Novel Synthetic Strategy of Cyclic Dithiocarbamates Catalyzed by Triton-B

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A simple, rapid and green methodology to synthesize cyclic dithiocarbamates (compounds **1-9**) was developed by the reaction of 1° amines, CS₂ and ethyl 3-bromo-2-oxopropanoate (ethyl bromopyruvate) facilitated by Triton-B as phase transfer catalyst. These compounds (**1-9**) were characterized with the help of elemental analysis, IR, NMR and mass spectroscopic methods. This efficient green approach requires mild conditions and gives good yield of product. *In vitro* antimicrobial activities of these compounds are reported against the pathogenic bacteria and fungi.

Keywords: Carbon disulfide, Primary amine, Dithiocarbamates, Triton-B, Phase transfer catalyst.

INTRODUCTION

Dithiocarbamates, an analog of carbamates in which both the oxygen atoms are substituted by sulphur. Dithiocarbamates are the privileged molecules with multifarious usages and applications in pharmaceuticals [1-4], agriculture as pesticides [5], fungicides [6], insecticides [7], herbicides [8], group transfer radical cyclization reactions [9]. They have strong tendency to form stable metal-complexes due to their strong binding properties *via* sulphur atom [10]. Technetium and rhenium dithiocarbamates complexes found application in molecular electronics [11], radiopharmaceutical for medical imaging [12]. Dithiocarbamates have been utilized to treat intense poisoning by cadmium and copper complexes likewise have been explored as SOD inhibitors [13]. Recently, they have been reported to be used as chemicals against pest, fungi, insects *etc.* in agriculture [3,4,14]. They show numerous biological activities [1,15-21]. Furthermore, it has been comprehended through a number of available reports that biological activities of molecules increase diversely by incorporating dithiocarbamate moiety into it [22]. Organic dithiocarbamates have been used as the synthon for various synthesis [23-32] *etc.* and considered as the important biological moiety.

Dithiocarbamates are lipophilic in nature, which enables them to pass through cell barrier to reach the site in the body [33-36]. Dithiocarbamates are found to have toxicological activity [37]. Due to their inclusive remarkable applications, dithiocarbamates chemistry have gained the consideration of organic chemists during recent spans. Traditional method uses toxic chemicals such as phosgene and its derivatives to prepare organic dithiocarbamates are costly and require longer reaction time and temperature. Number of highly effectual green methods is described in literature [38] to synthesize dithiocarbamates. The sustainable practices for synthesizing dithiocarbamates mediated by trimethylbenzyl ammonium hydroxide (Triton-B) as a catalyst [39] with carbon disulfide [40] as economical reagent, has emerged as the new safe methodology. This methodology involves low cost phase transfer catalyst, Triton-B that can be recovered after reaction. So recently methodologies using mild reaction conditions for synthesizing dithiocarbamates using Triton B as phase transfer catalyst are of great interest. In the current report, we describe a one pot, green synthesis of dithiocarbamate starting from the corresponding ethyl 3-bromo-2-oxopropanoate, 1° amines and carbon disulphide mediated by Triton-B.

EXPERIMENTAL

Chemicals bought from GLR, AVRA, Alfa-Aesar and Lobachem, Finar, Labchem. ABB Bomem MB-104-FTIR spectrophotometer was used for recording infrared spectra (4000-200 cm^{-1}). The AC-400F-nuclear magnetic resonance spectrometer, with Me_4Si as internal standard was used for recording ^1H NMR spectra at 400 MHz. The investigation of elements were conveyed with the help of a 1110-CNNO-S (Carlo-ErbaEA) analyzer. There is good covenant between observed and calculated values

Protocol: At room temperature, 2 mmol of amine and 10 mmol of CS_2 were stirred for 15 min. Then 1 mmol of Triton-B was added and solution was agitated for 15 more minutes. After that 1 mmol ethyl 3-bromo-2-oxopropanoate was added and stirred for 2 h. The TLC technique was used for observing the progress of reaction. When the reaction was achieved, added a small volume of water and extracted the product thrice by adding 20 mL of $\text{CH}_3\text{COOC}_2\text{H}_5$. The crude product was recovered from organic layer after separating and washing it with saturated brine followed by drying and purification.

Antimicrobial studies: Bacteria and fungus have displayed a notable capability of inertness towards chemotherapeutic agents and the quest for new potent drugs is in progress. Four bacterial and three fungal strains were selected for *in vitro* antimicrobial studies. *Staphylococcus aureus* (MTCC96), *Streptococcus pyogenes* (MTCC 442), *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC1688), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) are the tested strains for antibacterial and antifungal activities. Procurement of microbial culture was done from IMTech, Chandigarh.

Determination of MIC, antimicrobial potency of synthesized cyclic dithiocarbamates: MIC, measure of antimicrobial potency, is the minimum concentration of a range of antimicrobial dilutions that constrains detectable growth of microbes within a defined period of time. Andrew's micro dilution tube method [41] was adopted to determine the MIC of synthesized compounds. For comparison, standard drugs, chloramphenicol and nystatin were chosen as positive control whereas pure Dimethyl sulfoxide as negative control. After inoculation, tubes were incubating at 37 °C for 1 day. Subsequently, antimicrobial potency in turns of MIC was determined from observed turbidity in inoculated tubes.

Spectral data

Ethyl 3-(4-methoxybenzyl)-4-hydroxy-2-thioxothiazolidine-4-carboxylate (1): Yellowish viscous oily, m.f. $\text{C}_{13}\text{H}_{15}\text{NO}_4\text{S}_2$, Calculated C = 49.82; H = 4.82; N = 4.47; O = 20.42; S = 20.46. Found C = 49.91; H = 4.88; N = 4.52; O = 20.55; S = 20.68. IR (neat, cm^{-1}): 3219, 1746, 1583, 1471, 1393, 1332, 1195 (C=S); 1149; ^1H NMR 400 MHz (CDCl_3): δ 7.153 (d, J = 8.0 Hz, 2H), 6.931 (d, J = 8.4 Hz, 2H), 4.809 (s, 1H), 4.257 (q, J = 7.2 Hz, 2H), 4.032 (d, J = 12.0 Hz, 1H), 3.813 (s, 3H), 3.472 (d, J = 12.0 Hz, 1H), 1.308 (t, J = 6.8 Hz, 3H). MS (ESI): m/z = 314.17 $[\text{M}]^+$.

Ethyl 3-(4-(trifluoromethyl)benzyl)-4-hydroxy-2-thioxothiazolidine-4-carboxylate (2): Yellowish viscous oily, m.f.

$\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}_3\text{S}_2$, Calculated C = 46.02; H = 3.86; F = 15.60; N = 3.83; O = 13.14; S = 17.55. Found C = 46.20; H = 3.98; F = 15.82; N = 3.98; O = 13.35; S = 17.75. ^1H NMR 400 MHz (CDCl_3): δ 7.558 (d, J = 8.0 Hz, 2H), 7.473 (d, J = 8.0 Hz, 2H), 5.427 (d, J = 15.6 Hz, 1H), 4.927 (s, 1H), 4.550 (d, J = 15.6 Hz, 1H), 4.027-3.947 (m, 1H), 3.578 (d, J = 12.0 Hz, 1H), 3.511-3.385 (m, 2H), 1.042 (t, J = 7.2 Hz, 3H). MS (ESI): m/z (M) $^+$.

Ethyl 4-hydroxy-3-pentyl-2-thioxothiazolidine-4-carboxylate (3): Yellow oily, m.f. $\text{C}_{11}\text{H}_{19}\text{NO}_3\text{S}_2$, Calculated C = 47.63; H = 6.90; N = 5.05; O = 17.30; S = 23.12. Found C = 47.74; H = 6.98; N = 5.15; O = 17.36; S = 23.32. ^1H NMR 400 MHz (CDCl_3): δ 4.798 (bs, 1H), 4.430-4.341 (m, 2H), 3.692-3.597 (m, 2H), 3.435-3.350 (m, 2H), 1.387-1.208 (m, 6H), 0.925-0.805 (m, 6H). MS (ESI): m/z (M) $^+$ calculated = 277.08, Found (M+1) $^+$: 277.09.

Ethyl 3-(ethoxyethyl)-4-hydroxy-2-thioxothiazolidine-4-carboxylate (4): Yellow oily, m.f. $\text{C}_{10}\text{H}_{17}\text{NO}_4\text{S}_2$, Calculated C = 42.99; H = 6.13; N = 5.01; O = 22.91; S = 22.95. Found C = 43.12; H = 6.27; N = 5.11; O = 23.01; S = 23.15. ^1H NMR 400 MHz (CDCl_3): δ 6.395 (bs, 1H), 4.581-4.532 (m, 1H), 4.374-4.329 (m, 2H), 4.323-3.627 (m, 2H), 3.621-3.478 (m, 3H), 3.369-3.292 (m, 2H), 1.352 (t, J = 7.2 Hz, 3H), 1.257 (t, J = 6.8 Hz, 3H). MS (ESI): m/z (M) $^+$ calculated = 279.06, Found (M+1) $^+$: 280.11.

Ethyl 4-hydroxy-3-(2-methylpentan-2-yl)-2-thioxothiazolidine-4-carboxylate (5): Yellow oily, m.f. $\text{C}_{11}\text{H}_{19}\text{NO}_3\text{S}_2$, Calculated C = 47.63; H = 6.90; N = 5.05; O = 17.30; S = 23.12. Found C = 47.73; H = 6.95; N = 5.13; O = 17.45; S = 23.23 %. ^1H NMR 400 MHz (CDCl_3): δ 4.806 (bs, 1H), 4.468-4.317 (m, 3H), 3.629 (d, J = 12.0 Hz, 1H), 3.446 (d, J = 11.6 Hz, 2H), 1.419-1.288 (m, 9H), 0.923 (t, J = 6.8 Hz, 3H). MS (ESI): m/z (M) $^+$ calculated = 277.08, Found (M+1) $^+$ = 278.24.

Ethyl 4-hydroxy-3-isobutyl-2-thioxothiazolidine-4-carboxylate (6): Yellow oily, m.f. $\text{C}_{10}\text{H}_{17}\text{NO}_3\text{S}_2$, Calculated: C = 45.60; H = 6.51; N = 5.32; O = 18.22; S = 24.35. Found C = 45.75; H = 6.61; N = 5.43; O = 18.41; S = 24.55. ^1H NMR 400 MHz (CDCl_3): δ 4.770 (bs, 1H), 4.443-4.297 (m, 2H), 3.698-3.648 (m, 2H), 3.379 (d, J = 8.4 Hz, 1H), 3.224 (d, J = 8.4 Hz, 1H), 2.176-2.034 (m, 1H), 1.365 (t, J = 7.2 Hz, 3H), 0.925 (d, J = 6.4 Hz, 6H). MS (ESI): m/z (M) $^+$ calculated = 263.06, Found (M+1) $^+$ = 264.2.

Ethyl 3-cyclopentyl-4-hydroxy-2-thioxothiazolidine-4-carboxylate (7): Yellow oily, m.f. $\text{C}_{11}\text{H}_{17}\text{NO}_3\text{S}_2$, Calculated C = 47.98; H = 6.22; N = 5.09; O = 17.43; S = 23.29. Found C = 48.12; H = 6.32; N = 5.19; O = 17.53; S = 23.43. ^1H NMR 400 MHz (CDCl_3): δ 4.676 (bs, 1H), 4.395 (q, J = 7.2 Hz, 2H), 4.277-4.188 (m, 1H), 3.564 (d, J = 12.0 Hz, 1H), 3.372 (d, J = 12.0 Hz, 1H), 2.342-2.250 (m, 2H), 1.913-1.742 (m, 4H), 1.574-1.529 (m, 2H), 1.381 (t, J = 7.2 Hz, 3H). MS (ESI): m/z (M) $^+$ calculated = 275.06, Found (M+1) $^+$: 276.2.

Ethyl 3-cyclobutyl-4-hydroxy-2-thioxothiazolidine-4-carboxylate (8): Yellow oily, m.f. $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{S}_2$, Calculated C = 45.95; H = 5.78; N = 5.36; O = 18.36; S = 24.54. Found C = 46.12; H = 5.86; N = 5.47; O = 18.52; S = 24.75. ^1H NMR 400 MHz (CDCl_3): δ 4.806 (bs, 1H), 4.783-4.733 (m, 1H), 4.409-4.355 (m, 2H), 3.575 (d, J = 12.0 Hz, 1H), 3.269 (d, J = 12.0 Hz, 1H), 2.504-2.289 (m, 3H), 2.146-2.103 (m, 1H), 1.780-

1.633 (m, 2H), 1.371 (t, $J = 7.2$ Hz, 3H). MS (ESI): m/z (M)⁺ calculated = 261.05, Found ($M+1$)⁺ = 262.2.

Ethyl 3-ethyl-4-hydroxy-2-thioxothiazolidine-4-carboxylate (9): Yellow oily, m.f. $C_8H_{13}NO_3S_2$, Calculated C = 40.83; H = 5.57; N = 5.95; O = 20.40; S = 27.25. Found C = 40.98; H = 5.67; N = 6.12; O = 20.65; S = 27.45. 1H NMR 400 MHz ($CDCl_3$): δ 4.825 (bs, 1H), 4.434-4.332 (m, 2H), 3.768-3.667 (m, 2H), 3.597-3.508 (m, 1H), 3.368 (d, $J = 12.0$ Hz, 1H), 1.370 (t, $J = 7.2$ Hz, 3H), 1.232 (t, $J = 7.2$ Hz, 3H). MS (ESI): m/z (M)⁺ calculated = 235.03, Found ($M+1$)⁺ = 236.15.

RESULTS AND DISCUSSION

In this communication, prodigious scheme for the synthesis of dithiocarbamates is reported. In this solvent free method, addition of Triton-B was done to amine and CS_2 solution (at room temperature) with continuous stirring. The spectroscopic and analytical data confirms the product formation. The essential requirement for this reaction is to have amines with one hydrogen atom. A number of phase transfer catalyst is frequently used for the synthesis of cyclic dithiocarbamates [42]. On comparing the reaction condition it was comprehended that by using Triton-B, % yields of preferred product is upsurge than other types of phase transfer catalyst [34]. Triton-B gives 95 % yield. Earlier cyclic dithiocarbamates were produced from amines, CS_2 , formaldehyde using inorganic base [43,44].

Now a number of phase transfer catalyst is frequently used instead of inorganic base for their synthesis. The advantage of this scheme is (i) excess amounts of toxic reagents are avoided that adversely affects the health. (ii) high yield (iii) reduced

reaction time. (iv) Triton-B is recovered from the reaction mixture by filtration [44]. The use of inorganic base [45] for such coupling reactions are rejected on the basis of above aspects.

The electron-releasing group in aliphatic and aromatic amines has great impact on yield of products (Table-1). The reaction of primary amine, ethyl bromopyruvate (ethyl 3-bromo-2-oxopropanoate) and CS_2 catalyzed by Triton B at room temperature is shown in **Scheme-I**.

TABLE-1
EFFECT OF SUBSTITUENTS ON FORMATION
OF CYCLIC DITHIOCARBAMATES

Comp.	R	Time (h)	Yield (%)
1	4-OCH ₃ -Benzyl	1.5	90
2	4-CF ₃ -Benzyl	1.5	85
3	Pentyl	1.5	93
4	Ethoxyethyl	2.5	94
5	Methylpentan-2-yl	2.5	96
6	Isobutyl	2.0	90
7	Cyclopentyl	1.5	89
8	Cyclobutyl	1.5	88
9	Ethyl	2.5	92

Antimicrobial results: The antimicrobial potency of reported compounds was determined with the help of MIC. The outcomes of antimicrobial studies against four bacterial strain and three fungi strain are illustrated in Table-2. These chemical compounds show variable activity against these microbes (bacteria and yeast). MIC of these compounds ranged between 62.5-500 $\mu g/mL$ against bacteria (Gram-positive and

Scheme-I: Synthesis of cyclic dithiocarbamates catalyzed by Triton-B

TABLE-2
ANTIMICROBIAL POTENCY IN TERMS OF MIC ($\mu g/mL$) USING MICRO DILUTION TUBE TECHNIQUE

Compound	<i>S. aureus</i>	<i>S. pyogenus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>	<i>A. clavatus</i>
1	125	500	62.5	100	250	500	>1000
2	125	250	62.5	200	250	>1000	>1000
3	62.5	125	125	250	500	500	500
4	125	250	250	500	250	250	125
5	250	500	500	125	500	500	500
6	125	250	125	250	1000	1000	125
7	500	125	250	250	250	250	250
8	250	500	250	125	125	125	250
9	125	250	125	500	250	250	1000
Chloramphenicol	50	50	50	50	—	—	—
Nystatin	—	—	—	—	100	100	100

Gram-negative) and between 125-1000 µg/mL against yeast. Compound **3** shows lowest MIC of 62.5 µg/mL and is effective against *S. aureus* (Gram-positive bacteria) and compound **1, 2** exhibit good activity against Gram-negative bacteria, *E. coli* with minimum MIC of 62.5 µg/mL. Compound **8** is most susceptible to yeast (*C. albicans*, *A. niger*) with MIC of 125 µg/mL. Compound **6** also shows minimum MIC of 125 µg/mL against yeast *A. clavatus*. None of the compound shows resistant against the selected strains.

Conclusion

The rapid, highly proficient solvent-free one pot approach of three-components coupling reaction of different primary amines with ethyl bromopyruvate *via* CS₂/Triton-B has been demonstrated. A dramatic decrease in reaction time and increase in yield is observed for this procedure as compared to traditional methods to develop C-S bonds are important in organic syntheses. These compounds show variable activity against the tested microbes and none of the compound shows resistance to tested compounds. So they can be further explored in pharmaceutical industries as *in vivo* antimicrobial agent after further investigation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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