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A One-Pot Synthesis of Highly Functionalized Ketenimines by a Three-component 2-Thioxothiazolidin-4-one, Alkyl Isocyanides and Dialkyl Acetylenedicarboxylates

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Abstract

The 1:1 reactive intermediates produced in the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates were trapped with 2-thioxothiazolidin-4-one to generate to highly functionalized ketenimines. A series of new 2-thioxothiazolidin-4-one derivatives were synthesized in moderate yields. The advantages of the present method include good functional group tolerance and simple experimental procedure and purification.

***Key words**: Ketenimines, 2-Thioxothiazolidin-4-one, Acetylenic esters, Isocyanides.*

Introduction

Ketenimines are important reactive intermediates that occur as transient compounds in many thermal and photochemical reactions [1–4]. These compounds have attracted interest as dehydrating agents for peptide synthesis, as complexing agents for transition-metal ions, and as co-reagents for DMSO oxidations [5]. 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 [6]. In general, unsubstituted ketenimines and those with small unbranched alkyl substituents are elusive substances. Ketenimines play a role as discrete but transient intermediates in many interconversions, especially in elimination–addition processes and in the formation of heterocyclic ring systems [7–10]. In addition, novel synthetic approaches to carbocyclic and N-heterocyclic four-, five-, and six-membered rings using ketenimine transition-metal complexes have been developed [11].

Methods for the synthesis of ketenimines have been extensively reviewed [12]. The addition

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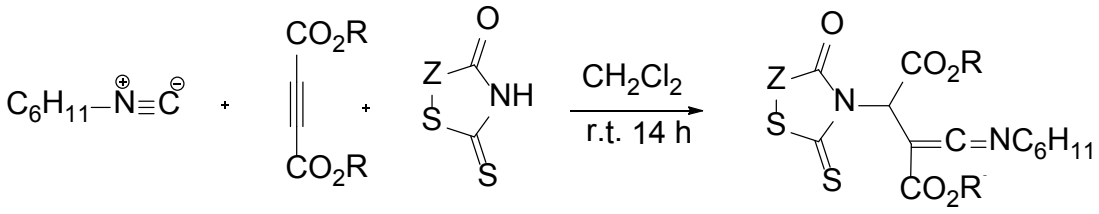
of nucleophilic carbenes, such as isocyanides, to dialkyl acetylenedicarboxylates was investigated in detail [13]. The trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with OH, NH, and CH acids has been widely studied [14-18]. In continuation of our interest in the application of isocyanides in multi-component reactions, MCR [19], we wish to report a simple one-pot preparation of ketenimines using cyclohexyl isocyanide, dialkyl acetylenedicarboxylates **2** and 5-arylidene-2-thioxothiazolidin-4-ones **3a-e** or 2-thioxothiazolidin-4-one **3g** as a proton source/nucleophile. This three-component condensation reaction produces highly functionalized ketenimines **3** in fairly good yields (Scheme 1).



1 **2a,b** **3a-g** **4a-h**

Acetylenic ester **2** R		Thioxothiazolidinone **3** Z		Product	Yield (%)
2a	Me	**3a**	*p*-Tolyl-CH=C	**4a**	75
2a	Me	**3b**	*m*-Tolyl-CH=C	**4b**	77
2a	Me	**3c**	4-O_2N-C_6H_4-CH=C	**4c**	75
2a	Me	**3d**	4-F-C_6H_4-CH=C	**4d**	70
2a	Me	**3e**	2-Thienyl-CH=C	**4**	71
2a	Me	**3f**	Ph-CH=C	**4f**	75
2a	Me	**3g**	CH_2	**4g**	72
2b	Et	**3g**	CH_2	**4h**	71

Scheme 1. Reaction of isocyanides, acetylenic esters and 2-thioxothiazolidin-4-ones.

Experimental

General

Chemicals were purchased from Merck and used without further purification. Compounds **3a-e** were prepared from **3g** by known method [12]. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid Analyzer. The results agreed favorably with the calculated values. The IR spectra were measured on a Shimadzu IR-460 instrument at 400–4000 cm^{-1} (in a KBr tablet). ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) were measured with a Bruker Avance DRX-300 spectrometer at 300 and 75 MHz, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV.

Synthesis of compounds **4**.

To a stirred solution of thioxothiazolidinone (**3**, 1 mmol) and acetylenic ester (**2**, 1 mmol) in 5 mL of CH_2Cl_2 was added drop wise cyclohexylisocyanide (**1**, 1 mmol) in 2 mL of CH_2Cl_2 at r.t. After completion of the reaction [12 h; TLC (AcOEt/hexane 2:1)], the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/AcOEt 4:1].

4a:

Pale yellow oil, yield: 0.43 g (79%). IR (ν_{max}/ cm^{-1}): 2071 (C=C=N), 1738 and 1734 (C=O). ^{1}H-NMR, δ: 1.27-1.97 (10 H, m, 5 CH_2), 2.44 (3 H, s, Me), 3.75 (3 H, s, MeO), 3.77 (3 H, s, MeO), 3.21 (1 H, m, CHN), 6.05 (1 H, s, CH), 7.26 (2 H, d, ^3J 8.1 Hz, 2 CH), 7.38 (2 H, d, ^3J 8.1 Hz, 2 CH), 7.76 (1 H, s, CH). 13C-NMR, δ: 22.1 (Me), 24.3 (CH2), 25.6 (CH2), 33.4 (CH2), 33.5 (CH2), 52.1 (CHN), 53.6 (MeO), 55.3 (MeO), 58.3 (CH), 60.9 (C=C=N), 121.7 (C), 130.5 (2 CH), 131.0 (C), 131.1 (2 CH), 133.9 (C), 141.1 (CH), 162.0, 167.4, 167.5, 170.1 and 192.4 (C=C=N, 3 C=O, C=S). Found (%): C, 59.3; H, 5.68; N, 5.70. Calc. for $C_{24}H_{26}N_2O_5S_2$ (%): C, 59.24; H, 5.39; N, 5.76.

4b:

Pale yellow oil, yield: 0.42 g (77%). IR (ν_{max}/ cm^{-1}): 2079 (C=C=N), 1745 and 1710 (C=O). ^{1}H-NMR, δ: 1.21-2.03 (10 H, m, 5 CH_2), 2.36 (3 H, s, Me), 3.69 (3 H, s, MeO), 3.76 (3 H, s, MeO), 3.99 (1 H, m, CHN), 6.12 (1 H, s, CH), 7.26-7.40 (4 H, m, 4 CH), 7.95 (1 H, s, CH). 13C-NMR, δ: 21.5 (Me), 25.7 (CH2), 25.9 (CH2), 27.1 (CH2), 33.2 (CH2), 51.4 (CHN), 52.3 (MeO), 57.1 (MeO), 59.4 (CH), 60.8 (C=C=N), 120.4 (C), 128.0 (CH), 129.6 (CH), 131.6 (CH), 133.3 (CH), 135.9 (C), 139.5 (C), 145.1 (CH), 159.9, 163.4, 166.0, 166.5 and 187.1 (C=C=N, 3 C=O, C=S). Found (%): C, 59.21; H, 5.25; N, 5.68. Calc. for $C_{24}H_{26}N_2O_5S_2$ (%): C, 59.24; H, 5.39; N, 5.76.

4c:

Yellow oil, yield: 0.39 g (73%). IR (ν_{max}/ cm^{-1}): 2058 (C=C=N), 1741 and 1710 (C=O). ^{1}H-NMR, δ: 1.21-1.99 (10 H, m, 5 CH_2), 3.43 (1 H, m, CHN), 3.70 (3 H, s, MeO), 3.81 (3 H, s, MeO), 6.15 (1 H, s, CH), 7.70 (2 H, d, ^3J 8.1 Hz, 2 CH), 8.02 (1 H, s, CH), 8.35 (2 H, d, ^3J 8.1 Hz, 2 CH). 13C-NMR, δ: 24.2 (CH2), 25.5 (CH2), 25.6 (CH2), 33.3 (CH2), 52.2 (CHN), 53.5 (MeO), 53.9 (MeO), 57.9 (CH), 60.8 (C=C=N), 117.6 (C), 124.8 (2 CH), 126.2 (C), 131.0 (2 CH), 131.4 (C), 139.8 (CH), 163.6, 165.0, 168.1, 169.5 and 174.1 (C=C=N, 3 C=O, C=S). Found (%): C, 53.36; H, 4.40; N, 8.20. Calc. for $C_{23}H_{23}N_3O_7S_2$ (%): C, C, 53.37; H, 4.48; N, 8.12.

4d:

Pale yellow oil, yield: 0.39 g (70%). IR (ν_{max}/ cm^{-1}): 2074 (C=C=N), 1740 and 1700 (C=O). ^{1}H-NMR, δ: 1.21-2.06 (10 H, m, 5 CH_2), 3.76

(3 H, s, MeO), 3.78 (3 H, s, MeO), 3.99 (1 H, m, CHN), 6.14 (1 H, s, CH), 7.18-7.25 (2 H, m, 2 CH), 7.48-7.57 (2 H, m, 2 CH), 7.88 (1 H, s, CH). ^{13}C-NMR, δ: 24.3 (CH2), 25.7 (CH_2), 31.4 (CH_2), 33.5 (CH_2), 34.3 (CH_2), 52.2 (CHN), 53.2 (MeO), 53.8 (MeO), 58.1 (CH), 60.9 (C=C=N), 115.1 (C), 117.0 (d, 2JCF 21.7 Hz , 2 CH), 121.1 (d, $^4J_{CF}$ 4.5 Hz , C),132.2 (d, $^1J_{CF}$ 330.0 Hz, C-F), 132.7 (d, $^3J_{CF}$ 8.2 Hz , 2 CH), 143.4 (CH), 165.5, 165.9, 167.0, 167.5 and 170.0 (C=C=N and 4 C=O). Found (%): C, 56.28; H, 4.82; N, 5.85. Calc. for $C_{23}H_{23}FN_2O_5S_2$ (%):C, 56.31; H, 4.73; F, 3.87; N, 5.71.

4e:

Pale yellow oil, yield: 0.39 g (71%). IR (ν_{max}/ cm^{-1}): 2076 (C=C=N), 1738 and 1711 (C=O). ^{1}H-NMR, δ: 1.22-2.06 (10 H, m, 5 CH_2), 3.72 (3 H, s, MeO), 3.78 (3 H, s, MeO), 3.99 (1 H, m, CHN), 6.12 (1 H, s, CH), 7.20 (H, dd, ^3J 4.8 Hz, ^3J 3.6 Hz, CH), 7.41 (H, d, ^3J 3.6 Hz, CH), 7.67 (H, d, ^3J 4.8 Hz, CH), 8.01 (1 H, s, CH). ^{13}C-NMR, δ: 24.3 (CH2), 25.7 (CH_2), 32.8 (CH_2), 52.1 (CHN), 53.2 (MeO), 53.7 (MeO), 58.2 (CH), 60.9 (C=C=N), 119.4 (C), 127.3 (C), 129.0 (CH), 132.5 (CH), 133.8 (CH), 138.0 (CH), 163.4, 165.3, 166.7, 167.5 and 198.0 (C=C=N, 3 C=O, C=S). Found (%): C, 52.54; H, 4.71; N, 5.64. Calc. for $C_{21}H_{22}N_2O_5S_3$ (%):C, 52.70; H, 4.63; N, 5.85.

4f:

Pale yellow oil, yield: 0.40 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 2082 (C=C=N), 1747 and 1705 (C=O). ^{1}H-NMR: δ_H = 1.22-2.04 (10 H, m, 5 CH_2), 3.48 (1 H, m, CHN), 3.71 (3 H, s, MeO), 3.77 (3 H, s, MeO), 6.12 (1 H, s, CH), 7.32-7.55 (5 H, m, 5 CH), 7.88 (1 H, s, CH). ^{13}C-NMR: δ_C = 22.0 (CH_2), 24.3 (CH_2), 33.4 (CH_2), 52.1 (CHN), 53.2 (MeO), 53.8 (MeO), 58.2 (CH), 60.8 (C=C=N), 120.1 (C), 130.2 (2 CH), 130.8 (2 CH), 130.7 (CH), 134.8 (C), 141.6 (CH), 165.5, 167.5, 167.7, 169.8 and 190.0 (C=C=N, 3C=O, C=S). Found (%): C, 58.37; H, 5.21; N, 5.92. Calc. for $C_{23}H_{24}N_2O_5S_2$ (%): C, 58.46; H, 5.12; N, 5.93.

4g:

Cream powder, yield: 0.31 g (72%). IR (ν_{max}/ cm^{-1}): 2052 (C=C=N), 1736 and 1705 (C=O). ^{1}H-NMR, δ: 1.20-1.81 (10 H, m, 5 CH_2), 3.48 (1 H, m, CHN), 3.70 (3 H, s, MeO), 3.77 (3 H, s, MeO), 3.99 (2 H, s, CH_2S), 5.99 (1 H, s, CH). ^{13}C-NMR, δ: 24.2 (CH_2), 33.4 (CH_2), 34.1 (CH_2), 35.9 (CH_2S), 52.2 (CHN), 53.2 (MeO), 53.7 (MeO), 57.7 (CH), 60.8 (C=C=N), 161.1, 167.4, 170.1, 170.5 and 191.0 (C=C=N 3 C=O and C=S). Found (%): C, 52.83; H, 5.32; N, 7.28 Calc. for $C_{16}H_{20}N_2O_6S_2$ (%): C, 49.98; H, 5.24; N, 7.29.

4h:

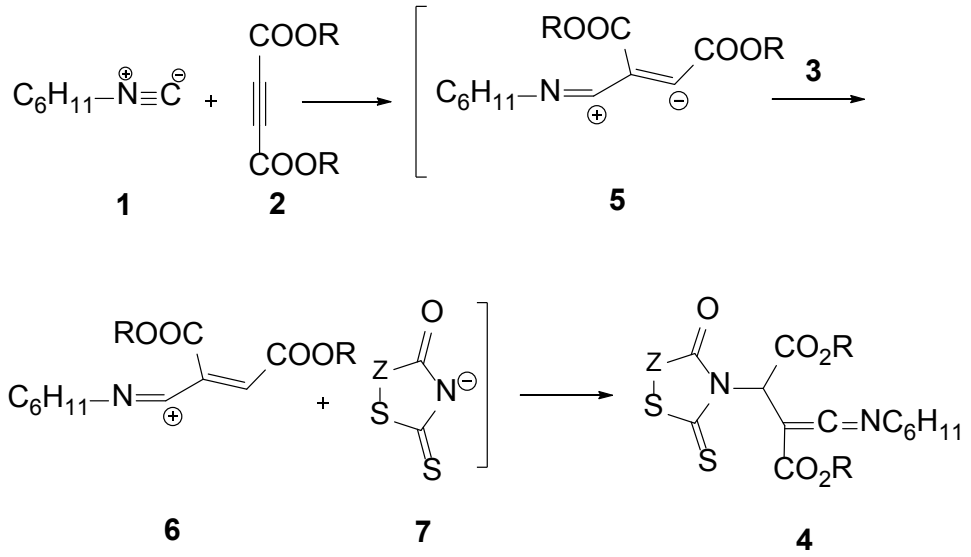
Cream powder, yield: 0.33 g (71%). IR (ν_{max}/ cm^{-1}): 2080 (C=C=N), 1742 and 1707 (C=O). ^{1}H-NMR, δ: 1.21 (3 H, t, ^3J 7.2 Hz, Me), 1.23 (3 H, t, ^3J 7.2 Hz, Me), 1.31-1.99 (10

H, m, 5 CH_2), 3.49 (1 H, m, CHN), 3.99 (2 H, s, CH_2S), 4.19 (2 H, q, ^3J 7.2 Hz, CH_2O), 4.27 (2 H, q, ^3J 7.2 Hz, CH_2O), 5.99 (1 H, s, CH). ^{13}C-NMR, δ: 14.5 (Me), 14.8 (Me), 24.1 (CH_2), 24.2 (CH_2), 33.4 (CH_2), 34.3 (CH_2S), 53.3 (CHN), 58.2 (CH_2O), 60.8 (CH_2O), 60.9 (CH), 62.9 (C=C=N), 160.4, 166.5, 170.0, 170.3 and 190.0 (C=C=N, 3C=O and C=S). Found (%): C, 54.60 H, 6.12; N, 7.11. Calc. for $C_{18}H_{24}N_2O_5S_2$ (%): C, 54.53; H, 6.10; N, 7.07.

Results and discussion

The reaction of cyclohexyl isocyanide **1** with electron deficient acetylenic esters **2** in the presence of **3** proceeded at room temperature in dichloromethane, and was completed within 12 h. The ^{1}HNMRspectrum of the reaction mixture indicated the formation of the stable ketenimines **4** (Scheme 1). The highly functionalized ketenimines **4** are quite stable; they were recovered unchanged after refluxing in toluene for 3 h. The structures of compounds 4 were deduced from their IR, ^{1}H-NMR, and ^{13}C-NMR spectral data. The ^{1}H-NMR spectrum of **4a** showed signals for methoxy (δ = 3.70 and 3.77 ppm), methyl (δ = 2.47 ppm), methine (δ = 6.05 ppm), aromatic (δ =7.32-7.45) and vinilic (δ = 7.76 ppm) protons, together with multiplet for the cyclohexyl (δ = 1.27-1.78 ppm and δ = 3.21 ppm) protons. The ^{13}C-NMR spectrum of **4a** exhibited 21 resonances in agreement with the proposed structure. ^{1}H- and ^{13}C-NMR spectra of **4b–h** were similar to those of **4a** except for the side chains, which exhibited characteristic resonances in the appropriate regions of the spectra. The sp^2-hybridized carbon atom of the ketenimine group in compounds **4** appear at δ = 58.2-60.2 ppm, as a result of strong electron delocalization. The structural assignments of compounds 4 made on the basis of their-NMR spectra are supported by their IR spectra. These compounds show strong absorption bands at about 2074-2082 cm^{-1} for the C=C=N moieties.

A plausible mechanism for formation of **4** is shown in Scheme 2. It is conceivable that the reaction involves the initial formation of the 1:1 zwitterionic intermediate **5** between isocyanide and the acetylenic ester. The protonation of **5** by the NH-acidic compound and the subsequent attack of the resulting nucleophile on the positively charged ion **6** afforded ketenimine **4** (Scheme 2).



Scheme 2. Proposed mechanism for the formation of compound **4**.

Conclusion

In conclusion, the three-component reaction of cyclohexyl isocyanides with dialkyl acetylenedicarboxylates in the presence of thioxothiazolidinones provides a simple one-pot synthesis of stable functionalized ketenimines of potential synthetic interest. This procedure has the advantages of high yields, mild reaction conditions, and simple experimental and work-up conditions.

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