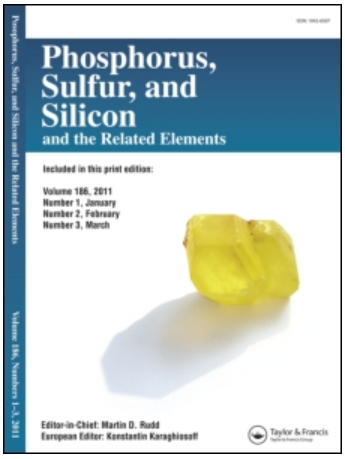

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Efficient Synthesis of Highly Functionalized, S -Alkyl 1-Alkyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioates

Issa Yavari[a]; Azizollah Habibi[a]
[a] University of Tarbiat Modarres, Tehran, Iran

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EFFICIENT SYNTHESIS OF HIGHLY FUNCTIONALIZED, *S*-ALKYL 1-ALKYL-4,4-DIMETHYL-2,5-DIOXO-PYRROLIDINE-3-CARBOTHIOATES

Issa Yavari and Azizollah Habibi
University of Tarbiat Modarres, Tehran, Iran

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5-Isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (the condensation product of Meldrum's acid and acetone) reacts with alkyl isocyanides in the presence of this to produce S*-alkyl 1-alkyl-4,4-dimethyl-2,5-dioxo-pyridine-3-carbothioates in good yield.*

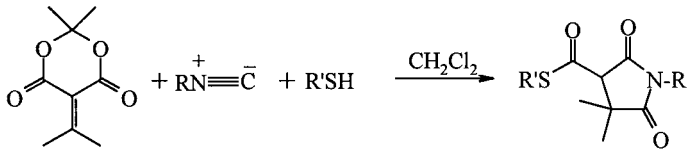
Keywords: Alkyl isocyanides; alkylidene Meldrum's acid; pyrrolidine; *S*-alkyl carbothioate; *S*-alkyl thioester; thiols

Three different type of thiocarboxylic esters exist: the thiol, thioxo-, and dithio- esters. Thiol carboxylic esters are the most common compounds among the three types of thioesters. They are activated derivatives of carboxylic acids and exhibit acylating properties similar to those of carbxylic acid anhydrides. They have therefore found widespread application in synthetic chemistry and have been used for preparing esters, amides, and peptides, especially macrocyclic ketones and lactones.[1–8] In view of the complex and sensitive nature of many target molecules synthesized today, mild and high-yield synthetic routes to thiol esters are desirable.[9–11]

Alkylidene Meldrum's acids are readily accessible from Meldrum's acid[12,13] (2,2-dimethyl-1, 3-dioxane-4,6-dione) and carbonyl compounds (ketones and aldehydes).[14] These compounds have been reported to be reasonably good Michael acceptors[15,16] as well as highly reactive dienophiles in Diels-Alder reactions.[17] However, synthetic applications of these Meldrum's acid derivatives have received little attention except the use of Meldrum's acid.

As part of our current studies on the reaction between isocyanides and electron-defficient alkenes,[18–19] we now report a simple one-flask

Address correspondence to Issa Yavari, Department of Chemistry, University of Tarbiat Modarres, PO Box 14115-175, Tehran, Iran. E-mail: isayavar@yahoo.com



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

2, 3, 4	R	R'	%Yield of **4**
a	Benzyl	*n*-Pentyl	80
b	^{t}Bu	Et	76
c	^{t}Bu	*n*-Propyl	83
d	^{t}Bu	*n*-Pentyl	69
e	Cyclohexyl	Et	74
f	Cyclohexyl	*n*-Propyl	70
g	Cyclohexyl	*n*-Pentyl	78

SCHEME 1

synthesis of highly functionalized thiol esters **4**. Thus, reaction of isopropylidene Meldrum's acid (5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione) **1** with alkyl isocyanides **2** in the presence of thiols **3** leads to the corresponding *S*-alkyl 1-alkyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioates **4** in good yields (Scheme 1).

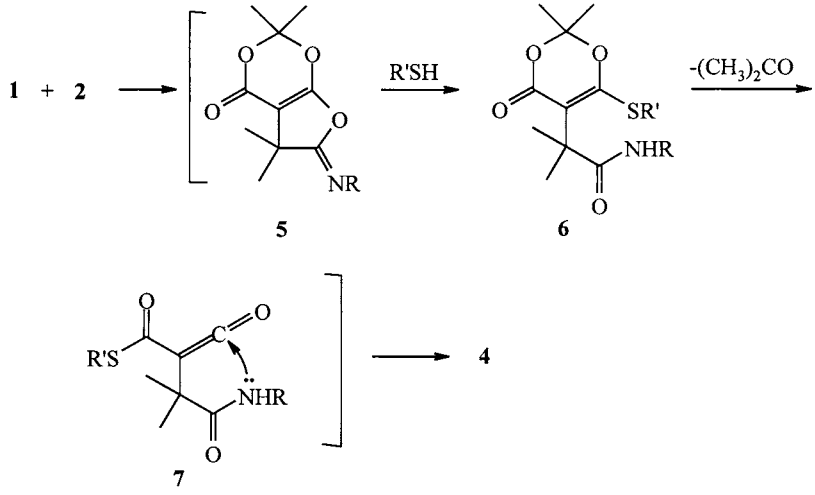
RESULTS AND DISCUSSION

The reaction of alkyl isocyanides **2** with isopropylidene Meldrum's acid in the presence of thiols proceeded slowly at room temperature in dichloromethane, and was complete within 24 h. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of *S*-alkyl 1-alkyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioates **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structures of compounds **4a–g** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. The mass spectra of these compounds displayed molecular ion peaks. The ^{1}H NMR spectrum of **4a** exhibited three single sharp lines readily recognized as arising from gem-dimethyl (δ 1.24 and 1.38) and methine (δ 3.66)

protons. The N—CH_2 protons are diastereotopic and exhibit an AB system ($\Delta\upsilon_{AB} = 22$ Hz, $J_{AB} = 14$ Hz). The pentyl and phenyl residues gave rise to charasteristic signals in the aliphatic and aromatic region of the spectrum. The ^{13}C NMR spectrum of **4a** shows signals for the carbonyl groups at δ 171.41 and 180.79 (2 C=O groups), and at δ 192.77 (for S—C=O), which confirms the presence of the dioxo-pyrrolidine-carbothioate structure in **4a**. The ^{15}N NMR spectrum of **4a** exhibits a single resonance at 178.09. This shift is in excellent agreement with the previously reported values for N-alkylsuccinimide.[20] The ^{15}N resonance of the imino nitrogen atom is expected to appear above δ 300.[21]

The ^1H and ^{13}C NMR spectra of **4b–g** are similar to those of **4a** except for the thiol ester and N-alkyl moieties, which exhibited characteristic resonances with appropriate chemical shifts. Partial assignments of ^1H and ^{13}C resonances in ^1H and ^{13}C NMR spectra of compounds **4a–g** are given in the Experimental section.

Although the mechanism of the reaction between isopropylidene Meldrum's acid and alkyl isocyanides in the presence of thiols has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[22,23] the first step of this mechanism involves the [4 + 1] cycloaddition reaction of the electron-defficient heterodiene moiety of isopropylidene Meldrum's acid with the isocyanide, producing an iminolactone intermediate **5**. Conjugate addition by the thiol on the enone moiety of 5, followed by cleavage of the five-membered ring gives **6** and hence the ketene **7** by well precedented[24] electrocyclic ring opening



SCHEME 2

of *O*-alkylated Meldrum's acids. The ketene **7** can then undergo intramolecular reaction between the amide and ketene moieties to give **4**.

We anticipate that the reaction described here presents a simple entry into the synthesis of polyfunctional thiol esters of synthetic interest. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches.[1–8]

EXPERIMENTAL

Isopropylidene Meldrum's acid was prepared by condensation of Meldrum's acid and acetone. Alkyl isocyanides and Meldrum's acid were obtained from Fluka (Buchs, Switzerland). Melting point was measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN—O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded at 500.1, 125.7, and 50.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with $CDCl_3$ as solvent.

Preparation of *S*-*n*-Pentyl 1-Benzyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4a)

General Procedure

To a magnetically stirred solution of 0.36 g isopropylidene Meldrum's acid (2 mmol) and 0.21 g *n*-pentyl thiol (2 mmol) in 10 mL of dichloromethane, was added dropwise a solution of 0.23 g benzyl isocyanide (2 mmol) in dichloromethane at room temperature over 2–3 min. The mixture was allowed to stand at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was separated by column chromatography using hexaneethyl acetate mixture as eluent. The solvent was evaporated at reduced pressure and the product **4a** was obtained as brown oil, 0.55 g, yield 80%. IR (KBr) (υ_{max}, cm^{-1}): 1771, 1701 and 1666 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ0.86 (3H, t, $^{3}J_{HH} = 7$ Hz, $CH_2\mathit{Me}$), 1.24 and 1.38 (6H, 2s, CMe_2), 1.33, 1.35, 1.60 (6H, 3m, $3CH_2$), 2.94 (2H, m, SCH_2) 3.66 (1H, s, CH), 4.66 (2H, ABq, $\Delta\upsilon_{AB} = 22$ Hz, $^{1}J_{HH} = 14$ Hz, NCH_2), 7.30 (5H, m, C_6H_5). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ13.87 ($CH_2\mathit{Me}$), 20.02 and 22.07 ($C\mathit{Me}_2$), 26.69, 28.77, 29.75, 30.84 ($4CH_2$), 42.75 (NCH_2), 44.04 (CMe_2), 55.16 (CH), 127.89, 128.23, 128.66, and 135.32 (C_6H_5), 171.41 and 180.79 (2C=O), 192.77 (SC=O). ^{15}N NMR (50.7 MHz, $CDCl_3$, liquid NH_3): δ_N 178.09 ppm

(imide N). MS (*m/z*, %): 347 (M^+, 5), 243 (10), 186 (10), 132 (14), 106 (18), 91 (100), 82 (20), 65 (16). Anal. Calcd for $C_{19}H_{25}NO_3S$ (347.5): C, 65.68; H, 7.25; N, 4.03%. Found: C, 65.7; H, 7.3; N, 4.1%.

S-*Ethyl 1*-tert-*Butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4b)*

Yellow powder, m.p. 40–42°C, 0.41 g, yield 76%. IR (KBr) υ_{max}, cm^{-1}): 1769, 1698 and 1668 (C=O). ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.20 and 1.35 (6H, 2s, CMe_2), 1.28 (3H, t, $^3J_{HH} = 7$ Hz, CH_2CH_3), 1.58 (9H, s, CMe_3), 2.97 (2H, m, CH_2), 3.53 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.38 (CH_2Me), 19.69 and 24.17 (CMe_2), 26.99 (CH_2), 28.17 (CMe_3), 43.51 (CMe_2), 58.78 (CMe_3), 65.89 (CH), 172.48 and 182.22 (2C=O), 193.38 (SC=O). MS (*m/z*, %): 271 (M^+, 5), 216 (48), 183 (26), 154 (70), 126 (38), 83 (82), 82 (100), 54 (100), 52 (70), 35 (56). Anal. Calcd for $C_{13}H_{21}NO_3S$ (271.4): C, 57.54; H, 7.80; N, 5.16%. Found: C, 58.0; H, 7.7; N, 5.1%.

S-n-*Propyl 1*-tert-*Butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4c)*

Brown wax, 0.47 g, yield 83%. IR (KBr) (υ_{max}, cm^{-1}): 1769, 1699, and 1671 (C=O). ^1H NMR (500.1 MHz, $CDCl_3$): δ 0.88 (3H, t, $^3J_{HH} = 7$ Hz, CH_2CH_3), 1.10 and 1.25 (6H, 2s, CMe_2), 1.48 (9H, s, CMe_3), 1.54 (2H, m, CH_2Me), 2.9 (2H, m, SCH_2), 3.45 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.17 (CH_3), 19.62 and 22.57 (CMe_2), 26.90 (CH_2Me), 28.10 (CMe_3), 31.48 (SCH_2), 43.41 (CMe_2), 58.64 (CMe_3), 65.92 (CH), 172.36 and 182.10 (2C=O), 193.32 (SC=O). MS (*m/z*, %): 285 (M^+, 4), 230 (24), 210 (10), 183 (20), 154 (46), 126 (22), 83 (36), 82 (100), 54 (52). Anal. Calcd for $C_{14}H_{23}NO_3S$ (285.4): C, 58.92; H, 8.12; N, 4.91%. Found: C, 58.8; H, 8.0; N, 4.8%.

S-n-*Pentyl 1*-tert-*Butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4d)*

Brown viscous oil, 0.43 g, yield 69%. IR (KBr) (υ_{max}, cm^{-1}): 1760, 1697, and 1670 (C=O). ^1H NMR (500.1 MHz, $CDCl_3$): δ 0.89 (3H, t, $^3J_{HH} = 7$ Hz, CH_2Me), 1.20 and 1.34 (6H, 2s, CMe_2), 1.57 (9H, s, CMe_3), 1.32, 1.34, 1.60 (6H, 3m, $3CH_2$), 2.94 (2H, m, SCH_2) 3.54 (1H, s, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.9 (CH_2Me), 19.73 and 21.0 (CMe_2), 28.19 (CMe_3), 27.02, 28.87, 29.69, 30.89 ($4CH_2$), 43.53 (CMe_2), 58.78 (CMe_3), 66.02 (CH), 172.52 and 182.26 (2C=O), 193.45 (SC=O). MS (*m/z*, %): 313 (M^+, 4), 298 (2), 258 (20), 183 (54), 154 (100), 127 (74), 126 (36), 112 (24), 83 (74), 82 (100), 54 (100). Anal. Calcd for $C_{16}H_{27}NO_3S$ (313.5): C, 61.31; H, 8.67; N, 4.47%. Found: C, 62.1; H, 8.5; N, 4.6%.

S-*Ethyl 1-Cyclohexyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4e)*

Brown wax, 0.44 g, yield 74%. IR (KBr) (υ_{max}, cm^{-1}): 1766, 1695, and 1665 (C=O). ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.25 and 1.38 (6H, 2s, CMe_2), 1.29–2.11 (10H, m, $5CH_2$, 1.38 (3H, t, $^3J_{HH} = 7$ Hz, CH_3), 2.95 (2H, m, SCH_2), 3.59 (1H, s, CH), 3.95 (1H, t of t, $^3J_{HH} = 12$ Hz, 4 Hz, NCH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.40 (CH_2*Me*), 19.78 and 24.07 (C*Me*$_2$), 24.22, 25.75, 25.79, 26.96, and 28.76 ($5CH_2$), 44.16 (*C*Me_2), 52.17 (NCH), 65.25 (CH), 171.68 and 181.25 (2C=O), 193.10 (SC=O). MS (*m/z*, %): 297 (M^+, 5), 216 (30), 154 (34), 131 (20), 126 (14), 89 (34), 82 (100), 65 (10), 52 (40), 35 (20). Anal. Calcd for $C_{15}H_{23}NO_3S$ (297.4): C, 60.58; H, 7.8; N, 4.71%. Found: C, 60.7; H, 7.9; N, 4.6%.

S-n-*Propyl 1-Cyclohexyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4f)*

Brown viscous oil, 0.43 g, yield 70%. IR (KBr) (υ_{max}, cm^{-1}): 1755, 1698, and 1674 (C=O). ^1H NMR (500.1 MHz, $CDCl_3$): δ 0.84 (3H, t, $^3J_{HH} = 7$ Hz, CH_2*CH*$_3$), 1.07 and 1.24 (6H, 2s, C*Me*$_2$), 1.15 1.98 (10H, m, $5CH_2$), 1.49, 2.79 (4H, 2m, $2CH_2$), 3.49 (1H, s, CH), 3.80 (1H t, of t, $^3J_{HH} = 12$ Hz, 4Hz, NCH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.10 (CH_2*Me*), 19.64 and 24.90 (C*Me*$_2$), 22.51 (*CH*$_2$Me), 25.61, 25.65, 26.73, 28.35 and 28.61 ($5CH_2$), 31.42 (SCH_2), 48.10 (NCH), 51.87 (CMe_2), 65.15 (CH, 171.47 and 181.03 (2C=O), 192.97 (SC=O). MS (*m/z*, %): 311 (M^+, 4), 230 (10), 154 (36), 126 (10), 83 (30), 82 (100), 65 (10), 52 (40), 35 (20). Anal. Calcd for $C_{16}H_{25}NO_3S$ (311.4): C, 61.70; H, 8.09; N, 4.50%. Found: C, 61.6; H, 8.1; N, 4.6%.

S-n-*Pentyl 1-Cyclohexyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carbothioate (4g)*

Brown viscous oil, 0.53 g, yield 78%. IR (KBr) (υ_{max}, cm^{-1}): 1741, 1697 and 1667 (C=O). ^1H NMR (500.1 MHz, $CDCl_3$): δ 0.87 (3H, t, $^3J_{HH} = 7$ Hz, CH_2*CH*$_3$), 1.24 and 1.35 (6H, 2s, CMe_2), 1.31, 1.34, and 1.61 (6H, 3m, $3CH_2$), 1.28–2.14 (10H, m, $5CH_2$), 2.93 (2H, m, SCH_2), 3.58 (1H, s, CH), 3.95 (1H, t of t, $^3J_{HH} = 12$ Hz, 4Hz, NCH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.86 (CH_2*Me*), 19.75 and 22.14 (C*Me*$_2$), 26.91, 28.76, and 29.69 ($3CH_2$), 25.07, 25.80, 28.49, 28.85 and 29.66 ($5CH_2$), 30.86 (SCH_2), 43.45 (NCH), 52.07 (*C*Me_2), 65.31 (CH), 171.60 and 181.15 (2C=O), 193.10 (SC=O). MS (*m/z*, %): 239 (M^+, 5), 236 (10), 154 (40), 128 (28), 89 (28), 82 (100), 67 (30), 52 (68), 35 (32). Anal. Calcd for $C_{18}H_{29}NO_3S$ (339.5): C, 63.68; H, 8.61; N, 4.13%. Found: C, 63.6; H, 8.7; N, 4.0%.

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