One-pot synthesis of functionalised keteneimines by three component reaction of isocyanides, dialkyl acetylenedicarboxylates, and 4-phenylaminocoumarin

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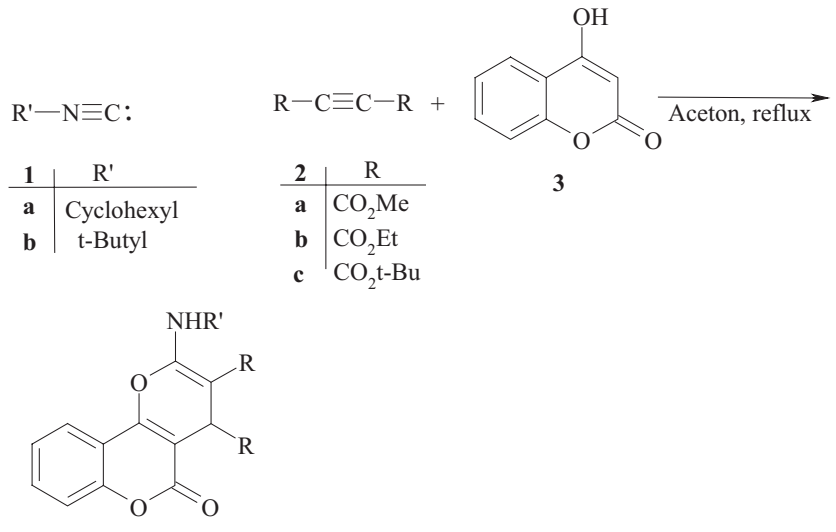
The reactive intermediate generated by the reaction of alkyl isocyanides and dialkyl acetylenedicarboxylates was trapped by 4-phenylaminocoumarin to produce dialkyl 2-cyclohexylamino-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylates in good yields.

Keywords: alkyl isocyanides, acetylenic esters, 4-phenylaminocoumarin, multi component reactions

Isocyanides by virtue of their carbenic character, react readily with most common multiple bonds.[1-3] The reaction of isocyanides with electron-deficient acetylenic compounds leads to a zwitterionic intermediate which may then be trapped by various electrophiles.[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 organic acidic compounds, in order to trap the zwitterionic intermediate.[6-9] In the presence of alcohols, keteneimine and unsaturated iminoesters were obtained as the main products.[7] The reaction between isocyanides and dimethyl acetylenedicarboxylate (DMAD) in the presence of naphthols and phenols respectively yields benzochromene[8] and chromene derivatives.[9] Similar products were reported for the reaction between DMAD, cyclohexyl isocyanide and 4-hydroxycoumarins.[10] We have studied the reaction between isocyanides and acetylenic esters in the presence of organic acids,[10,11] here we report the results of our study on the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates, in the presence 4-phenylaminocoumarin. We have also reinvestigated the reaction of alkyl isocyanides with acetylenic esters in the presence of 4-hydroxycoumarin. Thus three-component reaction between acetylenic esters **2** and alkyl isocyanides **1** in the presence of 4-hydroxycoumarin **3** produces dialkyl 2-alkylamino-5-oxo-4*H*,5*H*-pyrano[3,2-*c*] chromene-3,4-dicarboxylates **4a–d** in excellent yields (Scheme 1).

The structures of compounds **4a–d** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values.

The ^{1}H NMR spectrum of compound **4a** exhibited three single sharp lines readily recognisable as arising from methoxy (δ = 3.71 and 3.75 ppm), and methine (δ = 4.74 ppm) protons, along with multiplets (δ = 7.27–7.72 ppm) for aromatic



1	R'
a	Cyclohexyl
b	t-Butyl

2	R
a	CO_2Me
b	CO_2Et
c	CO_2t-Bu

4	R	R'	Yield(%)
a	CO_2Me	Cyclohexyl	97
b	CO_2Et	Cyclohexyl	95
c	CO_2t-Bu	Cyclohexyl	95
d	CO_2Et	t-Butyl	90

Scheme 1

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protons. A singlet observed at δ = 8.73 ppm, which arises from NH proton, disappeared after addition of a few drops of D_2O to $CDCl_3$ solution of compound **4a**. The N*CH* proton appeared as a multiplet at 3.75 ppm and the signals related to methylene groups of cyclohexyl moiety were observed as multiplets at 1.42–1.84 ppm. The ^{13}C NMR spectrum of compound **4a** showed 22 distinct resonances in agreement with the proposed structure. The methylene carbons of cyclohexyl moiety are diastereotopic and show distinct signals.

The formation of compound **4a** can be rationalised as shown in Scheme 2. The reaction starts with nucleophilic attack of cyclohexyl isocyanide on dimethyl acetylenedicarboxylate and subsequent protonation by 4-hydroxycoumarin. The addition of conjugate anion of 4-hydroxycoumarin on the positively charged intermediate **6** leads to keteneimine **7** which then cyclises to product **4a**.

The three-component reaction between alkyl isocyanides, dialkyl acetylendicarboxylates and 4-phenylaminocoumarin **8** produced keteneimine derivatives **9a–c** in good yields (Scheme 3).

The ^1H NMR spectrum of compound **9a** exhibited three single sharp lines readily recognisable as arising from tert-butyl (δ = 1.43 ppm), methine (δ = 5.79 ppm) and N–C=CH (δ = 5.98 ppm) protons, along with multiplets (δ = 6.81–7.63 ppm) for aromatic protons. Protons of ethyl groups are observed as a triplet (δ = 1.2 ppm, $^3J_{HH}$ = 7 Hz) and a multiplet (δ = 4.17 ppm). IR spectrum of compound **9a** shows a strong absorption bond at 2040 cm^{-1} which arises from the keteneimine moiety.

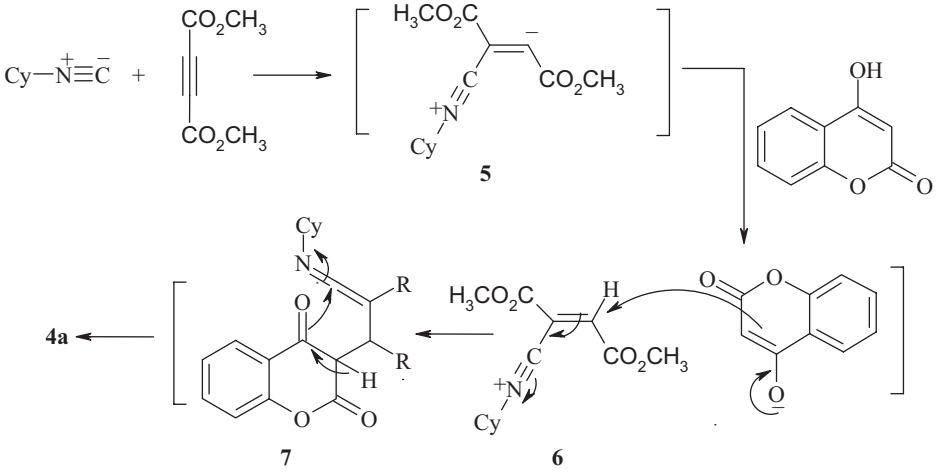
A plausible mechanism for the formation of compounds **9a–c** is proposed in Scheme 4. The Michael addition of conjugate anion of NH-acid on cation **10** leads to keteneimines **9a–c**.

In summary, reactions reported here provide simple entries to the synthesis of dialkyl 2-alkylamino-5-oxo-4H,5H-pyrano[3,2-c]chromene-3,4-dicarboxylates and functionalised keteneimine derivatives of potential synthetic interest. The present method carries the advantage that the reaction is performed under neutral conditions and the substances can be mixed without any activation or modification.

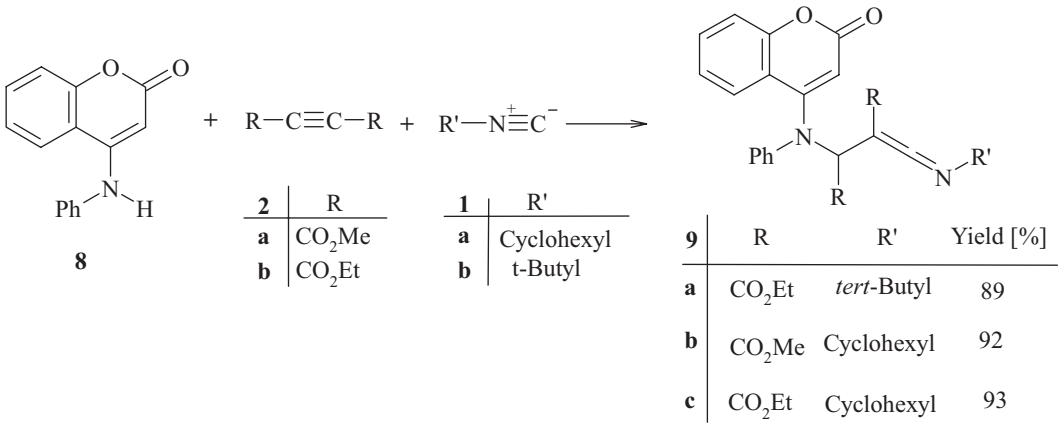
Experimental

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. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. ^1H and ^{13}C NMR spectra were obtained on solution in d_6-DMSO using TMS as internal standard. Column chromatography was performed on Merck silica gel 60, 230–400 mesh. 4-phenylaminocoumarin prepared by a previously reported method.[13] The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Dimethyl 2-cyclohexylamino-5-oxo-4H,5H-pyrano[3,2-c] chromene-3,4-dicarboxylates (**4a**): *Typical procedure*: to a magnetically stirred solution of 4-hydroxycoumarin (0.16 g, 1 mmol) and cyclohexyl isocyanide (0.11 g, 1 mmol) in 10 ml acetone was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) in 5 ml acetone at room temperature. 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



Scheme 2

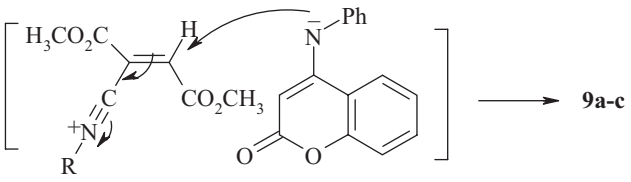


2	R
a	CO_2Me
b	CO_2Et

1	R'
a	Cyclohexyl
b	t-Butyl

9	R	R'	Yield [%]
a	CO_2Et	*tert*-Butyl	89
b	CO_2Me	Cyclohexyl	92
c	CO_2Et	Cyclohexyl	93

Scheme 3



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Scheme 4

chromatography using hexane–ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product as a white powder, m.p. 207–209°C (0.40 g, 97%). IR (KBr) (ν_{max}/cm^{-1}): 3265 (NH), 1730 and 1668 (C=O ester). Anal. Calcd for $C_{22}H_{23}NO_7$ (413.43): C, 63.9; H, 5.6; N, 3.4. Found: C, 64.1; H, 5.7; N, 3.4%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.41–1.84 (10 H, m, 5 CH_2), 3.71, and 3.75 (6 H, 2 s, 2 OCH_3), 3.84 (1 H, m, NC*H*), 4.73 (1 H, s, CH), 7.27–7.72 (4 H, m, aromatic protons), 8.73 (1 H, s, N*H*). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 24.8, 24.9, 25,8, 33.9, and 34.1 (5 CH_2), 36.7 and 51.1 (2 CH), 51.6 and 53.1 (2 OCH_3), 72.5, 103.4, and 114.0 (3 C), 117.5, 122.4, 125.0, and 133.1 (4 CH), 153.2, 155.3, 158.7, 161.1, 169.7, and 173.5 (3 C and 3 CO). MS, *m/z* (%): 413 ($M^{+\cdot}$, 35).

Diethyl 2-cyclohexylamino-5-oxo-4H,5H-pyrano[3,2-c]chromene-3,4-dicarboxylates (**4b**): White powder, m.p. 166–167°C (0.42 g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 3230 (NH), 1736, 1727, 1689 (3 C=O). Anal. Calcd for $C_{24}H_{27}NO_7$ (441.47): C, 65.3; H, 6.2; N, 3.2. Found: C, 65.3; H, 6.4; N, 3.1%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.20–2.09 (16 H, m, 5 CH_2 and 2 CH_3), 3.88 (1 H, m, N–CH), 4.17 (4 H, m, 2 OCH_2), 4.72 (1 H, s, CH), 7.28–7.72 (4 H, m, arom), 8.72 (1 H, s, N*H*). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 14.6 and 14.9 (2 CH_3), 24.8, 24.9, 25,8, 33.9, and 34.2 (5 CH_2), 36.9 and 51.0 (2 CH), 60.2 and 61.8 (2 OCH_2), 72.7, 103.5, and 114.1 (3 C), 117.5, 122.4, 124.9, and 133.0 (4 CH), 153.2, 155.3, 158.5, 161.2, 169.4, and 173.4 (3 C and 3 CO). MS, *m/z* (%): 441 ($M^{+\cdot}$, 15).

Di-tert-butyl 2-cyclohexylamino-5-oxo-4H,5H-pyrano[3,2-c]chromene-3,4-dicarboxylates (**4c**): White powder, m.p. 79–81°C, (0.44 g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 3235 (NH), 1732, 1717, 1676 (3 C=O). Anal. Calcd for $C_{28}H_{35}NO_7$ (497.58): C, 67.6; H, 7.1; N, 2.8. Found: C, 67.3; H, 7.1; N, 2.7%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 1.20–1.96 (28 H, m, 5 CH_2 and 6 CH_3), 3.82 (1 H, m, N–C*H*), 4.55 (1 H, s, CH), 7.04–7.70 (4 H, m, arom), 8.66 (1 H, s, N*H*). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 25.1, 25.2, 25.9, 34.0, and 34.4 (5 CH_2), 28.3 and 29.0 (6 CH_3 of *tert*-butyl groups), 38.3 and 51.1 (2 CH), 80.3 and 81.7 (2 OC of t-butyl groups), 74.2, 103.9, and 114.2 (3 C), 117.3, 122.4, 124.8, and 132.8 (4 CH), 153.1, 155.2, 158.4, 161.1, 169.1, and 172.9 (3 C and 3 CO). MS, *m/z* (%): 497 ($M^{+\cdot}$, 7).

Diethyl 2-tert-butylamino-5-oxo-4H,5H-pyrano[3,2-c]chromene-3,4-dicarboxylates (**4d**): White powder, m.p. 191–193°C (0.37 g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 3235 (N–H), 1719, 1679, 1643(3 C=O). Anal. Calcd for $C_{22}H_{25}NO_7$ (415.43): C, 63.6; H, 6.1; N, 3.4. Found: C, 63.5; H, 6.0; N, 3.4%. ^{1}H NMR (500 MH_Z, $CDCl_3$, Me_4Si): δ 1.23 and 1.28 (6 H, 2 t, $^3J_{HH}$ = 7.1 H_Z, 2 CH_3), 1.52 (9 H, s, CMe_3), 4.11–4.22 (4 H, m, 2 OCH_2), 4.71 (1 H, s, CH), 7.34–7.83 (4 H, m, arom), 9.01 (1 H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 14.16 and 14.46 (2 CH_3), 30.60 (CH), 59.98 and 61.47 (2 OCH_2), 63.06 (C of *t*-butyl), 73.25, 103.16 and 113.62 (3 C), 117.22, 122.37, 124.61, and 132.63 (4 CH), 152.76, 155.06, 159.48 (=C–N and 2=C–O), 160.85, 169.19 and 172.99 (3 CO). MS, *m/z* (%):415($M^{+\cdot}$, 25).

Diethyl 2-(N-(2-oxo-2H-chromen-4-yl)-N-phenylamino)-3-[(t-butylimino)methylene]succinate (**9a**): Colourless crystals; m.p. 147–148°C, (0.43 g, 89%;). IR (KBr) (ν_{max}, cm^{-1}): 3030 (NH), 2040 (C=C=N), 1720 and 1687 (C=O). Anal. Calcd for $C_{28}H_{30}N_2O_6$ (490.55): C, 68.6; H, 6.2; N, 5.7;%. Found: C, 68.5; H, 6.2; N, 5.5%. ^{1}H NMR (500 MH_Z, $CDCl_3$, Me_4Si): δ 1.21 (6 H, t, $^3J_{HH}$ = 7 H_Z, 2 CH_3), 1.43 (9 H, s, CMe_3), 4.17–4.32 (4 H, m, 2 OCH_2), 5.79 and 5.98 (2 H, 2 s, N–CH and C=CH), 6.81–7.63 (9 H, m, arom). ^{13}C NMR (125.8 MH_Z, $CDCl_3$, Me_4Si): δ 14.47 and 14.67 (2 CH_3), 30.56 (3 CH_3 of *t*-butyl), 53.18 (N–*C*H), 60.18 and 60.91 (2 OCH_2), 62.75 (*C*=*C*=N), 64.66 (C of *t*-butyl), 103.04, 116.94, 117.64, 123.34, 125.77, 125.90, 127.30, 129.75, 131.21, 147.06, 154.69, 159.87 (10 C aromatic and *C*=*C*H), 162.34, 163.07, 170.01, 170.16 (*C*=*C*=N and 3 CO). MS (*m/z*,%): 490 (M, 1).

Dimethyl 2-(N-(2-oxo-2H-chromen-4-yl)-N-phenylamino)-3-[(cyclohexylimino)methylene]succinate (**9b**): Colourless crystals; m.p. 131–132°C, (0.44 g, 92%). IR (KBr) (ν_{max}, cm^{-1}): 2910 (CH), 2055 (*C*=*C*=N), 1723 and 1694 (C=O). Anal. Calcd for $C_{28}H_{28}N_2O_6$ (488.53): C, 68.8; H, 5.8; N, 5.7%. Found: C, 68.5; H, 5.7; N, 5.8%. ^{1}H NMR (500 MH_Z, $CDCl_3$, Me_4Si): δ 1.31–1.96 (10 H, m, 5 CH_2), 3.69 and 3.75 (6 H, 2 s, 2 OCH_3), 3.85(1 H, m, CH), 5.83 and 5.98 (2 H, 2 s, N–CH and C=CH), 6.84–7.34 (9 H, m, arom). ^{13}C NMR (125.8 MH_Z, $CDCl_3$, Me_4Si): δ 24.27, 24.30, 25.45, 33.48, and 33.62 (5 CH_2), 52.20 and 53.30 (2 OCH_3), 58.55 (CH), 61.04 (*C*=*C*=N), 64.88 (CH of cyclohexyl), 102.86, 117.58, 117.69, 123.40, 125.81, 125.91, 127.28, 129.86, 131.28, 147.04, 154.71, 155.20 (10 C arom and *C*=*C*H), 162.41, 162.61, 170.44, 170.56 (C=C=*N* and 3 CO). MS (*m/z*,%): 488 (M).

Diethyl 2-(N-(2-oxo-2H-chromen-4-yl)-N-phenylamino)-3-[(cyclohexylimino)methylene]succinate (**9c**): Colourless crystals; m.p. 130–131°C, (0.48 g, 93%). IR (KBr) (ν_{max}, cm^{-1}): 2905 (CH), 2035 (*C*=*C*=N); 1723, 1666 (C=O). Anal. Calcd for $C_{30}H_{32}N_2O_6$ (516.58): C, 69.7; H, 6.2; N, 5.4;%. Found: C, 69.5; H, 6.2; N, 5.5%. ^{1}H NMR (500 MH_Z, $CDCl_3$, Me_4Si): δ 1.22 (6 H, m, 2 CH_3), 1.32–1.95 (10 H, m, 5 CH_2), 3.87 (1 H, m, CH cyclohexyl), 4.18–4.71 (4 H, m, 2 OCH_2), 5.81 and 5.93 (2 H, 2 s, N–CH and C=CH), 6.81–7.38 (9 H, m, arom).^{13}C NMR (125.8 MH_Z, $CDCl_3$, Me_4Si): δ 14.49, 14.71 (2 CH_3), 24.10, 24.15, 25.15, 33.45 and 33.58 (5 CH_2), 58.97 (CH), 60.96, 60.98 (2 OCH_2), 62.57 (*C*=*C*=N), 64.96 (CH of cyclohexyl), 102.79, 117.62, 117.67, 123.37, 125.81, 125.95, 127.34, 129.78, 131.24, 147.21, 154.44, 155.17 (10 C arom and *C*=*C*H), 162.43, 163.46, 169.88, 170.07 (*C*=*C*=N and 3 CO). MS (*m/z*,%): 516 (M, 1).

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