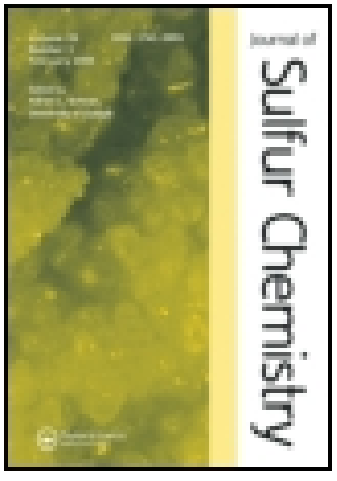

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Three-component reaction of isocyanide with dialkyl acetylenedicarboxylate and alkyl mercaptan: preparation of new derivatives of stable ketenimines

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SHORT COMMUNICATION

Three-component reaction of isocyanide with dialkyl acetylenedicarboxylate and alkyl mercaptan: preparation of new derivatives of stable ketenimines

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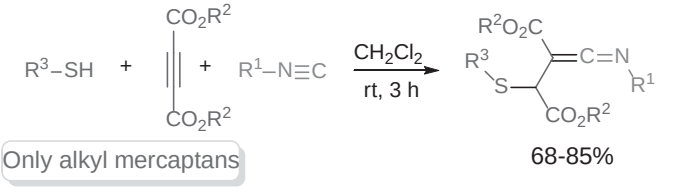
Three-component synthesis of stable ketenimines containing a sulfur group based on a capture profile of a zwitterionic intermediate is described. Thus, the reactions of zwitterions, generated from isocyanide and dialkyl acetylenedicarboxylate, react with alkyl mercaptans in CH_2Cl_2 to afford ketenimines in good yields.



Keywords: organosulfur; ketenimine; multicomponent reaction; isocyanide; zwitterion

1. Introduction

The formation of carbon–sulfur (C−S) bonds is a valuable goal in organic synthesis, because organosulfur compounds are broadly present in nature and play a key role in the biochemistry of almost all living organisms.[1] Also, organosulfur compounds are inescapably present in many synthetic drugs and bioactive natural products.[2] Interestingly, all of the 10 top selling drugs in 2012 were organosulfur compounds.[3]

Ketenimines are important intermediates that can be used in a wide range of chemical transformations. They are involved in inter- or intra-molecular cycloaddition reactions for the synthesis of a large variety of cyclic compounds.[4] Additionally, ketenimines participate in nucleophilic, electrophilic, and radical addition reactions.[5] The syntheses of ketenimines have been divided into four classes in which (i) substitution reactions of heterocumulenes (C=C=O, C=C=S), (ii) substitution of nitrogen on nitrile anion or nitrile radical, (iii) addition reactions of isocyanide with acetylene, cyclopropenone, or carbene, and (iv) elimination-rearrangement

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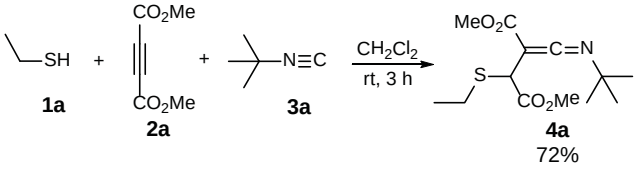


Scheme 1. Synthesis of ketenimine **4a.**

reactions.[6, 7] Recently, ketenimines have been prepared by isocyanide-based multicomponent reactions (IMCRs).[8, 9] In these cases, addition of alkyl or aryl isocyanide to dialkyl acetylenedicarboxylate (DAAD) generates highly reactive zwitterionic intermediates, which are trapped by NH acid-like amides [8–10] and oximes [11] leading to the formation of stable ketenimines.

Continuing with these studies aimed at exploiting the utility of IMCRs for the preparation of elaborated ketenimines,[12] herein we illustrate the synthesis of ketenimine compounds containing a sulfur group based on a capture profile of zwitterionic intermediates.

2. Results and discussion

An initial study was performed using the reaction of ethanethiol (**1a**), dimethyl acetylenedicarboxylate (DMAD, **2a**), and *tert*-butyl isocyanide (**3a**) in CH_2Cl_2 at room temperature (rt). To our delight, we observed the formation of product **4a** in 72% yield after 3 h (Scheme 1). A survey of different solvents including toluene, THF, CH_3CN, DMF, MeOH, and EtOH (Table 1, Entries 3–7) demonstrated that product **4a** was formed in slightly lower yields (Table 1, Entries 3–8).

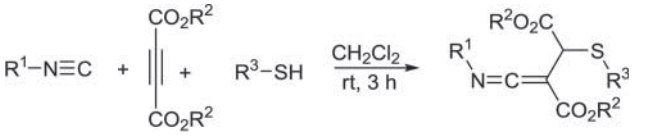
The formation of compounds **4a** was confirmed by IR, NMR (^{1}H and^{13}C) spectral data. The IR spectra revealed the presence of an absorption band at 2065 cm^{-1} corresponding to the C=C=N stretching frequency. The ^{1}H NMR spectrum of **4a** exhibited a singlet at 4.28 ppm, ascribable to the CH proton, 2 singlets identified as 2 methoxy groups at 3.69 and 3.78 ppm, a quartet band at δ 2.62 ppm (2H, CH_2S), a singlet at 1.40 ppm (9H, CMe_3), and a triplet at 1.15 ppm (3H, CH_3). The ^{13}C NMR spectra display the characteristic signals of all carbons corresponding to the structure of compound **4a (**showed 11 distinct resonances).

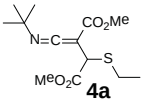
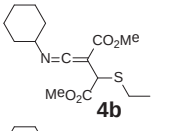
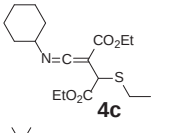
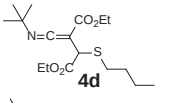
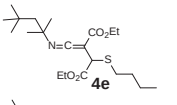
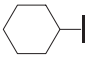
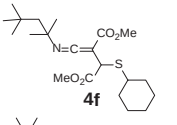
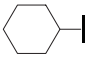
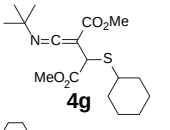
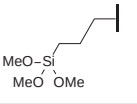
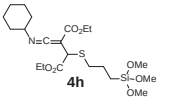
The scope and limitations of this three-component reaction were explored by using of five alkyl mercaptans, two DAAD and three alkyl isocyanides. The results show that the three-component reaction is general affording the expected ketenimine compounds **4a–h** in good yields. Note that these reactions are synthetically useful because they form complex structures and two importance bonds (C–S and C=C=N). As shown in Table 2, this protocol proceeded

Table 1. Solvent effect on the preparation of **4a.**

Entry	Solvent	Temp. (°C)	Yield (%)
1	CH_2Cl_2	Room temp.	72
2	CH_2Cl_2	Reflux	71
3	Toluene	Room temp.	58
4	THF	Room temp.	60
5	CH_3CN	Room temp.	67
6	DMF	Room temp.	52
7	MeOH	Room temp.	Trace
8	EtOH	Room temp.	Trace

Table 2. Ketenimine derivatives (**4a–h**) formed containing a sulfur group.

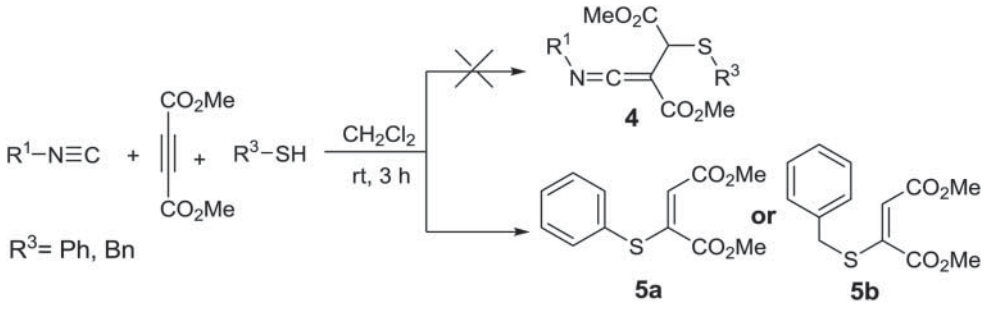


Entry	R^1	R^2	R^3	Product	Yield (%)
1		Me		 **4a**	72
2		Me		 **4b**	76
3		Et		 **4c**	70
4		Et		 **4d**	68
5		Et		 **4e**	81
6		Me		 **4f**	80
7		Me		 **4g**	77
8		Et		 **4h**	85

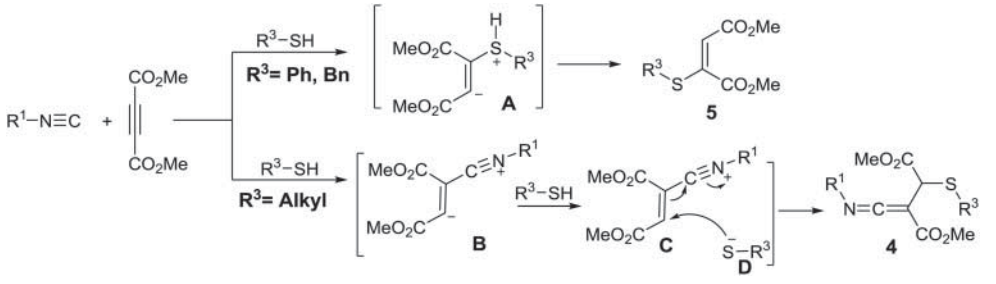
efficiently and led to ketenimine derivatives **4a–h** containing a sulfur group in good yields (Table 2).

In a continuation of our research, thiophenol and benzyl mercaptan were used as reagents in similar reactions and conditions. In these two cases, the expected ketenimines were not obtained and instead the respective vinyl thioethers **5a–b** were isolated from the reaction mixtures (Scheme 2). The formation of **5a–b** can be explained as a result of the addition of the respective thiols to the C–C triple bond of DMAD. These results are probably due to the higher nucleophilicity of these mercaptans in comparison with the isocyanide.[13]

Plausible mechanisms for the formations of compounds **4** and **5** are depicted in Scheme 3. Simple nucleophilic additions of thiophenol or benzyl mercaptan species to DMAD produce vinyl thioethers **5a–b**. But in the presence of alkyl mercaptans, zwitterionic intermediate **B** was initially formed from the reaction of isocyanide with the acetylenic ester. The protonation of



Scheme 2. Synthesis of vinyl thioethers **5a–b**.



Scheme 3. Proposal mechanism.

intermediate **B** by the alkyl mercaptan and the subsequent attack of the resulting anion **D** on the positively charged species **C** afforded ketenimine 4 (Scheme 3).

3. Conclusions

In summary, we have explored an efficient and easy method for the preparation of ketenimine derivatives containing a sulfur group through the reaction of the zwitterions derived from isocyanides and DAAD with alkyl mercaptans in CH_2Cl_2 at room temperature. The present procedure has advantages such as availability of the starting material, good yields of products, and mild reaction conditions without the need to use any catalyst or other means of activation.

4. Experimental

IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with $CDCl_3$ as the solvent, on a Bruker DRX-300 Avances pectrometer operating at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C. The chemical shifts are reported in ppm relative to TMS (internal reference). The coupling constants are reported in Hz. For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and bs, broad singlet. The chemicals used in this work were purchased from Merck and Fluka chemical companies. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography (using silica gel 60 and *n*-hexane:AcOEt (4:1)).

4.1. *General procedure for the preparation of 4a–h (exemplified to 4a)*

4.1.1. *Synthesis of dimethyl 2-((tert-butylimino)methylene)-3-(ethylthio)succinate (**4a**)*

To a magnetically stirred solution of ethanethiol (0.06 g, 1.0 mmol) and DMAD (0.14 g, 1.0 mmol) in CH_2Cl_2 (5 mL) was added, *tert*-butyl isocyanide (0.08 g, 1.0 mmol). The mixture was stirred for 3 h at room temperature. After completion of the reaction as indicated by TLC, the solvent was removed under vacuum. The obtained residue was chromatographed on a silica gel column using a mixture of *n*-hexane and AcOEt (4:1) as eluent to yield **4a** as a yellow oil (0.20 g, 72%); IR (KBr) $\nu_{max} = 2934, 2065, 1739, 1696\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.15$ (3H, t, 7.2 Hz, CH_3), 1.40 (9H, s, $(CH_3)_3$), 2.62 (2H, q, 7.2 Hz, SCH_2), 3.69 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.28 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 26.2 (CH_3), 42.3(CH_2S), 51.7, 52.5 (OCH_3), 58.3 (C–N), 62.2 (CHS), 63.5 (C=C), 167.2 (N=C), 169.4, 171.4 (C=O) ppm.

4.1.1.1. *Dimethyl 2-((cyclohexylimino)methylene)-3-(ethylthio)succinate (**4b**)* Yellow oil (0.24 g, 76%); IR (KBr) $\nu_{max} = 2929, 2055, 1741, 1701\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (3H, t, 7.4 Hz, CH_3), 1.17–1.92 (10H, m, $5CH_2$ of cyclohexyl), 2.53 (2H, q, 7.4 Hz, SCH_2), 3.56 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.71 (1H, bs, CH–N), 4.18 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 23.9, 25.1, 28.5, 33.1, 33.2 (CH_2), 42.2 (CH_2S), 51.5 (CHN), 52.3, 52.9 (OCH_3), 60.6 (CHS), 61.7 (C=C), 166.6 (N=C), 169.2, 171.3 (C=O) ppm.

4.1.1.2. *Diethyl 2-((cyclohexylimino)methylene)-3-(ethylthio)succinate (**4c**)* Yellow oil (0.24 g, 70%); IR (KBr) $\nu_{max} = 2933, 2061, 1735, 1690\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$–1.96 (19H, m, $3CH_3$, and $5CH_2$ of cyclohexyl), 2.65 (2H, bs, SCH_2), 3.80 (1H, bs, CH–N), 4.12–4.17 (4H, m, $2OCH_2$),4.28 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9$, 14.1, 14.3 (CH_3), 23.8, 24.7, 25.2, 33.1, 33.2 (CH_2), 42.4 (CH_2S), 50.9 (CHN), 60.4 (CHS), 60.6 (C=C), 61.5, 62.2 (OCH_2), 167.4 (N=C), 169.1, 171.0 (C=O) ppm.

4.1.1.3. *Diethyl 2-((tert-butylimino)methylene)-3-(butylthio)succinate (**4d**)* Yellow oil (0.23 g, 68%); IR (KBr) $\nu_{max} = 2973, 2057, 1734, 1694\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (3H, t, 7.1 Hz, CH_3), 0.81–1.96 (19H, m, $2CH_3$,$CH_3CH_2CH_2$ and $(CH_3)_3$), 2.63 (2H, bs, SCH_2), 4.13–4.17 (4H, m, $2OCH_2$), 4.25 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.0$, 13.7, 14.6 (CH_3), 22.0 (CH_2), 29.4 (CH_3), 30.8 (CH_2), 43.6 (CH_2S), 60.3 (CN), 61.4 (CHS), 61.8 (C=C), 63.9, 64.0 (OCH_2), 168.0 (N=C), 169.1, 170.9 (C=O) ppm.

4.1.1.4. *Diethyl 2-(butylthio)-3-((2,4,4-trimethylpentan-2-ylimino)methylene)succinate (**4e**)* Yellow oil (0.32 g, 81%); IR (KBr) $\nu_{max} = 2982, 2041, 1727, 1683\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$–1.64 (30H, m, $(CH_3)_3$, $(CH_3)_2$, CH_2, $2CH_3$, $CH_3CH_2CH_2$), 2.64–267 (2H, m, SCH_2), 4.13–4.23 (4H, m, $2OCH_2$), 4.30 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.2$, 14.3, 14.5 (CH_3), 22.7 (CH_2), 29.4, 31.2 (CH_3), 31.4, 31.8 (CH_2), 43.6 (CH_2S), 51.4 (CMe_2), 51.9 (C–N), 54.7 (CHS), 59.8 (C=C), 60.9, 61.5 (OCH_2), 167.9 (N=C), 170.0, 171.3 (C=O) ppm.

4.1.1.5. *Dimethyl 2-(cyclohexylthio)-3-((2,4,4-trimethylpentan-2-ylimino)methylene)succinate (**4f**)* Yellow oil (0.32 g, 80%); IR (KBr) $\nu_{max} = 2998, 2037, 1708, 1691\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$–1.97(33H, m, $(CH_3)_3$, $(CH_3)_2$, CH_2, $2CH_3$, and $5CH_2$ of cyclohexyl), 2.68 (1H, bs, SCH of cyclohexyl), 3.64 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.33 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.7$, 26.9, 28.8 (CH_2), 31.5, 31.7 (CH_3), 33.2, 33.3,

33.7 (CH_2), 44.5 (CHS), 51.4, 52.4 (OCH_3), 52.5 (CCH_2), 54.6 (C–N), 56.6 (CHS), 65.1 (C=C), 165.86 (N=C), 171.0, 172.6 (C=O) ppm.

4.1.1.6. *Dimethyl 2-((tert-butylimino)methylene)-3-(cyclohexylthio)succinate (**4g**)* Yellow oil (0.26 g, 77%); IR (KBr) $\nu_{max} = 2929, 2054, 1714, 1701\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.19–1.96$ (19H, m, $(CH_3)_3$, $5CH_2$ of cyclohexyl), 2.79 (1H, bs, SCH of cyclohexyl), 3.64 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 4.28 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.6, 25.9, 26.0$ (CH_2), 30.2 (CH_3), 33.2, 33.4 (CH_2), 41.2 (CHS), 44.5 (C–N), 51.7, 52.5 (OCH_3), 62.2 (CHS), 64.3 (C=C), 167.6 (N=C), 169.4, 171.9 (C=O) ppm.

4.1.1.7. *Diethyl 2-((cyclohexylimino)methylene)-3-(3-(trimethoxysilyl)propylthio)succinate (**4h**)* Yellow oil (0.40 g, 85%); IR (KBr) $\nu_{max} = 2929, 2054, 1714, 1701\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 073–2.01$ (20H, m, $SiCH_2CH_2$, $2CH_3$, $5CH_2$ of cyclohexyl), 2.69–2.71 (2H, bs, SCH_2), 3.57 (9H, s, $3OCH_3$), 3.86 (1H, bs, CH–N), 4.14–4.23 (4H, m, $2OCH_2$),4.30 (1H, s, CH–S) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2, 14.3$ (CH3), 15.2, 20.1, 24.8, 24.9, 25.8, 32.9, 33.1 (CH2), 40.8 (CH2S), 51.4 (CHN), 53.3 (OCH3), 60.5 (CHS), 60.8 (C=C), 62.0, 62.3, 166.8 (N=C), 169.2, 171.5 (C=O) ppm.

4.1.1.8. *Dimethyl 2-(phenylthio)maleate (**5a**)* Yellow oil (0.13 g, 51%); IR (KBr) $\nu_{max} = 1738, 1714\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.41$ (3H, s, OCH_3),3.67 (3H, s, OCH_3),6.41 (1H, s, C=CH), 7.20–7.53 (5H, m, H-Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.7, 52.1$ (OCH_3), 119.0 (HC=C), 128.7, 131.1, 133.5, 133.8 (C–Ar), 150.1 (HC=C), 165.2, 168.0 (C=O) ppm.

4.1.1.9. *Dimethyl 2-(benzylthio)maleate (**5b**)* Colorless solid. M. p. 70–72°C,[14] IR (KBr) $\nu_{max} = 1721, 1708, 1597\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.69$ (3H, s, OCH_3),3.74(3H, s, OCH_3), 4.29 (2H, s, SCH_2), 4.35 (1H, s, C=CH), 7.23–7.56 (5H, m, H-Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 38.6$ (CH_2), 52.7, 53.8 (OCH_3), 117.2 (HC=C), 124.7, 126.6, 126.1, 132.9 (C–Ar), 144.5 (HC=C), 159.8, 160.7 (C=O) ppm.

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