Three-component synthesis of dialkyl 2-(cyclohexyliminomethylene)-3-arylsulfonylamino succinate

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The reactive 1:1 intermediate produced in the reaction between cyclohexyl isocyanide and dialkyl acetylenedicarboxylates was trapped by arylsulfonamides to yield highly functionalised stable ketenimines under mild reaction conditions in fairly good yields.

Keywords: multicomponent reactions**,** ketenimines, sulfonamides**,** zwitterion

Multicomponent reactions (MCRs) provide a powerful tool towards the one-pot synthesis of diverse and complex compounds on the one hand and small and 'drug-like' heterocycles on the other hand. MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds. A number of advantages make MCRs very popular in the community of combinatorial chemists: superior atom economy, simple procedures, the one-pot character, and the high and ever-increasing number of accessible backbones. Sulfonamide-containing compounds have a high potential as pharmaceutical and agricultural agents due to their diverse biological profiles. The ability to serve as amide surrogates, with unique physical properties, have made them ideal functional groups for the development of novel peptidomimetics.[1–3] In addition, sulfonamides have served as key functional groups in the development of novel nonpeptidal HIV protease inhibitors,[4,5] matrix metalloproteinase inhibitors,[6,7] thrombin inhibitors,[8,9] and fibrinogen receptor antagonists.[10]

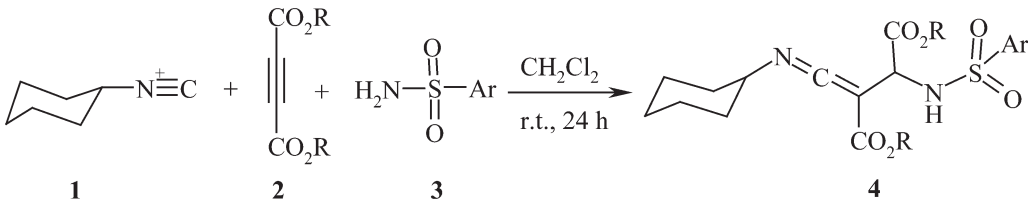
On the other hand, ketenimines are important reactive intermediates that occur as transient compounds in many thermal and photochemical reactions.[11–13] There has been intense interest in their addition reactions, such as cycloaddition,[14,15] nucleophilic,[12,16,17] and electrophilic,[18,19] addition. Ketenimines have been extensively used in organic synthesis as versatile building blocks for the preparation of a large variety of cyclic compounds via inter- or intramolecular cycloaddition reactions.[20,21]

Although the trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylate and isocyanides with OH, NH, and CH acids has been widely studied,[22–25] trapping of the initially formed 1:1 intermediate with arylsulfonamides has not been reported. In the course of our works on the reaction between isocyanides and acetylenic esters,[26–29] we now report a simple one-pot three-component reaction between dialkyl acetylenedicarboxylates, cyclohexyl isocyanide, and arylsulfonamide leading to dialkyl 2-cyclohexyliminomethylene-3-arylsulfonylamino succinate derivatives.

Results and discussion

The reaction of cyclohexyl isocyanide **1** with dialkyl acetylenedicarboxylate **2** in the presence arylsulfonamides **3** proceeds with a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature, to produce dialkyl 2-cyclohexyliminomethylene-3-arylsulfonylamino succinates **4** in 80–89% yields (Scheme 1).

The structures of compounds **4a–f** were deduced from their mass spectra, elemental analyses, IR, and high-field ^{1}H and ^{13}C NMR spectra.



1 **2** **3** **4**

4	Ar	R	%Yield
a	p-CH_3-phenyl	Et	89
b	p-NO_2-phenyl	Et	85
c	p-NO_2-phenyl	Me	82
d	p-CH_3-phenyl	Me	80
e	phenyl	Me	82
f	phenyl	Et	85

Scheme 1

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The mass spectrum of compound **4a** displayed the molecular-ion peak at *m/z* = 450. The IR spectrum of **4a** exhibited the absorption band for the ketenimine moiety at 2065 cm^{-1}, for the ester carbonyl groups at 1737 and 1685 cm^{-1} and for the NH group at 3345 cm^{-1}.

The ^1H NMR spectrum of compound **4a** exhibited a multiplet readily recognized as arising from two methyl group protons (δ = 1.18), and the signals related to methylene groups of the cyclohexyl moiety were observed as multiplets at 1.26–1.96 ppm. A single signal was observed at 2.41 ppm which arises from tolyl methyl protons. Two multiplets were observed for the methylene protons of the ethyl groups and the methine proton of the cyclohexyl group at 4.08 and 3.80 ppm respectively. The methine and NH protons couple to each other and two doublets were observed for them at 4.65 and 5.78 ppm, respectively. When the ^1H NMR spectrum was recorded after addition of some D_2O to the $CDCl_3$ solution of **4a** the doublet relating to the NH proton disappeared and the doublet relating to the methine proton was converted to a singlet. The protons of the aryl group exhibited characteristic signals in the aromatic region of the spectrum.

The ^{13}C NMR spectrum of compound **4a** showed 19 distinct resonances in agreement with the proposed structure. The sp^2-hybridised carbon atom of the ketenimine residue appears at δ = 62.47 ppm, as a result of strong electron delocalisation. Partial assignments of these resonances are given in the Experimental section.

Although we have not established the mechanism of the reaction between isocyanides and acetylenic esters in the presence of the arylsulfonamide in an experimental manner, a possible explanation is proposed in (Scheme 2).

On the basis of the well-established chemistry of isocyanides,[30–35] it is reasonable to assume that the functionalised ketenimine **4** apparently results from initial addition of the cyclohexyl isocyanide **1** to the acetylenic ester **2** and subsequent protonation of the 1:1 adduct **5** by arylsulfonamide **3**. Then, the positively charged ion **6** is attacked by anion **7** to give the product **4**.

Conclusion

In conclusion, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of aryl sulfonamide provides a simple one-pot entry into the synthesis of dialkyl 2-cyclohexyliminomethylene-3-arylsulfonylamino succinate derivatives of potential synthetic and pharmaceutical interest. The advantages of the suggested method are simple reaction conditions, good yields and using starting materials without any activation or modification.

Experimental

Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization 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 solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

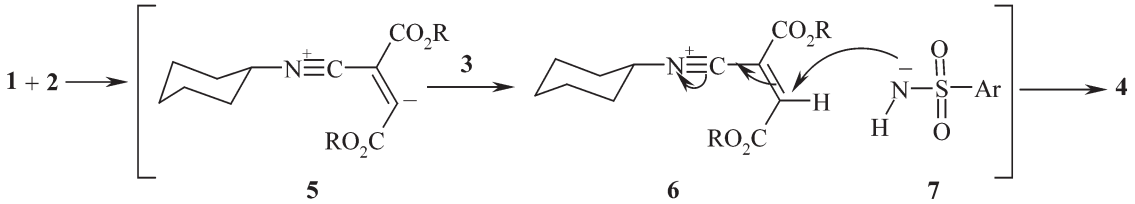
To a magnetically stirred solution of cyclohexyl isocyanide (1 mmol) and aryl sulfonamide (1 mmol) in CH_2Cl_2 (10 ml) was added a solution of dialkyl acetylenedicarboxylate (1 mmol) in CH_2Cl_2 (5 ml) dropwise at room temperature. over 10 min. The mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, hexane–EtOAc, 5:1) to afford the pure title compounds.

Diethyl 2-cyclohexyliminomethylene-3-(4-methyl-benzenesulfonyl-amino) succinate **(4a):** Yellow oil; yield 0.40 g (89%); IR (KBr) (ν_{max}, cm^{-1}): 3345 (NH), 2065 (N=C=C), 1737, 1685 (C=O, ester). MS (*m/z*, %): 450 (M^+, 7). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.18 (6 H, m, $2OCH_2CH_3$), 1.26–1.96 (10 H, m, 5 CH_2 of cyclohexyl), 2.41 (3 H, s, CH_3), 3.80 (1 H, m, CH of cyclohexyl), 4.04–4.12 (4 H, m, $2OCH_2CH_3$), 4.65(1 H, d, $^3J_{HH}$ = 8 Hz, CH), 5.78 (1 H, d, $^3J_{HH}$ = 8 Hz, NH), 7.28 (2 H, d, $^3J_{HH}$ = 6.8 Hz, arom), 7.74 (2 H, d, $^3J_{HH}$ = 6.8 Hz, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 13.93 (OCH_2CH_3), 14.28 (OCH_2CH_3), 21.50 (CH_3), 25.15, 23.79, 33.28 and 33.35 (5 CH_2 of cyclohexyl), 53.78 (CH of cyclohexyl), 60.33 (OCH_2CH_3), 60.76 (OCH_2CH_3), 62.25 (CH), 62.47(N=C=*C*), 127.15, 129.45, 137.61, 143.27 (C arom), 166.12 (N=*C*=C), 168.12 (CO_2Et), 169.77 (CO_2Et) ppm. Anal. Calcd for $C_{22}H_{30}N_2O_6S$: C, 58.65; H, 6.71; N, 6.22. Found: 58.71; H, 6.59; N, 6.29%.

Diethyl -2-cyclohexyliminomethylene-3-(4-nitro-benzenesulfonyl-amino) succinate **(4b):** Yellow oil; yield 0.40 g (85%); IR (KBr) (ν_{max}, cm^{-1}): 3230 (NH), 2050 (N=C=C), 1750, 1663 (C=O, ester). MS (*m/z*, %): 481 (M^+, 9). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.19 (6 H, m, $2OCH_2CH_3$), 1.25–1.96 (10 H, m, 5 CH_2 of cyclohexyl), 3.71 (1 H, m, CH of cyclohexyl), 4.01–4.13 (4 H, m, $2OCH_2CH_3$), 4.70 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 6.06 (1 H, d, $^3J_{HH}$ = 7.7 Hz, NH), 8.05 (2H, d, $^3J_{HH}$ = 6.8 Hz, arom), 8.31 (2 H, d, $^3J_{HH}$ = 6.8 Hz, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 14.37 (OCH_2CH_3), 14.50 (OCH_2CH_3), 23.08, 24.05, 25.52, 32.31 and 33.68 (5 CH_2 of cyclohexyl), 54.55 (CH of cyclohexyl), 60.98 (OCH_2CH_3), 61.15 (OCH_2CH_3), 61.99 (CH), 62.92 (N=C=*C*), 124.42, 128.83, 147.15, 150.32 (C arom), 165.09 (N=*C*=C), 168.80 (CO_2Et), 169.42 (CO_2Et) ppm. Anal. Calcd for $C_{21}H_{27}N_3O_8S$: C, 52.38; H, 5.65; N, 8.73. Found: 52.31; H, 5.65; N, 8.65%.

Dimethyl 2-cyclohexyliminomethylene-3-(4-nitro-benzenesulfonyl-amino) succinate **(4c):** Yellow oil; yield 0.37 g (82%); IR (KBr) (ν_{max}, cm^{-1}): 3415 (NH), 2075 (N=C=C), 1742, 1717 (C=O, ester). MS (*m/z*, %): 453 (M^+, 11). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.26–2.01 (10 H, m, 5 CH_2 of cyclohexyl), 3.59 (3 H, s, OCH_3), 3.69 (3 H, s, OCH_3), 3.83 (1 H, m, CH of cyclohexyl), 4.74 (1 H, br, CH), 6.01 (1 H, br, NH), 8.05 (2H, d, $^3J_{HH}$ = 8.5 Hz, arom), 8.34 (2 H, d, $^3J_{HH}$ = 8.5 Hz, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): 23.84, 25.05, 29.69, 32.58 and 33.38 (5 CH_2 of cyclohexyl), 51.72 (OCH_3), 53.33 (OCH_3), 54.09 (CH of cyclohexyl), 60.89 (CH), 61.12 (N=C=*C*), 124.04, 128.40, 146.57 and 149.97 (C arom), 164.34 (N=*C*=C), 168.92 (CO_2Me), 169.55 (CO_2Me) ppm. Anal. Calcd for $C_{19}H_{23}N_3O_8S$.: C, 50.32; H, 5.11; N, 9.27. Found: 50.45; H, 5.01; N, 9.32%.

Dimethyl 2-cyclohexyliminomethylene-3-(4-methyl-benzenesulfonyl-amino) succinate **(4d):** Yellow oil; yield 0.33 g (80%); IR (KBr) (ν_{max}, cm^{-1}): 3205 (NH), 2075 (N=C=C), 1754, 1661 (C=O, ester). MS (*m/z*, %): 422 (M^+, 9). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.17–1.90 (10 H, m, 5 CH_2 of cyclohexyl), 2.41(3 H, s, CH_3), 3.55 (3 H, s, OCH_3), 3.71 (3 H, s, OCH_3), 3.80 (1 H, m, CH of cyclohexyl), 4.70 (1 H, d, $^3J_{HH}$ = 8.9 Hz, CH), 5.77 (1 H, d, $^3J_{HH}$ = 8.9 Hz, NH), 7.29 (2H, d, $^3J_{HH}$ = 8.2 Hz, arom), 7.74 (2 H, d, $^3J_{HH}$ = 8.2 Hz, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): 24.99, 25.04, 25.87, 32.99 and 33.07 (5 CH_2 of cyclohexyl), 21.49 (CH_3), 49.14 (CH of cyclohexyl), 53.39 (OCH_3), 53.98 (OCH_3), 61.29 (CH), 62.39 (N=C=*C*), 127.69, 130.02, 137.57 and 143.95 (C arom), 164.71 (N=*C*=C), 169.71 (CO_2Me), 170.34 (CO_2Me) ppm. Anal. Calcd for $C_{20}H_{26}N_2O_6S$: C, 56.86; H, 6.20; N, 6.63. Found: 56.78; H, 6.29; N, 6.71 %.



Scheme 2

Dimethyl 2-benzenesulfonylamino-3-cyclohexyliminomethylene succinate **(4e):** Yellow oil; yield 0.33 g (80%); IR (KBr) (ν_{max}, cm^{-1}): 3345 (NH), 2070 (N=C=C), 1736, 1685 (C=O, ester). MS (*m/z*, %): 408 (M^+, 9). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.14–1.89 (10 H, m, 5 CH_2 of cyclohexyl), 3.49 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.80 (1 H, m, CH of cyclohexyl), 4.70 (1 H, d, $^3J_{HH}$ = 9 Hz, CH), 5.91 (1 H, d, $^3J_{HH}$ = 9 Hz, NH), 7.48–7.89 (5H, m, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): 24.57, 24.62, 25.42, 29.66 and 32.53 (5 CH_2 of cyclohexyl), 48.74 (CH of cyclohexyl), 52.91 (OCH_3), 53.55 (OCH_3), 60.27(CH), 62.14 (N=C=*C*), 127.15, 128.87, 132.64 and 140.37 (C arom), 164.49 (N=*C*=C), 169.01 (*C*O_2Me), 169.89 (*C*O_2Me) ppm. Anal. Calcd for $C_{19}H_{24}N_2O_6S$: C, 55.87; H, 5.92; N, 6.86. Found: 55.79; H, 5.99; N, 6.79%.

Diethyl 2-benzenesulfonylamino-3-cyclohexylimin)methylene succinate **(4f):** Yellow oil; yield 0.37 g (85%); IR (KBr) (ν_{max}, cm^{-1}): 3345 (NH), 2065 (N=C=C), 1733, 1675 (C=O, ester). MS (*m/z*, %): 436 (M^+, 6). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.18(6 H, m, $2OCH_2CH_3$), 1.25–1.92 (10 H, m, 5 CH_2 of cyclohexyl), 3.78 (1 H, m, CH of cyclohexyl), 4.03–4.29 (4 H, m, $2OCH_2CH_3$), 4.64 (1 H, d, $^3J_{HH}$ = 8.6 Hz, CH), 6.06 (1 H, d, $^3J_{HH}$ = 9 Hz, NH), 7.40–7.88 (5H, m, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 14.17 (OCH_2CH_3), 14.52 (OCH_2CH_3), 23.09, 24.99, 25.04, 30.09 and 33.68 (5 CH_2 of cyclohexyl), 49.11 (CH of cyclohexyl), 60.77 (OCH_2CH_3), 61.16 (OCH_2CH_3), 62.58 (CH), 62.84 (N=C=*C*), 127.64, 129.31, 133.06, and140.75 (C arom), 164.98 (N=*C*=C), 168.94 (*C*O_2Et), 169.82 (*C*O_2Et) ppm.

Anal. Calcd for $C_{21}H_{28}N_2O_6S$: C, 57.78; H, 6.47; N, 6.42. Found: 57.82; H, 6.57; N, 6.35%.

Received 25 November 2010; accepted 21 December 2010
Paper 1000446 doi: 10.3184/174751911X12964930076881
Published online: 10 February 2011

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