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A New and Facile Protocol for the Synthesis of Dithiocarbamate-linked 3,4-Dihydro-2*H*-pyran Using *N*-Halo Catalysts Under Mild Conditions Reaction

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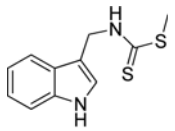
A new and facile protocol for the synthesis of dithiocarabamate in EtOH/H_2O is described. Reaction of aromatic and aliphatic amines with CS_2 and 3,4-dihydro-2*H*-pyran in the presence of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [PBBS] gives the corresponding dithiocarbamates in good to high yields.

Key Words : Dithiocarabamates, Amine, Carbon disulfide (CS_2), 3,4-Dihydro-2*H*-pyran (DHP), TBBDA, PBBS

Introduction

The development of simple, versatile, and environmentally friendly processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis. Organic sulfur compounds are widespread in numerous natural products and widely used as various artificial chemicals. Dithiocarbamates, in particular, are precursors with extensive uses in organic synthesis.[1-5] Synthesis of organic molecules *via* green, mild, and simple procedures is currently receiving considerable attention. Also, reducing or eliminating the use and generation of hazardous substances is a goal of green chemistry. In this context, EtOH/H_2O is the preferred choice as a solvent. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, are simple to handle, cheaper to operate, and are especially important in industry.[6] The development of efficient methods for the synthesis of dithiocarbamate has attracted significant interest. Dithiocarbamates are valuable compounds due to their interesting chemistry and wide utilities and applications. Reports in the literature demonstrate that the dithiocarbamate containing molecules show antibacterial, anthelmintic, anti-cancer, fungicidal, and growth depressant properties[7,8] and HIV-I NCp7 inhibitors.[9] The utility of dithiocarbamate group as linkers in solid phase organic synthesis[10,11] and in certain photochemical applications[12] is also well documented. The dithiocarbamate functionality chelates heavy metals that make them versatile ligands.[13] Dithiocarbamate (DTC) derivatives are well known as organic intermediates, rubber additive, additive of polluted water, and vulcanizing agents.[14] Brassinin[15] as shown in (Fig. 1), a crucial plant defense first isolated from cabbage, had cancer preventive activity. The antibacterial effect of dithiocarbamates was reported to arise by reaction with HS-groups of physiologically important enzymes by transfering the alkyl group of the dithioester to the HS-function of the enzyme.[16] Earlier approaches for the



Brassinin

Figure 1

synthesis of dithiocarbamate esters employed the reaction of an amine with expensive and toxic reagents such as thiophosgene and its derivatives.[17] Synthesis of substituted dithiocarbamates is carried out by a reaction of amine and carbon disulfide (CS_2) on electron-deficient alkene through Michael-type reaction in the presence of a base or solid alkaline Al_2O_3,[18] ionic liquid,[19] Cs_2CO_3, tetrabutylammonium iodide (TBAI),[20] and K_3PO_4,[21] however, in spite of their potential utility, many of these methods involve various drawbacks such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction time, tedious manipulations in the isolation of the pure products.

Result and Discaussion

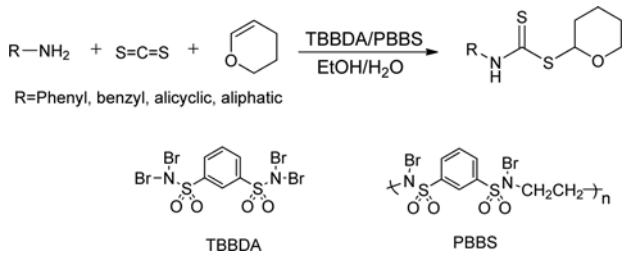
In a continuation of our interest in the application of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) (PBBS),[22] (Scheme 1), in organic synthesis,[23-35] we wish to report here a facile and improved protocol for preparation of dithiocarbamate derivatives, from amines, carbon disulfide (CS_2) and 3,4-dihydro-2*H*-pyran in the presence of TBBDA and PBBS as catalysts in EtOH/H_2O at ambient conditions (Scheme 1).

The advantages of TBBDA and PBBS are as follows:

1. The preparation of TBBDA and PBBS are easy.

2. TBBDA and PBBS are stable under atmospheric conditions for two months.

3. After completion of the reaction, the catalysts are recovered and can be reused several times without decreasing



Scheme 1. One-pot synthesis of *mono*-, *bis*-, and *tris* dithiocarbamate derivatives.

Table 1. Optimization of reaction conditions in room temperature

Entry	Solvent/Condition	TBBDA (g)	TBBDA	
			Time (h)	Yield (%)
1	CH_2Cl_2	0.05	10	30
2	CH_3CN/rt	0.05	4	35
3	CCl_4/rt	0.05	4	35
4	THF/rt	0.05	5	10
5	DMSO/rt	0.05	4.5	20
6	DMF/rt	0.05	7	35
7	CH_3OH/rt	0.05	5	60
8	CH_3CO_2Et/rt	0.05	5	45
9	EtOH/rt	0.05	6	70
10	Neat/rt	0.05	6	55
11	H_2O/rt	0.05	5.3	65
12	EtOH/H_2O/rt	No catalyst	12	40
13	EtOH/H_2O/rt	0.05	6	75
14	EtOH/H_2O/rt	0.06	1	95
15	EtOH/H_2O/rt	0.07	4.5	95
16	EtOH/H_2O/rt	0.100	3	95

[a]Standardization of reaction conditions: cyclohexylamine (6 mmol), carbondisulfide (7 mmol), 3,4-dihydro-2*H*-pyran isocyanide (7 mmol).

the yield.

Synthesis of organic molecules *via* green, mild, and simple procedures is currently receiving considerable attention. Also, reducing or eliminating the use and generation of hazardous substances is a goal of green chemistry. In this context, EtOH/H_2O is the preferred choice as a solvent. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, are simple to handle, cheaper to operate, and are especially important in industry.[36] Initially, we decided to explore the role of our catalysts in EtOH/H_2O as solvent system for the preparation of tetrahydro-2*H*-pyran-2-yl cyclohexylcarbamodithioate as a model compound. In the absence of catalyst, no product was observed, even after prolonged reaction time. Since, the synthesis of tetrahydro-2*H*-pyran-2-yl cyclohexylcarbamodithioate failed in the absence of catalyst, (Table 1, entry 12) the effect of catalysts was also investigated in various conditions. Since synthesis of this product was not suitable yields (Table 1, entries 1-11). We found that the best results were achieved using EtOH/H_2O (Table 1, entry 14). These results encouraged us to investigate the scope and generality of this new protocol for various amines, carbon disulfide and 3,4-dihydro-2-pyran (DHP) under optimized conditions.

To test the generality and versatility of this new procedure in the synthesis of dithiocarbamate derivatives, we examined a number of aliphatic, aromatic and alicyclic amines, in the presence of carbon disulfide (CS_2) and 3,4-dihydro-2*H*-pyran under optimized conditions (Table 2). The reaction was carried out in EtOH/H_2O (5 mL) at room temperature for appropriated time, using amine (6 mmol), carbondisulfide (7 mmol), 3,4-dihydro-2*H*-pyran (7 mmol) in the presence of TBBDA (0.108 mmol, 0.06 g) or PBBS (0.12 g). Since TBBDA contain bromine atoms which are attached to nitrogen atoms, it is very likely that they release Br^+ *in situ* which can act as Lewis acid catalyst in this reaction.

The possible mechanism for the formation of product is shown in Scheme 2. The generation of dithiocarbamat derivatives from reaction of amines, carbon disulfide (CS_2), and 3,4-dihydro-2*H*-pyran (DHP) most likely involves a Br^+ transfer from catalysts to amine and formation of *N*-bromoaminium (**A**)[35] then 3,4-dihydro-2*H*-pyran (DHP) activated by H^+ and generation tetrahydropyrylium (**B**) in cuntinued tetrahydropyrylium as electrophilic substrate was attacked by dithiocarbamate -SH group (**C**) for preparation of intermediate (**D**) in final elimination of Br produces the product (**E**) (Scheme 2).

Conclusion

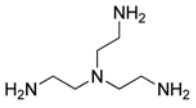
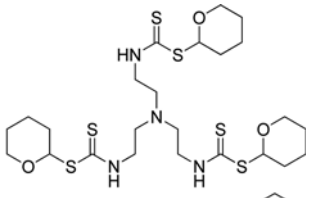
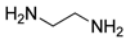
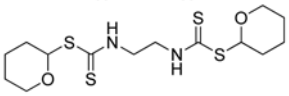
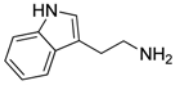
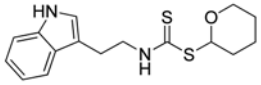
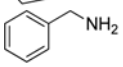
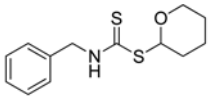
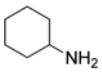
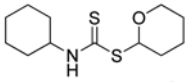
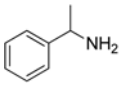
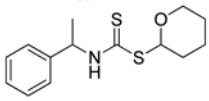
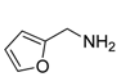
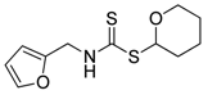
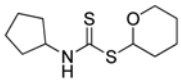
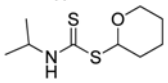
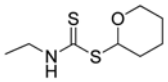
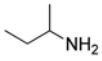
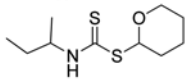
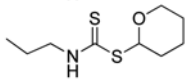
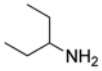
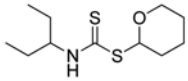
In summary, we have developed a new facile protocol for the synthesis of new aliphatic and aromatic dithiocarbamate derivatives, from the reaction of amines, carbondisulfide and 3,4-dihydro-2*H*-pyran compounds using TBBDA and PBBS under ambient temperature.

General Procedure for the Synthesis of Dithiocarbamate Derivatives. To a mixture of cyclohexyl amine (6 mmol), carbon disulfide (7 mmol), 3,4-dihydro-2*H*-pyran (7 mmol) in EtOH/H_2O (5 mL), TBBDA (0.108 mmol, 0.06 g) or PBBS (0.12 g) was added. The reaction mixture was stirred vigorously at room temperature for 60 min. Then, the products were extracted with ethyl acetate (2 × 20) and the combined organic layers were washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the products with high purity in most of the cases. If needed, the products were purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether; 3/5). The products were characterized by their IR, ^1H and ^{13}C NMR spectra and CHN analyses.

1: Tris(tetrahydro-2*H*-pyran-2-yl)(nitrilotris(ethane-2,1-diyl))tricarbamodithioate; mp 68-70 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (br s, 7.2 Hz, 3H), 6.43 (t, 6H), 4.00 (t, 6H), 3.94 (t, 6H), 1.96-2.53 (m, 18H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.8, 90.7, 68.6, 66.1 (2C), 50.4 (2C), 32.2, 27.7, 24.7; mass (*m/z*): 627; Anal. Calcd for $C_{24}H_{42}N_4O_3S_6$: C, 45.96; H, 6.75; N, 8.94. Found: C, 46.08; H, 6.77; N, 8.96.

2: Bis(tetrahydro-2*H*-pyran-2-yl) ethane-1,2-diyldicarbamodithioate: IR (neat) ν_{max} 2939, 1473, 1427, 1280, 1244, 1227, 1131, 1110, 1004, 892, 852, 800, 648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (s br, 2H), 6.03 (d, J = 4.1 Hz, 2H), 3.99 (m, 4H), 1.79-2.45 (m, 12H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.02, 90.6, 68.3, 54.2, 31.8, 25.8, 24.1, 24.4;

Table 2. Synthesis of *mono*-, *bis*,- and *tris* dithiocarbamate derivatives using *N*-halo catalysts

Entry	Substrate	Product	TBBDA		PBBS	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1			80	65	100	60
2			75	70	90	70
3			20	90	40	80
4			35	95	40	85
5			60	95	60	90
6			25	85	30	80
7			60	94	75	90
8			50	80	60	65
9			30	90	55	80
10			45	95	65	94
11			40	94	45	90
12			50	94	75	85
13			30	85	40	80

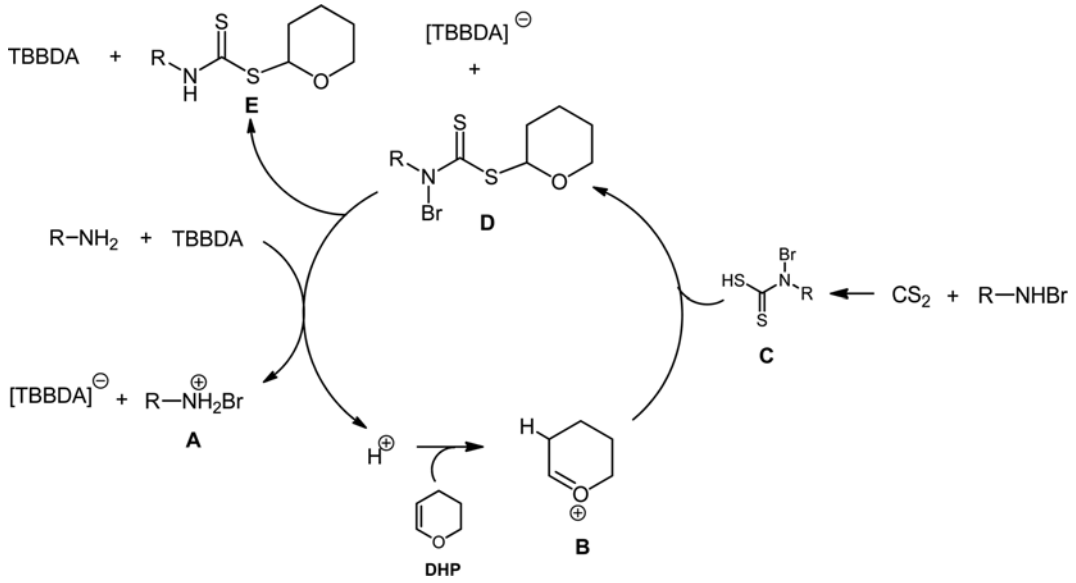
[a]Isolated yield

mass (*m/z*): 380; Anal. Calcd for $C_{14}H_{24}N_2O_2S_4$: C, 44.18; H, 6.36; N, 7.36. Found: C, 44.37; H, 6.38; N, 7.34.

3: Tetrahydro-2*H*-pyran-2-yl (2-(1*H*-indol-3-yl)ethyl)carbamodithioate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (br, 1H, NH), 8.20 (br, 1H, NH), 7.66 (d, *J* = 7.8 Hz, 1H), 7.39-7.11 (m, 4H), 5.77 (dd, *J* = 3.2, 7.4 Hz, 1H), 4.03 (m, 2H), 3.78 (m, 2H), 3.13 (m, 2H), 2.18 (m, 2H), 1.96-1.78 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.2, 136.2, 127.1, 122.4, 122.2, 119.4, 118.3, 112.1, 111.1, 86.2, 67.6, 46.7, 30.9, 24.6, 24.1; mass (*m/z*): 320; Anal. Calcd for $C_{16}H_{20}N_2OS_2$: C, 59.96; H, 6.29; N, 8.74. Found: C, 60.06; H, 6.31; N, 8.70.

4: Tetrahydro-2*H*-pyran-2-yl benzylcarbamodithioate: IR (neat) ν_{max} 3275, 2975, 1516, 1383, 1336, 1237, 1048, 932, 734, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (br, 1H, NH), 7.35 (m, 5H), 6.02 (br, 1H), 4.87-4.97 (m, 2H), 3.99 (m, 2H), 2.46-1.79 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 197.1, 136.6, 129.3, 128.3,128.2, 86.9, 68.9, 50.7, 31.9, 31.6, 24.7; mass (*m/z*): 267; Anal. Calcd for $C_{13}H_{17}NOS_2$: C, 58.39; H, 6.41; N, 5.24. Found: C, 58.60; H, 6.46; N, 5.24.

5: Tetrahydro-2*H*-pyran-2-yl cyclohexylcarbamodithioate: mp 50-52 °C, IR (neat) ν_{max} 3242, 2930, 2855, 1515, 1447, 1387, 1246, 1151, 1041, 986, 932, 886, 675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (br, 1H, NH), 5.94 (dd, *J* = 3.2, 7.2 Hz, 1H), 4.39 (m, 1H), 4.01 (m, 2H), 2.28 (m, 1H), 1.90-



Scheme 2. proposed mechanism for preparation of dithiocarbamate.

2.08 (m, 6H), 1.66-1.69 (m, 2H), 1.31-1.41 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.2, 86.4, 68.3, 54.4, 33.1, 32.5, 32.4, 25.3, 24.3, 22.1; mass (*m/z*): 259; Anal. Calcd for $C_{12}H_{21}NOS_2$: C, 55.56; H, 8.16; N, 5.40. Found: C, 55.64; H, 8.20; N, 5.36.

6: Tetrahydro-2*H*-pyran-2-yl (1-phenylethyl)carbamodithioate: IR (neat) ν_{max} 3274, 2977, 1516, 1494, 1435, 1377, 1136, 1094, 735, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br, 1H, NH), 7.26-7.39 (m, 5H), 5.95-6.04 (m, 1H), 5.75 (m, 1H), 3.94 (m, 2H), 2.29 (m, 1H), 2.04 (m, 1H), 1.87-1.95 (m, 3H), 1.60 (dd, *J* = 2.5, 6.8 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.2, 141.5, 128.7, 127.5,125.8, 86.6, 67.9, 54.9, 31.1, 24.3, 21.3, 20.9; mass (*m/z*): 281; Anal. Calcd for $C_{14}H_{19}NOS_2$: C, 59.75; H, 6.80; N, 4.98. Found: C, 60.05; H, 6.83; N, 5.06.

7: Tetrahydro-2*H*-pyran-2-yl (furan-2-ylmethyl)carbamodithioate: IR (neat) ν_{max} 3279, 2979, 1504, 1376, 1321, 1192, 1047, 932, 742, 599 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (br, 1H, NH), 7.34 (1H, s, CH), 6.29-6.30 (m, 2H), 5.96 (dd, *J* = 3.2, 7.2 Hz, 1H), 4.78-4.90 (m, 2H), 3.94 (m, 2H), 2.24 (m, 2H), 1.97 (m, 2H), 1.82-1.88 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 197.1, 149.6, 143.0, 111.0, 109.0, 87.1, 68.5, 49.1, 43.5, 31.6, 24.7; mass (*m/z*): 257; Anal. Calcd for $C_{11}H_{15}NO_2S_2$: C, 51.33; H, 5.87; N, 5.44. Found: C, 51.48; H, 5.88; N, 5.46.

8: Tetrahydro-2*H*-pyran-2-yl cyclopentylcarbamodithioate: mp 53-55 °C, IR (neat) ν_{max} 2970, 2868, 1464, 1436, 1250, 1185, 1161, 1053, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 3.9, 7.2 Hz, 1H), 3.83-3.94 (m, 4H), 3.51 -3.83 (m, 2H), 2.38 (m, 1H), 2.12 (m, 1H), 1.89 -2.02 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 191.0, 98.6, 68.3, 53.8, 50.6, 31.8, 25.8, 24.4, 24.0; mass (*m/z*): 245; Anal. Calcd for $C_{11}H_{19}NOS_2$: C, 53.84; H, 7.80; N, 5.71. Found: C, 54.06; H, 7.83; N, 5.78.

9: Tetrahydro-2*H*-pyran-2-yl isopropylcarbamodithioate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, b, NH), 5.92 (dd, *J* = 3.2, 7.4 Hz, 1H), 4.63 (m, 1H), 3.97 (m, 2H), 2.26 (m, 1H), 1.83-2.00 (m, 5H), 1.23-1.27 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.7, 86.3, 68.6, 47.9, 32.5, 30.9, 24.2, 22.2, 21.2; mass (*m/z*): 245; Anal. Calcd for $C_9H_{17}NOS_2$: C, 49.28; H, 7.81; N, 6.39. Found: C, 49.41; H, 7.83; N, 6.38.

10: Tetrahydro-2*H*-pyran-2-yl ethylcarbamodithioate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (br, 1H, NH), 5.97 (dd, *J* = 3.2, 7.2 Hz, 1H), 4.01 (dd, *J* = 6.2, 7.2 Hz, 2H), 3.37-3.76 (m, 2H), 2.31 (m, 2H), 1.87-2.05 (m, 4H), 1.25-1.30 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.2, 86.4, 67.9, 41.3, 32.5, 31.1, 24.6, 13.3; mass (*m/z*): 205; Anal. Calcd for $C_8H_{15}NOS_2$: C, 46.79; H, 7.36; N, 6.82. Found: C, 47.01; H, 7.37; N, 6.88.

11: Tetrahydro-2*H*-pyran-2-yl sec-butylcarbamodithioate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (br, 1H, NH), 5.94 (dd, *J* = 3.0, 7.4 Hz, 1H), 4.00 (m, 2H), 3.49 (m, 2H), 2.25 (m, 1H), 1.86-2.04 (m, 4H), 0.94-1.00 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.1, 86.2, 68.2, 53.5, 31.0, 28.1, 25.2, 20.0, 19.5; mass (*m/z*): 233; Anal. Calcd for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00. Found: C, 51.60; H, 8.22; N, 6.08.

12: Tetrahydro-2*H*-pyran-2-yl propylcarbamodithioate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (br, 1H, NH), 5.94 (m, 1H), 3.98-4.03 (m, 2H), 3.61 (m, 2H), 2.33 (m, 1H), 1.76-2.1 (m, 3H), 1.66 (m, 2H), 0.92 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.0, 86.2, 67.8, 47.9, 30.9, 23.9, 21.3,11.2; mass (*m/z*): 219 Anal. Calcd for $C_9H_{17}NOS_2$: C, 49.28; H, 7.81; N, 6.39. Found: C, 50.01; H, 7.82; N, 6.40.

13: Tetrahydro-2*H*-pyran-2-yl pentan-3-ylcarbamodithioate: IR (neat) ν_{max} 2975, 2933, 1486, 1410, 1141, 1268, 1056, 918, 831 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 3.9, 7.3 Hz, 1H), 3.90-4.03 (m, 4H), 3.65 (m, 2H), 2.42 (m, 1H), 2.21 (m, 1H), 1.96 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.0, 99.5, 68.4, 48.6, 46.8, 32.0, 24.9, 24.8, 12.4, 11.4; mass (*m/z*): 247; Anal. Calcd for $C_{11}H_{21}NOS_2$: C, 53.40; H, 8.55; N, 5.66. Found: C, 53.62; H, 8.56; N, 5.68.

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