especially, in elimination–addition processes and in the formation of heterocyclic ring systems.[11–14] We report a regioselective one-pot synthesis of highly functionalised ketenimines **3**. Thus, the reaction of dialkyl acetylenedicarboxylates **1** with N^1-alkyl-N^2-(4-nitrophenyl)ethanediamide **2** in the presence of *tert*-butyl isocyanide leads to dialkyl 2-{[2-(alkylamino)-2-oxo-



1a R = Me
1b R = Et
1c R = Bu^t

2a R′ = Bn
2b R′ = Allyl

3a R = Me, R′ = Bn
3b R = Et, R′ = Bn
3c R = Bu^t, R′ = Bn
3d R = Me, R′ = Allyl
3e R = Bu^t, R′ = Allyl

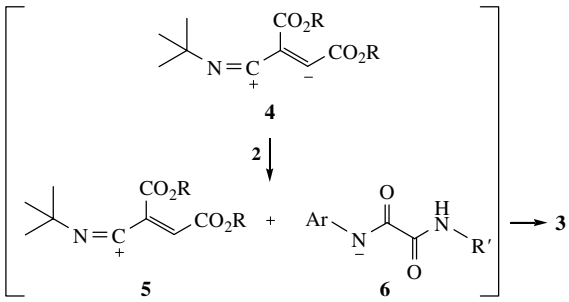
Scheme 1

acetyl]-4-nitroanilino}-3-[(*tert*-butylimino)methylene]succinates **3a**–**e** in good yields (Scheme 1).†

The reaction of *tert*-butyl isocyanide with electron-deficient acetylenic esters **1** in the presence of NH acids **2** proceeded in dichloromethane at room temperature and was complete within 24 h. The IR, ^{1}H NMR and ^{13}C NMR spectra of the crude products clearly indicated the formation of stable ketenimines **3** (Scheme 1).

The ^{1}H NMR spectrum of **3a** ($CDCl_3$) showed signals for *tert*-butyl (δ 1.36 ppm), methoxy (δ 3.69 and 3.80 ppm), methylene (δ 4.32 ppm, d, $^3J_{HH}$ 5 Hz), methine (δ 5.58 ppm) and NH (δ 7.48 ppm) protons together with aromatic protons at δ 7.19–8.22 ppm. The ^{13}C NMR spectrum of **3a** exhibited 20 sharp signals in agreement with the proposed structure. The sp^2-hybridised carbon atom of the ketenimine residue appears at δ 59.1 ppm, as a result of strong electron delocalization. The structural assignments of compounds **3a**–**e** made on the basis of their NMR spectra were supported by their IR spectra. These compounds show strong absorption bands at about 2020 cm^{-1}.

Mechanistically, it is conceivable that the reaction involves the initial formation of 1:1 zwitterionic intermediate **4** between *tert*-butyl isocyanide and the acetylenic ester.[2,4] The protonation of **4** by diamide **2** and the subsequent attack of the resulting nucleophile on positively charged ion **5** afforded ketenimine **3**. In this reaction, the stronger NH acid of **2** acts as a source of protons (Scheme 2).



Scheme 2

The three-component reaction of N^1-alkyl-N^2-(4-nitrophenyl)-ethanediamide with dialkyl acetylenedicarboxylates in the presence of *tert*-butyl isocianide provides a simple, one-pot and regioselective synthesis of polyfunctionalised ketenimines of potential synthetic interest.

† The ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE instrument in $CDCl_3$ as a solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

Preparation of N^1-*benzyl*-N^2-*(4-nitrophenyl)ethanediamide* **2a**: benzylamine (1.07 g, 10 mmol) was added to a stirred solution of ethyl 2-(4-nitroanilino)-2-oxoacetate (2.38 g, 10 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred for 4 h. The product precipitated as a white powder, which was filtered off and washed with Et_2O. Product **2** was obtained as a white powder; yield 2.93 g (98%), mp 169–170 °C.

*General procedure for the preparation of dimethyl 2-{[2-(benzylamino)-2-oxoacetyl]-4-nitroanilino}-3-[(*tert*-butylimino)methylene]succinate* **3a**: to a stirred solution of 0.60 g *N*^{1}-benzyl-*N*^{2}-(4-nitrophenyl)ethanediamide (2 mmol) and 0.28 g dimethyl acetylenedicarboxylate (2 mmol) in 6 ml CH_2Cl_2, was added dropwise at 0 °C for 10 min 0.45 g *tert*-butyl isocyanide (2 mmol) in 2 ml CH_2Cl_2. The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure and the product was extracted with *n*-hexane–EtOAc (5:1) and crystallised at –20 °C. Pale yellow crystals; yield: 0.79 g (75%), mp 116–118 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ_H: 1.36 (s, 9H, CMe_3), 3.69 and 3.80 (2s, 6H, 2OMe), 4.32 (d, 2H, NCH_2, $^3J_{HH}$ 5 Hz), 5.58 (s, 1H, CH), 7.19–7.36 (m, 5H, Ph), 7.48 (br. s, 1H, NH), 7.54 and 8.22 (2d, 4H, C_6H_4, $^3J_{HH}$ 9 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si) δ_C: 30.1 (C*Me*$_3$), 43.5 (NCH_2), 51.9 and 53.0 (2OMe), 59.1 (*C*=C=N), 61.7 (N–*C*Me$_3$), 62.4 (CH), 124.2, 127.8, 127.9, 128.8, and 129.0 (9CH), 136.7, 146.9 and 147.1 (3C), 158.7, 161.1, 161.5, 168.7 and 169.7 (C=*C*=N and 4C=O). IR (KBr, ν/cm^{-1}): 3300 (NH), 2022 (C=C=N), 1738 and 1653 (C=O). MS, *m*/*z* (%): 524 (M$^+$, 3), 299 (25), 91 (100), 65 (25). Found (%): C, 59.5; H, 5.4; N, 10.7. Calc. for $C_{26}H_{28}N_4O_8$ (524.5) (%): C, 59.54; H, 5.38; N, 10.68.

For **3b**: pale yellow crystals; yield 0.94 g (85%), mp 125–127 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ_H: 1.28 and 1.36 (2t, 6H, 2Me, $^3J_{HH}$ 7 Hz), 1.40 (s, 9H, CMe_3), 4.19 and 4.29 (2q, 4H, 2OCH_2, $^3J_{HH}$ 7 Hz), 4.32 (d, 2H, NCH_2, $^3J_{HH}$ 5 Hz), 5.52 (s, 1H, CH), 7.22–7.35 (m, 5H, Ph), 7.49 (br. s, 1H, NH), 7.59 and 8.26 (2d, 4H, C_6H_4, $^3J_{HH}$ 9 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si) δ_C: 14.6 and 14.8 (2Me), 30.5 (C*Me*$_3$), 43.8 (NCH_2), 60.1 and 62.2 (*C*=C=N and N–*C*Me$_3$), 60.9 and 62.5 (2OCH_2), 62.6 (CH), 124.5, 128.2, 128.3, 129.1 and 129.4 (9CH), 137.4, 147.4 and 147.5 (3C), 159.2, 162.1, 162.8, 168.4 and 169.6 (C=*C*=N and 4C=O). IR (KBr, ν_{max}/cm^{-1}): 3310 (NH), 2020 (C=C=N), 1730 and 1675 (C=O). MS, *m*/*z* (%): 552 (M$^+$, 2), 299 (28), 91 (100). Found (%): C, 60.9; H, 5.8; N, 10.1. Calc. for $C_{28}H_{32}N_4O_8$ (552.6) (%): C, 60.86; H, 5.84; N, 10.14.

For **3c**: pale yellow crystals; yield 1.10 g (90%), mp 140–142 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ_H: 1.36, 1.40 and 1.48 (3s, 27H, 3CMe_3), 4.30 (d, 2H, NCH_2, $^3J_{HH}$ 5 Hz), 5.48 (s, 1H, CH), 7.21–7.38 (m, 5H, Ph), 7.52 (br. s, 1H, NH), 7.56 and 8.22 (2d, 4H, C_6H_4, $^3J_{HH}$ 9 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si) δ_C: 28.0, 28.3 and 30.0 (3C*Me*$_3$), 43.5 (NCH_2), 61.4 and 62.1 (*C*=C=N and N–*C*Me$_3$), 61.9 (CH), 80.9 and 83.2 (2$OCMe_3$), 124.4, 128.1, 128.3, 129.2 and 130.0 (9CH), 137.3, 147.1 and 147.5 (3C), 159.5, 161.9, 162.7, 167.9 and 169.1 (C=*C*=N and 4C=O). IR (KBr, ν_{max}/cm^{-1}): 3290 (NH), 2023 (C=C=N), 1725, 1681 and 1652 (C=O). MS, *m*/*z* (%): 608 (M$^+$, 2), 299 (20), 91 (100), 57 (90). Found (%): C, 63.1; H, 6.6; N, 9.2. Calc. for $C_{32}H_{40}N_4O_8$ (608.7) (%): C, 63.14; H, 6.62; N, 9.20.

For **3d**: pale yellow crystals; yield 0.87 g (92%), mp 112–114 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ_H: 1.35 (s, 9H, CMe_3), 3.70 and 3.76 (2s, 6H, 2OMe), 3.82 (m, 2H, NCH_2), 5.15 (m, 2H, =CH_2), 5.57 (s, 1H, CH), 5.75 (m, 1H, =CH), 7.33 (br. s, 1H, NH), 7.52 and 8.21 (2d, 4H, C_6H_4, $^3J_{HH}$ 9 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si) δ_C: 30.1 (C*Me*$_3$), 41.7 (NCH_2), 51.9 and 52.9 (2OMe), 59.0 and 61.7 (*C*=C=N and N–*C*Me$_3$), 62.4 (CH), 117.2 (=CH_2), 124.1 (2CH), 129.0 (CH), 132.7 (2CH), 147.0 and 147.6 (2C), 158.5, 161.3, 163.3, 168.7 and 169.6 (C=*C*=N and 4C=O). IR (KBr, ν_{max}/cm^{-1}): 3335 (NH), 2022 (C=C=N), 1734, 1679 and 1654 (C=O). MS, *m*/*z* (%): 474 (M$^+$, 3), 249 (100), 57 (20), 41 (30). Found (%): C, 55.7; H, 5.5; N, 11.8. Calc. for $C_{22}H_{26}N_4O_8$ (474.5) (%): C, 55.69; H, 5.52; N, 11.81;

For **3e**: pale yellow crystals; yield 1.05 g (94%), mp 146–148 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ_H: 1.46, 1.47 and 1.54 (3s, 27H, 3CMe_3), 3.80 (m, 2H, NCH_2), 5.20 (m, 2H, =CH_2), 5.34 (s, 1H, CH), 5.53 (m, 1H, =CH), 7.39 (br. s, 1H, NH), 7.58 and 8.25 (2d, 4H, C_6H_4, $^3J_{HH}$ 9 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si) δ_C: 28.4, 28.7 and 30.5 (3C*Me*$_3$), 42.1 (NCH_2), 61.7 and 62.2 (*C*=C=N and N–*C*Me$_3$), 62.2 (CH), 81.0 and 83.3 (2$OCMe_3$), 117.5 (=CH_2), 124.3 (2CH), 129.9 (CH), 133.2 (2CH), 147.2 and 147.4 (2C), 159.2, 161.5, 161.9, 167.6 and 168.9 (C=*C*=N and 4C=O). IR (KBr, ν_{max}/cm^{-1}): 3330 (NH), 2020 (C=C=N), 1730, 1680, and 1650 (C=O). MS, *m*/*z* (%): 558 (M$^+$, 2), 333 (25), 57 (100), 41 (35). Found (%): C, 60.2; H, 6.8; N, 10.0. Calc. for $C_{28}H_{38}N_4O_8$ (558.6) (%): C, 60.20; H, 6.86; N, 10.03.

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