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RESEARCH ARTICLE

An efficient, basic resin-mediated, one-pot regioselective synthesis of 2-hydroxy alkyl dithiocarbamates from corresponding epoxides

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A mild and efficient one-pot regioselective synthesis of 2-hydroxy alkyl dithiocarbamates was accomplished in high yields from the corresponding amines and epoxides using carbon disulfide mediated by Amberlite IRA 400 (basic resin).

Keywords: Amines; Amberlite IRA 400; Carbon disulfide; Epoxides; 2-Hydroxy alkyl dithiocarbamates

1. Introduction

2-Hydroxy alkyl dithiocarbamates have extensively been used as agrochemicals [1–5], pharmaceuticals [6–8], intermediates in organic synthesis [9–11], as multi-functional lubricant additives [12, 13] and electrophotographic liquid developer [14, 15]. Traditionally, the method for preparation of 2-hydroxy alkyl dithiocarbamates includes the reaction of dithiocarbamic salts, obtained from primary or secondary amines and carbon disulfide with epoxides [16, 17] or 2-hydroxy alkyl halides and the reaction of amino thio carboxylic halides with 1, 2-mercapto ethanol derivatives. Although, these methods are reliable, since two-step reaction is required and strong basic condition is not suitable for the reaction containing these sensitive groups. Though, Nedolya *et al.* [18] have reported that the addition of epoxides and 2-fold excess of carbon disulfide to Et_2NH at -20 to $-10^{\circ}C$ could give the corresponding 2-hydroxy alkyl dithiocarbamates, the examples are few and could not be successful to synthesize similar compounds using this method. Recently, Li and Saidi *et al.* [19–21] have reported the synthesis of 2-hydroxy alkyl carbamates from the corresponding epoxides and amines but both of these methods require longer reaction time and product purification through chromatographic techniques. Thus, we were prompted to embark on the improved procedures. Our group [22–33]

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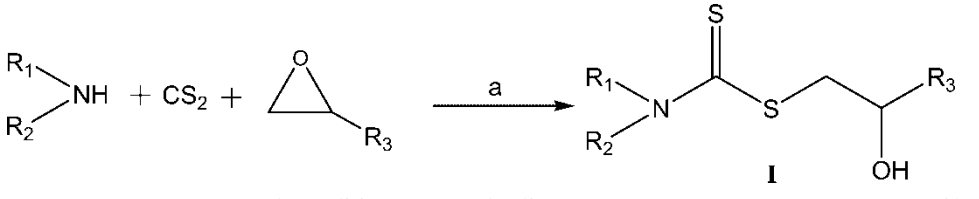
has been engaged from past several years for the development of new methodologies for the preparation of carbamates, dithiocarbamates and related compounds using cheap, abundantly available, and safe reagents like CO_2 and CS_2 respectively. More recently, we found [34–38] that Amberlite IRA 400 (basic resin) is the best reagent for the synthesis of carbamates, dithiocarbamates and dithiocarbonates (xanthates). In the present communication, we report here an efficient, one-pot, regioselective synthesis of 2-hydroxy alkyl dithiocarbamates by nucleophilic attack of dithiocarbamate anion to corresponding epoxides using basic resin/CS_2 system.

2. Results and discussion

In connection with our ongoing interest pertaining to the use of Amberlite IRA 400 (basic resin) for the synthesis of carbamates, dithiocarbamates and related compounds [34–38]. We now wish to report a simple and effective one-pot regioselective procedure for the preparation of 2-hydroxy alkyl dithiocarbamates from the corresponding epoxides, mediated by basic resin. Thus, a mixture of amine and CS_2 were taken in dry DMSO and Amberlite IRA 400 (basic resin) was added in it. Reaction mixture was stirred for 15 min and then the corresponding epoxide was slowly added to the above stirring reaction mixture at room temperature. It is proposed that the nucleophilic attack of the dithiocarbamate anion to the corresponding epoxides would lead to the formation of 2-hydroy alkyl dithiocarbamates. The reaction proved to be successful and the desired products isolated and further confirmed by various spectroscopic and analytical techniques. Since the products were simply obtained by concentration of organic layer after filtration of basic resin from the reaction mixture followed by extraction with ethyl acetate, indicates the novelty of the method among the reported procedures. Reactions have also been tried without using Amberlite resin, but no products could be observed, indicates the necessity of basic resin in carrying out the reaction. Thus, various kinds of aliphatic and heterocyclic amines were reacted with variety of epoxides to afford the corresponding 2-hydroxy alkyl dithiocarbamates regioselectively in high yields (78–98%) in 1–1.5 h. The results are summarized in table 1. This method was not successful while using aromatic amine especially aniline. The whole reaction conditions are shown in scheme 1.



SCHEME 1 Reagents and Conditions: (a) Amberlite IRA 400, CS_2, Dry DMSO, RT, 1–1.5 h.

We tried several solvents like *n*-heptane, *n*-hexane, acetonitrile, benzene, toluene, methanol, dichloromethane, chloroform, DMSO, DMF, hexamethylphosphoric triamide of which dry DMSO proved to be most suitable at room temperature.

In conclusion, we have developed a convenient and efficient protocol for one-pot, three components coupling of various amines with variety of epoxides via CS_2 bridge using basic resin (Amberlite IRA 400). This method generates the corresponding 2-hydroxy alkyl dithiocarbamates regioselectively in good to excellent yields. Furthermore, this method exhibits substrate versatility, mild reaction conditions and experimental convenience. This synthetic protocol

developed in our laboratory is believed to offer a more general method for the formation of carbon–sulfur bonds essential to numerous organic syntheses.

3. Experiment

Chemicals were procured from Merck, Aldrich and Fluka chemical companies. Amberlite IRA 400 (basic resin) was also perchased from Merck. Reactions were carried out under an atmosphere of nitrogen. IR spectra (4000–200 cm^{-1}) were recorded on Bomem MB-104–FTIR spectrophotometer where as NMRs were scanned on AC-300F, NMR (400 MHz), instrument using $CDCl_3$ and some other deutrated solvents and TMS as internal standard. Elemental analysis were made by Carlo-Erba EA 1110-CNNO-S analyzer and agreed favorably with calculated values.

3.1 *Typical experimental procedure*

To a stirred solution of amine (3 mmol) in anhyd. DMSO (5 mL) was slowly added, carbon disulfide (8 mmol) and basic resin (5 mmol) at room temperature. Then the mixture was stirred for 15 min. at room temperature. Now, corresponding epoxide (3 mmol) was added over a period of 5 min. The reaction mixture was further stirred till the completion of reaction (cf table 1) under argon. The reaction mixture was filtered to remove resin. The filtrate was poured into water (20 mL) and organic layer was extracted with EtOAc (3 × 10 mL). The organic layer was washed with 0.1 N HCl (20 mL), saturated solution of sodium bicarbonate (25 mL), brine (30 mL) and dried (Na_2SO_4) and concentrated to get the desired compound.

3.2 *Data for dithiocarbamates*

Butyl-dithiocarbamic acid 2-hydroxy-propyl ester (1). IR (Neat): $\ddot{v}$ (cm^{-1}) = 3225, 2962, 2932, 1511, 1458, 1394, 1336, 1305, 1124, 926; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.21–1.68 (m, 7H, CH_3 and CH_2CH_2), 2.96 (br, 1H, –OH), 3.11–3.18 (dd, 1H, $J = 7.2$, 14.2 Hz, SCH_2), 3.35–3.45 (m, 1H, *H*-SCH_2), 3.64 (m, 2H, NCH_2), 4.08 (m, 1H, *CH*OH), 8.17 (br, 1H, NH); Analysis : $C_8H_{17}NOS_2$, Calcd: C, 46.35; H, 8.28; N, 6.77; Obsd: C, 46.59; H, 8.35; N, 6.37.

Table 1. Conversion of epoxides into dithiocarbamates of general formula I.

Entry	R_1	R_2	R_3	Time (*h*)	Isolated yield (%)
1	C_4H_9	H	CH_3	1	92
2	C_4H_9	H	CH_2SCH_3	1	85
3	C_4H_9	H	$CH_2OC_6H_4 \cdot NO_2-P$	1.5	78
4	R_1=R_2=Piperidine		CH_3	1	98
5	R_1=R_2=Piperidine		CH_2SCH_3	1	95
6	R_1=R_2=Piperidine		$CH_2OC_6H_4 \cdot NO_2-P$	1.5	83
7	$R_1 = R_2 =$ 		CH_3	1	90
8	$R_1 = R_2 =$ 		CH_2SCH_3	1	87
9	$R_1 = R_2 =$ 		$CH_2OC_6H_4 \cdot NO_2-P$	1.5	83
10	C_6H_5	H	CH_2SCH_3	No reaction	–

Note: All the products were characterized by IR, NMR and Mass spectroscopic data.

Butyl-dithiocarbamic acid 2-hydroxy-3-methyl sulfanyl-propyl ester (2). IR (Neat): $\ddot{\nu}$ (cm^{-1}) = 3255, 2960, 2933, 2873, 1655, 1516, 1396, 1208, 1034, 928; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.29–1.68 (m, 4H, CH_2), 2.16 (s, 3H, S*CH*$_3$), 2.61–2.90 (m, 2H, $MeSCH_2$), 3.20–3.59 (m, 3H, SCH_2 and OH), 3.64 (m, 2H, N*CH*$_2$), 4.03 (m, 1H, *CH*$_2$OH), 7.90 (br, 1H, -NH); Analysis: $C_9H_{19}NOS_3$, Calcd: C, 42.65; H, 7.56; N, 5.52; Obsd: C, 42.81; H, 7.60; N, 5.11.

Butyl-dithiocarbamic acid 2-hydroxy-3-(4-nitro-phenoxy)-propyl ester (3). IR (Neat): $\ddot{\nu}$ (cm^{-1}) = 3310, 2959, 2930, 2871, 1593, 1514, 1460, 1340, 1264, 1176, 1115, 1028, 923; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.30–1.42 (m, 2H, CH_2), 1.55–1.68 (m, 2H, CH_2), 2.78 (br, 1H, OH), 3.47–3.55 (dd, 1H, $J = 7.0, 15.4$ Hz, SCH_2), 3.64–3.83 (m, 3H, N*CH*$_2$ and S*CH*$_2$), 4.12 (m, 2H, *CH*OH and ArO*CH*$_2$), 4.33 (m, 1H, $ArOCH_2$), 6.98 (d, 2H, $J = 9.0$ Hz), 7.54 (br, 1H, N*H*); 8.20 (d, 2H, $J = 9.0$ Hz, Ar); Analysis: $C_{14}H_{20}N_2O_4S_2$, Calcd: C, 4882; H, 5.85, , 8.13; Obsd: C, 48.86; H, 5.85; N, 7.82.

Piperidine-1-carbodithioc acid 2-hydroxy-propyl ester (4). IR (KBr): $\ddot{\nu}$ (cm^{-1}) = 3325, 2936, 2851, 1474, 1279, 1228, 1115, 1006; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.69 (br, 6H, CH_2), 2.58 (s, 1H, O*H*), 3.32–3.40 (dd, 1H, $J = 7.2, 14.4$ Hz, S*CH*$_2$), 3.62–3.69 (dd, 1H, $J = 3.6, 14.4$ Hz, SCH_2), 3.92 and 4.26 (br, 4H, NCH_2), 4.08 (m, 1H, CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 195.74, 66.79, 53.45, 51.52, 44.78, 25.98, 25.40, 24.17, 22.38$; Analysis: $C_9H_{17}NOS_2$: Calcd: C, 50.66; H, 7.81; N, 6.39; Obsd: C, 50.40, H, 7.70, N, 6.14.

Piperidine-1-carbodithioc acid 2-hydroxy-3-methylsulfanyl ester (5). IR (KBr): $\ddot{\nu}$ (cm^{-1}) = 3364, 2938, 2917, 1476, 1434, 1235, 1110, 1036, 975; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.65$ (br, 6H, CH_2), 2.10 (s, 3H, CH_3), 2.55–2.62 (dd, 1H, $J = 7.8, 13.8$ Hz, $MeSCH_2$), 2.70–2.76 (dd, 1H, $J = 5.1, 13.8$ Hz, $MeSCH_2$), 3.18 (br, 1H, OH), 3.39–3.46 (dd, 1H, $J = 7.2, 14.4$ Hz, S*CH*$_2$), 3.70–3.76 (dd, 1H, $J = 3.6, 14.4$ Hz, S*CH*$_2$), 3.87 and 4.23 (br, 4H, N*CH*$_2$), 4.04 (m, 1H, *CH*OH); Analysis : $C_{10}H_{19}NOS_3$: Calcd: C, 45.25; H, 7.22; N, 5.27; Obsd: C, 45.48, H, 7.36; N, 4.96.

Piperidine-1-carbodithioc acid 2-hydroxy-3-(4-nitro-phenoxy) propyl ester (6). IR (KBr): $\ddot{\nu}$ (cm^{-1}) = 3408, 2946, 2860, 1596, 1515, 1430, 1340, 1275, 1245, 1115, 1027, 980; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.71$ (br, 6H, CH_2), 2.68 (br, 1H, OH), 3.63–3.70 (dd, 1H, $J = 6.9, 14.7$ Hz, S*CH*$_2$), 3.81–3.87 (dd, 1H, $J = 4.2, 14.7$ Hz, S*CH*$_2$), 3.92 and 4.28 (br, 4H, N*CH*$_2$), 4.14 (m, 2H, *CH*OH and OCH_2), 4.36 (m, 1H, O*CH*$_2$), 6.97 (d, 2H, $J = 9.3$ Hz, Ar), 8.17 (d, 2H, $J = 9.3$ Hz, Ar); Analysis: $C_{15}H_{20}N_2O_4S_2$, Calcd: C, 50.54; H, 5.66; N, 7.86; Obsd: C, 50.45; H, 5.72, N, 7.70.

3,4-Dihydro-1*H*-isoquinoline-2-carbodithioc acid 2-hydroxy-propyl ester (7). IR (Neat): $\ddot{\nu}$ (cm^{-1}) = 3407, 2970, 2928, 1410, 1282, 1220, 1115, 960, 750; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.34$ (d, 3H, $J = 6.3$ Hz, CH_3), 2.60 (br, 1H, OH), 3.05 (br, 2H, Ar*CH*$_2$), 3.40–3.48 (dd, 1H, $J = 7.2, 14.2$ Hz, S*CH*$_2$), 3.72–3.76 (d, 1H, $J = 14.1$ Hz, S*CH*$_2$), 4.16 (m, 2H, *CH*OH), 4.48 (br, 1H, NCH_2), 5.08 and 5.34 (br, 2H, $ArCH_2N$), 7.25 (m, 4H, Ar); Analysis : $C_{13}H_{18}NOS_2$, Calcd: 58.39, H, 6.41; N, 5.24; Obsd: C, 57.80, H, 6.29; N, 5.02.

3,4-Dihydro-1 *H*-isoquinoline-2-carbodithioc acid 2-hydroxy-3-methyl sulfanyl propyl ester (8). IR (KBr): $\ddot{v}$ (cm^{-1}) = 3332, 2918, 1420, 1373, 1283, 1240, 1064, 960, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3H, CH_3), 2.62–2.70 (dd, 1H, J = 7.8, 13.8 Hz, MeSCH_2), 2.80–2.86 (dd, 1H, J = 4.8, 13.8 Hz, MeSCH_2), 3.02 (br, 3H, ArCH_2 and –OH), 3.51–3.58 (dd, 1H, J = 7.2, 14.4 Hz, MeSCH_2), 3.84–3.90 (d, 1H, J = 14.4 Hz, SCH_2), 4.12 (m, 2H, CHOH and NCH_2), 4.46 (br, 1H, NCH_2), 5.06 and 5.34 (br, 2H, ArCH_2N), 7.25 (m, 4H, Ar); Analysis: $C_{14}H_{19}NOS_3$: Calcd: 53.64; H, 6.11; N, 4.47; Obsd: C, 53.85; H, 6.40; N, 4.65.

3,4-Dihydro-1 *H*-isoquinoline-2-carbodithioc acid 2-hydroxy-3-(4-nitro-phenoxy)- propyl ester (9). IR (KBr): $\ddot{v}$ (cm^{-1}) = 3385, 2916, 1592, 1509, 1415, 1272, 1093, 1023, 846, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (br, 1H, OH), 3.00 (br, 2H, ArCH_2), 3.66–3.73 (dd, 1H, J = 7.0, 14.5 Hz, SCH_2), 3.84–3.90 (d, 1H, J = 15 Hz, SCH_2), 4.12–4.22 (m, 3H, ArOCH_2, CHOH), 4.35–4.44 (m, 2H, NCH_2), 5.04 and 5.31 (br, 2H, $ArCH_2N$), 6.97 (d, 2H, J = 9.3 Hz, p-NO_2-Ph-), 7.20 (m, 4H, Ar-); Analysis: $C_{19}H_{20}N_2O_4S_2$, Calcd: C, 56.41; H, 4.98; N, 6.93; Obsd: C, 56.44; H, 5.25; N, 6.73.

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