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An efficient synthesis of aryldithiocarbamic acid esters from Michael addition of electron-deficient alkenes with arylamines and CS_2 in solid media alkaline Al_2O_3

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ABSTRACT

An efficient synthesis of dithiocarbamic acid esters from Michael addition of electron-deficient alkenes with arylamines and CS_2 in solid media alkaline Al_2O_3 was presented. This method was suitable for a wide range of amines and a variety of Michael receptors. Specially, a series of aryldithiocarbamic acid esters was obtained from arylamines through this method. The protocol offers clean reactions and high yields with simple experimental procedures. Besides, the alkaline Al_2O_3 could be reused.

1. Introduction

Besides being widely used as fungicides to protect crops from fungal diseases,[1] dithiocarbamic acid esters have a number of other applications such as in photochemistry,[2] catalysis in the sulfur vulcanization of rubber,[3] detection and analysis of biological NO produced endogenously from NO synthases,[4] and polymerization.[5] Furthermore, functionalized carbamates are an important class of compounds and their medicinal and biological properties warrant study.[6] Dithiocarbamic acid esters were recently reported as potent anticancer agents[7] and cell apoptosis inhibitors.[8]

Because of the reasons mentioned above, the synthesis of dithiocarbamates has received considerable attention. In the past, dithiocarbamic acid esters could be prepared from the reaction of amines with expensive and toxic reagents, such as thiophosgene and isothiocyanate.[9] Recently, a one-pot reaction of amines with CS_2 and electrophilic reagents has been developed. Much effort has been focused on the exploration of reaction conditions for one-pot reaction.[10] Various bases, for instance, NaOH, $NaOC_2H_5$, Et_3N, Cs_2CO_3, and guanidine as well as different solvents such as DMF, DMSO, and methanol, have been used to catalyze or improve the reaction. Ranu and co-workers sped up the Michael reaction to generate dithiocarbamate derivatives by using ionic liquid.[11] Our group has recently found that anhydrous K_3PO_4 was a very effective base, and various classes of dithiocarbamic acid esters have been prepared in the presence of anhydrous K_3PO_4.[10h] Meanwhile, we extended this method to the epoxides and electrophilic alkenes as electrophilic reagents. More recently, Saidi's group has reported that the one-pot reaction could be performed without catalyst in water[12] or solvent free.[13] However, it is still a challenge to synthesize aryldithiocarbamic acid esters from arylamines, because few previous reports used aryl amines as substrates to participate in the synthesis of dithiocarbamates through Michael addition reactions since their low reactivity. In addition, yields for those reactions were generally low.[13b] Therefore, the need for the development of more general and environmentally benign methods remains. Herein, we wish to report an efficient synthesis of aryldithiocarbamic acid esters from Michael addition of arylamines, CS_2, and electrophilic alkenes in solid media alkaline Al_2O_3.

2. Results and discussion

During the course of developing new methodologies for the preparation of dithiocarbamic acid esters and related compounds, we have noticed that alkaline Al_2O_3 could boost the Michael reaction of aniline with CS_2 and methyl acrylate. This result arose our interest to develop an efficient procedure for the synthesis of aryldithiocarbamic acid esters.

Firstly, aniline or tetrahydropyrrole was chosen to react with CS_2 and methyl acrylate to screen the solid media. As shown in Table 1, alkaline Al_2O_3 exhibited the best effect among screened four kinds of solid media, i.e., silica gel, bentonite, Celite, and alkaline Al_2O_3.

After optimizing the conditions, we then examined the generality of these conditions to other substrates by using different arylamines and α,β-unsaturated compounds. The results are summarized in Table 2. All the reactions were performed smoothly under optimized conditions by stirring all reagents together in the

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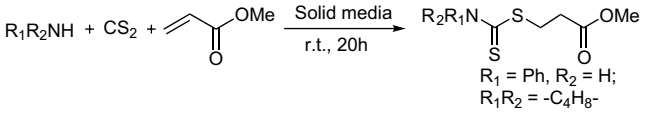
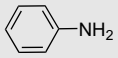
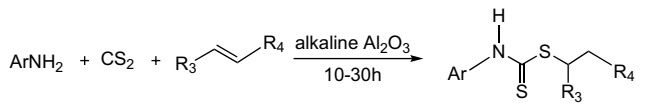
Table 1
The screen of solid media



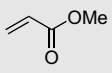
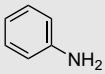
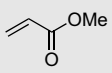
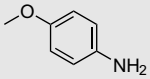
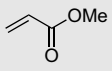
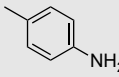
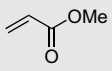
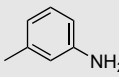
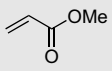
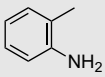
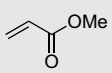
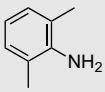
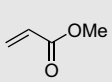
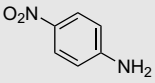
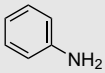
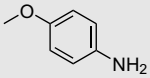
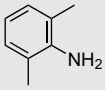
Solid media	Yield %	
		
Silica gel	Trace	84
Bentonite	Trace	61
Celite	Trace	58
Alkaline Al_2O_3	88	95

presence of alkaline Al_2O_3. Using methyl acrylate as Michael receptor, all tested arylamines, except 4-nitroaniline, gave the expected products in good to excellent yields (Table 2, entries 1–6, 64–93%). When methyl acrylate was used instead of acrylonitrile as Michael receptor, moderate yields were obtained (Table 2, entries 8–10). The property and the position of substituted groups in arylamines obviously influence the reactivity. Electron-donating substitute is favored to the reaction (Table 2, entries 2 and 3). Increasing of steric hindrance might lead the decreasing of yield (entry 6).

Table 2
The Michael addition reactions of aryl amines as Michael donors

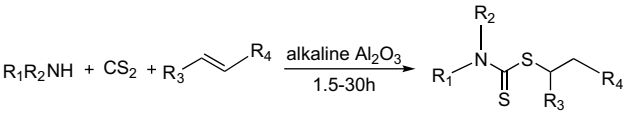


1

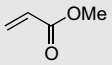
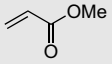
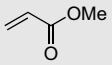
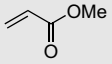
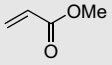
Entry	$R_3CH{=}CHR_4$	$ArNH_2$	Product	Yield[a] %
1			**1a**	88
2			**1b**	93
3			**1c**	92
4			**1d**	85
5			**1e**	80
6			**1f**	64
7			**1g**	0
8			**1h**	30
9			**1i**	58
10			**1j**	52

[a] Isolated yields.

Table 3
The Michael addition reactions of aliphatic amines as Michael donors



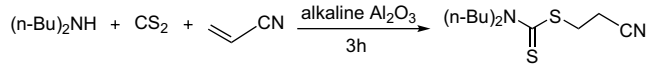
2

Entry	$R_3CH{=}CHR_4$	R_1R_2NH	Product	Yield[a] %
1			**2a**	95
2			**2b**	78
3			**2c**	95
4		$(n\text{-Bu})_2NH$	**2d**	94
5			**2e**	80
6			**2f**	91
7			**2g**	75
8			**2h**	93
9		$(n\text{-Bu})_2NH$	**2i**	92
10			**2j**	81
11			**2k**	95
12			**2l**	76
13			**2m**	92
14			**2n**	71
15			**2o**	70

[a] Isolated yields.

To explore the scope of the reaction, we also investigated the reaction of aliphatic amines and CS_2 with Michael acceptors. As shown in Table 3, all the aliphatic amines, including primary amines, acyclic or cyclic secondary amines, could afford the corresponding products in high yields when reacted with a variety of Michael acceptors such as methyl acrylate, acrylonitrile, cyclohexenone, 2-nitrovinylbenzene, chalcone, and 4-phenyl butene-2-one.

Table 4
The yield of the reactions using recycled alkaline Al_2O_3



Entry	Yield %
1	93
2[a]	91
3[b]	90
4[c]	88

[a] The first reuse.
[b] The second reuse.
[c] The third reuse.

Finally, recyclability of alkaline Al_2O_3 was examined through the reaction of dibutyl amine, CS_2, and acrylonitrile in alkaline Al_2O_3. After the reaction completed, the product was washed off with ethyl acetate from solid reaction mixture, and then the recovered alkaline Al_2O_3 was dried and reused. It was found from Table 4 that alkaline Al_2O_3 was recycled for three times without obvious loss of yield.

3. Conclusion

In summary, we have developed a novel and efficient method for the preparation of dithiocarbamic acid esters by Michael addition of electron-deficient alkenes with amines and CS_2 in solid media alkaline Al_2O_3. A wide range of amines, especially aryl amines, reacted with CS_2 and an array of Michael receptors to afford the Michael addition products in high yields. Notably, the reaction is clean and the alkaline Al_2O_3 could be reused without complex work up, which is required for 'green chemistry'.

4. Experimental section

4.1. General methods

The mixture of amine (0.5 mmol), carbon disulfide (0.5 mmol), and alkaline Al_2O_3 (0.5 g, commercial available, HF_{254} for TLC, pH: 9–10) was stirred at room temperature for 5 min. After the Michael acceptor (0.5 mmol) was added, the whole mixture was stirred vigorously for 1.5–30 h. Then, the solid mixture was washed with ethyl acetate (10 mL), and alkaline Al_2O_3 was filtered off. The organic solvent was removed under reduced pressure to give the desired product. The crude product was purified by recrystallization or column chromatography over silica gel. The alkaline Al_2O_3 could be recycled.

4.2. Methyl 3-(phenylcarbamothioylthio)propanoate (1a)[13b]

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.79 (t, 2H, J=6.9 Hz, CH_2CO), 3.51 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.66 (s, 3H, OCH_3), 7.26–7.43 (m, 5H, C_6H_5), 9.60 (br, 1H, NH).

4.3. Methyl 3-(4-methoxyphenylcarbamothioylthio)-propanoate (1b)

White powder; mp 91–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.80 (t, 2H, J=6.9 Hz, CH_2CO), 3.52 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.88–6.93 (m, 2H, C_6H_5), 7.27 (br, 2H, C_6H_5), 9.28 (br, 1H, NH). Anal. Calcd for $C_{12}H_{15}NO_3S_2$: C, 50.50; H, 5.30; N, 4.91. Found: C, 50.38; H, 5.32; N, 4.79.

4.4. Methyl 3-(*p*-tolylcarbamothioylthio)propanoate (1c)

White powder; mp 79–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H, CH_3), 2.81 (t, 2H, J=6.9 Hz, CH_2CO), 3.54 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.71 (s, 3H, OCH_3), 7.19–7.29 (m, 5H, C_6H_5), 8.84 (br, 1H, NH). Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.12. Found: C, 53.76; H, 5.63; N, 4.79.

4.5. Methyl 3-(*o*-tolylcarbamothioylthio)propanoate (1d)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.29 (s, 3H, CH_3), 2.80 (t, 2H, J=6.9 Hz, CH_2CO), 3.52 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.69 (s, 3H, OCH_3), 7.26–7.29 (m, 4H, C_6H_5), 8.69 (br, 1H, NH). Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.12. Found: C, 53.63; H, 5.69; N, 5.18.

4.6. Methyl 3-(*m*-tolylcarbamothioylthio)propanoate (1e)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H, CH_3), 2.81 (t, 2H, J=6.9 Hz, CH_2CO), 3.54 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.70 (s, 3H, OCH_3), 7.06–7.31 (m, 4H, C_6H_5), 8.87 (br, 1H, NH). Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.12. Found: C, 53.21; H, 5.29; N, 5.03.

4.7. Methyl 3-(2,6-dimethylphenylcarbamothioylthio)-propanoate (1f)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.26 (s, 6H, $2CH_3$), 2.76 (t, 2H, J=6.9 Hz, CH_2CO), 3.46 (t, 2H, J=6.9 Hz, CS_2CH_2), 7.34–7.44 (m, 3H, C_6H_5), 8.90 (br, 1H, NH). Anal. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.09; H, 6.05; N, 4.94. Found: C, 55.20; H, 5.97; N, 5.16.

4.8. 2-Cyanoethyl phenylcarbamodithioate (1h)

White powder; mp 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.88 (t, 2H, J=6.9 Hz, CH_2CN), 3.53 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.66 (s, 3H, OCH_3), 7.26–7.43 (m, 5H, C_6H_5), 9.60 (br, 1H, NH). Anal. Calcd for $C_{10}H_{10}N_2S_2$: C, 54.02; H, 4.53; N, 12.60. Found: C, 53.81; H, 4.46; N, 12.55.

4.9. 2-Cyanoethyl 4-methoxyphenylcarbamodithioate (1i)

White powder; mp 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.88 (t, 2H, J=6.9 Hz, CH_2CN), 3.49 (t, 2H, J=6.9 Hz, CS_2CH_2), 3.83 (s, 3H, OCH_3), 6.87–6.95 (m, 2H, C_6H_5), 7.16–7.26 (m, 2H, C_6H_5), 9.05 (br, 1H, NH). Anal. Calcd for $C_{11}H_{12}N_2OS_2$: C, 52.35; H, 4.79; N, 11.10. Found: C, 52.49; H, 4.81; N, 11.13.

4.10. 2-Cyanoethyl 2,6-dimethylphenyl carbamodithioate (1j)

White powder; mp 108–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.28 (s, 6H, $2CH_3$), 2.86 (t, 2H, J=6.9 Hz, CH_2CN), 3.43 (t, 2H, J=6.9 Hz, CS_2CH_2), 7.10–7.28 (m, 3H, C_6H_5), 8.89 (br, 1H, NH). Anal. Calcd for $C_{12}H_{14}N_2S_2$: C, 57.56; H, 5.64; N, 11.19. Found: C, 57.50; H, 5.77; N, 11.06.

4.11. 3-(Pyrrolidine-1-carbothioylsulfanyl)-propionic acid methyl ester (2a)[13b]

White powder; mp 46–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.94–2.12 (m, 4H, CH_2CH_2), 2.83 (t, 2H, J=6.6 Hz, CH_2CO), 3.58 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.64 (t, 2H, J=6.9 Hz, CH_2N), 3.71 (s, 3H, OCH_3), 3.93 (t, 2H, J=6.9 Hz, CH_2N).

4.12. 3-(4-Methyl-piperazine-1-carbothioylsulfanyl)-propionic acid methyl ester (2b)

White powder; mp 50–51 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.34 (s, 3H, CH_3N), 2.51 (s, 4H, NCH_2, NCH_2), 2.82 (t, 2H, J=6.6 Hz, CH_2CO), 3.59 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.71 (s, 3H, OCH_3), 3.95 (br, 2H, $CH_2N\,CS_2$), 4.36 (br, 2H, $CH_2N\,CS_2$). ^{13}C NMR (75 MHz; $CDCl_3$): δ=31.5, 33.7, 45.6, 51.8, 54.3, 172.4, 196.2. Anal. Calcd for $C_{10}H_{18}N_2O_2S_2$: C, 45.77; H, 6.91; N, 10.68. Found: C, 45.80; H, 6.78; N, 10.54.

4.13. 3-Isopropylthiocarbamoylsulfanyl-propionic acid methyl ester (2c)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (d, 6H, J=6.6 Hz, $2CH_3$), 2.79 (t, 2H, J=6.6 Hz, CH_2CO), 3.50 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.71 (s, 3H, OCH_3), 4.67–4.74 (m, 1H, CH), 6.88 (br, 1H, NH). Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.41; H, 6.83; N, 6.33. Found: C, 43.47; H, 6.58; N, 6.23.

4.14. 3-Dibutylthiocarbamoylsulfanyl-propionic acid methyl ester (2d)[14]

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–0.98 (m, 6H, $2CH_3$), 1.31–1.39 (m, 4H, $2CH_2$), 1.64–1.72 (m, 4H, $2CH_2$), 2.81 (t, 2H, J=6.6 Hz, CH_2CO), 3.56 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.63 (t, 2H, J=7.8 Hz, CH_2N), 3.70 (s, 3H, OCH_3), 3.94 (t, 2H, J=7.8 Hz, CH_2N).

4.15. 3-Benzylthiocarbamoylsulfanyl-propionic acid methyl ester (2e)[15]

White powder; mp 63–64 °C (lit. 64–66 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.81 (t, 2H, J=6.6 Hz, CH_2CO), 3.54 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.70 (s, 3H, OCH_3), 4.90 (d, 2H, J=5.1 Hz, $PhCH_2N$), 7.31–7.40 (m, 5H, C_6H_5).

4.16. Pyrrolidine-1-carbodithioic acid 2-cyano-ethyl ester (2f)[13b]

White powder; mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.96–2.16 (m, 4H, CH_2CH_2), 2.90 (t, 2H, J=6.6 Hz, CH_2CN), 3.54 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.67 (t, 2H, J=6.9 Hz, CH_2N), 3.92 (t, 2H, J=6.9 Hz, CH_2N).

4.17. 4-Methyl-piperazine-1-carbodithioic acid 2-cyano-ethyl ester (2g)

White powder; mp 43–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.36 (s, 3H, CH_3N), 2.52 (s, 4H, NCH_2, NCH_2), 2.89 (t, 2H, J=6.6 Hz, CH_2CN), 3.56 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.96 (br, 2H, $CH_2N\,CS_2$), 4.36 (br, 2H, CH_2NHCS_2). Anal. Calcd for $C_9H_{15}N_3S_2$: C, 47.13; H, 6.59; N, 18.32. Found: C, 47.31; H, 6.60; N, 18.10.

4.18. Isopropyl-dithiocarbamic acid 2-cyano-ethyl ester (2h)[16]

White powder; mp 99–100 °C (lit. 96 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (d, 6H, J=6.6 Hz, $2CH_3$), 2.86 (t, 2H, J=6.6 Hz, CH_2CN), 3.50 (t, 2H, J=6.6 Hz, CS_2CH_2), 4.63–4.74 (m, 1H, CH), 7.02 (br, 1H, NH).

4.19. Dibutyl-dithiocarbamic acid 2-cyano-ethyl ester (2i)[14]

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94–1.00 (m, 6H, $2CH_3$), 1.32–1.41 (m, 4H, $2CH_2$), 1.65–1.75 (m, 4H, $2CH_2$), 2.89 (t, 2H, J=6.6 Hz, CH_2CN), 3.53 (t, 2H, J=6.6 Hz, CS_2CH_2), 3.65 (t, 2H, J=7.8 Hz, CH_2N), 3.93 (t, 2H, J=7.8 Hz, CH_2N).

4.20. Benzyl-dithiocarbamic acid 2-cyano-ethyl ester (2j)[17]

White powder; mp 52–53 °C (lit. 54 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.87 (t, 2H, J=6.6 Hz, CH_2CN), 3.53 (t, 2H, J=6.6 Hz, CS_2CH_2), 4.89 (d, 2H, J=5.1 Hz, $PhCH_2N$), 7.33–7.42 (m, 5H, C_6H_5).

4.21. Diisopropyl-dithiocarbamic acid 2-cyano-ethyl ester (2k)[18]

White powder; mp 96–97 °C (lit. 103–104.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.23–1.41 (m, 12H, $4CH_3$), 2.89 (t, 2H, J=6.6 Hz, CH_2CN), 3.55 (t, 2H, J=6.6 Hz, CS_2CH_2), 4.14 (br, 1H, CH), 4.91 (br, 1H, CH). EIMS: m/z (%)=230 (M^+, 100), 177 (59), 176 (51), 130 (40), 100 (28), 40 (83).

4.22. Pyrrolidine-1-carbodithioic acid 3-oxo-cyclohexyl ester (2l)[12b]

White powder; mp 62–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.87–2.46 (m, 10H, CH_2CH_2, $CH_2CH_2CH_2CO$), 2.54 (dd, 1H, J=9.6, 14.4 Hz, 1H of CH_2CO), 2.89 (dd, 1H, J=4.8, 14.4 Hz, 1H of CH_2CO), 3.62 (t, 2H, J=6.9 Hz, CH_2N), 3.91 (t, 2H, J=6.9 Hz, CH_2N), 4.36–4.42 (m, 1H, CS_2CH).

4.23. Pyrrolidine-1-carbodithioic acid 2-nitro-1-phenyl-ethyl ester (2m)[19]

White powder; mp 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.94–2.12 (m, 4H, CH_2CH_2), 3.52–3.66 (m, 2H, CH_2N), 3.92 (t, 2H, J=6.9 Hz, CH_2N), 4.89 (dd, 1H, J=10.5, 13.5 Hz, 1H of CH_2NO_2), 5.33 (dd, 1H, J=5.1, 13.5 Hz, 1H of CH_2NO_2), 5.78 (dd, 1H, J=5.1, 10.5 Hz, CS_2CH), 7.30–7.41 (m, 5H, C_6H_5).

4.24. Pyrrolidine-1-carbodithioic acid 3-oxo-1,3-diphenyl-propyl ester (2n)[13b]

White powder; mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.91–2.09 (m, 4H, CH_2CH_2), 3.55–3.65 (m, 2H, CH_2N), 3.75 (dd, 1H, J=9.6, 17.1 Hz, 1H of CH_2COPh), 3.92 (t, 2H, J=6.9 Hz, CH_2N), 4.14 (dd, 1H, J=4.5, 17.1 Hz, 1H of CH_2COPh), 5.76 (dd, 1H, J=4.5, 9.6 Hz, CS_2CH), 7.19–7.99 (m, 10H, $2C_6H_5$).

4.25. Pyrrolidine-1-carbodithioic acid 3-oxo-1-phenyl-butyl ester (2o)

White powder; mp 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.94–2.06 (m, 4H, CH_2CH_2), 2.14 (s, 3H, $COCH_3$), 3.17 (dd, 1H, J=9.6, 16.2 Hz, 1H of CH_2CO), 3.46–3.58 (m, 3H, 1H of CH_2CO, CH_2N), 3.89–3.94 (m, 2H, CH_2N), 5.60 (dd, 1H, J=5.1, 9.6 Hz, CS_2CH), 7.22–7.43 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz; $CDCl_3$): δ=24.1, 26.0, 29.8, 49.8, 50.2, 50.5, 54.8, 127.7, 128.2, 128.6, 139.2, 190.9, 205.7. Anal. Calcd for $C_{15}H_{19}NOS_2$: C, 61.39; H, 6.53; N, 4.77. Found: C, 61.17; H, 6.40; N, 4.66.

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Supplementary data

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