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Modular Green One-pot Synthesis of Ethyl Oxalyl Functionalized Dithiocarbamate

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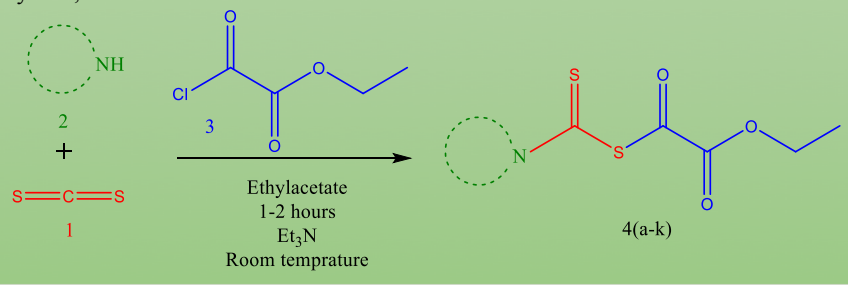
Abstract: Dithiocarbamates and their derivatives play a crucial role in medicinal chemistry and agriculture, especially when combined with novel systemic fungicides to enhance their effectiveness. To address the environmental concerns associated with traditional toxic organic solvents, the use of environmentally friendly reaction media, such as deep eutectic solvents and ethyl acetate, has emerged as a promising alternative. This report presents a one-pot synthesis of novel dialkylthiocarbamate derivatives using ethyl acetate as a green solvent. The reaction exhibits excellent yields, short reaction times and eliminates the need for harmful solvents and laborious work-up procedures.



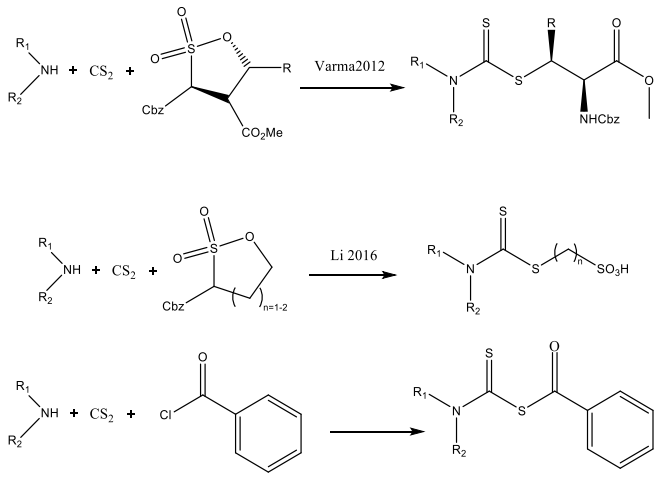
Introduction

Currently, one of the major challenges in organic chemistry is the design of the most efficient approaches for the synthesis of biologically active molecules from simple and commercially available reagents under cost-effective and green conditions for pharmaceutical industries.[1,2] In this regard, multicomponent reactions (MCRs), which can generate products from three or more reagents in a one-pot procedure, have drawn considerable attention to the preparation of diverse biologically active compounds. In line with green chemistry guidelines, the development of new MCRs in eco-friendly reaction media hold great importance across various fields, including drug design, membrane technology, and nano-medicine.[3-6]

Organic dithiocarbamates (DTCs) are considered as a promising synthetic structural motifs in many biologically active compounds.[7,8] They have attracted great interest for their widespread applications in the fields of biomedicine as anticancer agents, agrochemicals (fungicides and herbicides), material science and flotation materials.[9-11] Due to the existence of two sulfur within the structural framework of DTCs, their ligands exhibit a high capacity for metal binding; and this has been confirmed to be beneficial as enzyme inhibitors that finally affect their biological activities.[12,13] Dithiocarbamates are suitable ligands that enable of producing complexes with different transition metals and stabilize them in various oxidation states.[14] Additionally, the further derivatization of DTC ligands has provided various important biological properties such as antibacterial,[13,15,16] anticancer,[13] antioxidant,[17,18] antivirus and antimalarial activities.[19] Most therapeutic activities shown by DTC agents have been related to the C-S bonds, which are highly effective in fabricating novel biologically active intermediates with outstanding medicinal characteristics.[13] Hence, the synthesis of novel organic dithiocarbamate has devoted significant attention, and numerous articles have reported on the synthesis of these valuable compounds.[20-23] Nevertheless, there are several limitations in applying toxic and hazardous organic solvents such as low yields, harsh reaction conditions and restricted substrate ranges. Furthermore, most traditional approaches for the DTCs synthesis are consist of employing toxic and expensive starting materials, like isothiocyanates, thiophosgene and its derivatives.[24-26]

As part of our continued efforts to provide environmentally benign reaction media such as water and deep eutectic solvents for the preparation of natural biocompatible materials,[23,26,27] Herein, we have reported one-pot synthesis of dialkylthiocarbamate functionalized with ethyl oxalyl groups from secondary aliphatic amines, CS_2, and ethyl oxalyl chloride in ethyl acetate as a green solvent. This approach offers a suitable, cost-effective, time-saving synthesis procedure for constructing different functional dithiocarbamates with novel properties and uses.

In recent years researchers have synthesized various dithiocarbamate derivatives, and that Varma[28] et al., Li[9] et al., and our groups[29] synthesized novel DTCs using different sulfamidates (Scheme 1). By utilizing different sulfamidates, Varma et al. and Li et al. were able to synthesize novel dithiocarbamate derivatives with unique properties and potential applications. This highlights the versatility of both dithiocarbamates and sulfamidates in organic synthesis, and the potential for further research in this area.

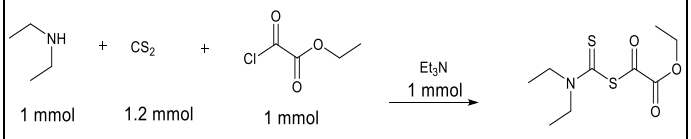


Scheme. 1. Previous works on preparing novel dithiocarbamates

Experimental

All the chemicals such as ethyl oxalyl chloride, CS_2, secondary amines, and N, N-Dimethyltrimethylsilylamine, were purchased from Merck company. The structures were confirmed by nuclear magnetic resonance spectroscopy (NMR) (500 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR, Agilent, USA) using deuterated solvents.

Table. 1. Optimization of experimental condition in the model reaction



Entry	Solvent (1 mL)	Time (hours)	Temperature (^{0}C)	Yield (%)
1	Water	4	R.T	30
2	Polyethylene glycol	4	R.T	45
3	Ethanol	4	R.T	47
4	Methanol	4	R.T	53
5	Urea/cholinechloride 2:1	4	R.T	36
6	$ZnCl_2$: Urea 2:1	4	R.T	48
7	Glycerol	4	R.T	34
8	Ethyl acetate	4	R.T	94
9	Acetonitrile	4	R.T	88
10	Tetrahydrofuran	4	R.T	73
11	Acetone	4	R.T	60
12	Glycerin	4	R.T	51
13	Ethyl acetate	2	R.T	95
14	Ethyl acetate	1	R.T	95
15	Ethyl acetate	0.5	R.T	78
16	Ethyl acetate	1	40	95
17	Ethyl acetate	1	60	93

General procedure for the synthesis of dithiocarbamate (4a-4k)

To a 5 mL round bottom flask with a magnetic stir bar, ethyl acetate (1 mL), secondary amine (1mmol), CS_2 (1.2 mmol) and triethylamine (1 mmol) were added respectively at room temperature and were stirred for 20 minutes. Then, ethyl oxalyl chloride (1 mmol) was added to the reaction mixture and stirred for another 1h at rt. After completion reaction (monitoring by TLC), water (10 mL) and ethyl acetate (10 mL) were added to the mixture. The organic phase was separated and evaporated by a rotary evaporator, and the crude product was collected. The crude products were purified by recrystallization in ethanol or diethyl ether to afford the pure dithiocarbamates. The products were identified by ^{1}H and ^{13}C NMR spectroscopy.

Selected Data
NMR data

4a- (Table 2, Entry1) ^{1}H NMR (500 MHz, $CDCl_3$) *δ:* 1.28 (t,3H, *J*= 7.10 Hz), 3.14 (s,3H), 3.23 (s,3H), 4.25 (q, 2H, *J*=7.10 Hz).

4b- (Table 2, Entry2) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 1.00-1.34 ppm (m,9H), 3.16-3.24 ppm (q,2H), 3.29-3.36 ppm (q,2H), 4.18-4.30 ppm (q, 2H, *J*=7.15 Hz).

4c- (Table 2, Entry3) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 0.79-1.03 ppm (m,6H), 1.07-1.15 ppm (t,3H), 1.63-1.67 ppm (m,4H), 3.15-3.36 ppm (t,2H), 3.31-3.52 ppm (t,2H), 4.15-4.20 (q,2H, *J*=7.10 Hz).

4d- (Table 2, Entry4) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 0.70-0.84 ppm (m,6H), 1.09-1.26 ppm (m,7H), 1.36-1.49 ppm (m,4H), 3.04-3.11 ppm (t,2H)- 3.17-3.25 ppm (t,2H)- 4.13-4.22 (q,2H, *J*=7.10 Hz).

4e- (Table 2, Entry5) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 0.52-0.66 ppm (m,6H), 0.90-1.11 ppm (m, 15H), 1.22-1.38 ppm (m,4H), 2.87-2.96 ppm (t,2H), 3.00-3.12 ppm (t,2H), 3.95-4.08 ppm (q,2H, *J*=7.11 Hz).

4f- (Table 2, Entry6) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 0.49-0.67 ppm (m,6H), 0.94-1.55 ppm (m,27H), 2.95-3.07 (t,2H), 3.15-3.21 (q,2H), 3.99-4.08 (q,2H, *J*=7.10 Hz).

4g- (Table 2, Entry7) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 1.16-1.24 ppm (t,3H), 1.71-1.86 ppm (m,4H), 3.31-3.46 ppm (m,4H), 4.11-4.21 ppm (q,2H, *J*=7.12 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 13.82, 23.74, 25.87, 46.36, 47.64, 62.18, 158.78, 161.72, 175.75.

4h- (Table 2, Entry8) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 1.18-1.28 ppm (t,3H), 1.49-1.58 ppm (m,2H), 1.84-2.01 ppm (m,4H), 3.29-3.51 ppm (m,4H), 4.13-4.21 ppm (q,2H, *J*=7.09 Hz).

4i- (Table 2, Entry9) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 1.22-1.39 ppm (t,3H), 3.36-3.48 ppm (m,2H), 3.54-3.74 ppm (m,6H), 4.20-4.37 ppm (q,2H, *J*=7.10 Hz).

4j- (Table 2, Entry10) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 0.89-0.96 ppm (d,3H), 1.27-1.35 ppm (t,3H), 1.46-1.72 ppm (m,5H), 3.27-3.42 ppm (m,4H), 4.18-4.30 ppm (q,2H, *J*=7.13 Hz).

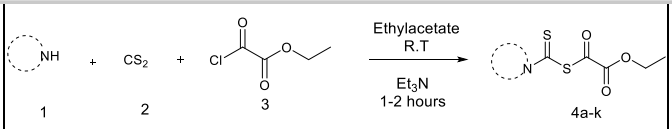
4k- (Table 2, Entry11) ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 0.89-1.01 ppm (t,3H), 1.26-1.38 ppm (m,5H), 1.47-1.54 ppm (m,2H), 3.15-3.28 ppm (s,3H), 3.41-3.57 ppm (t,2H), 4.21-4.32 ppm (q,2H, *J*=7.11 Hz).

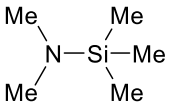
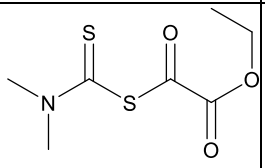
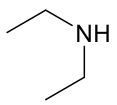
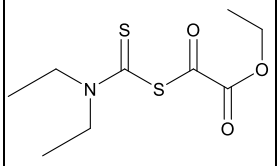
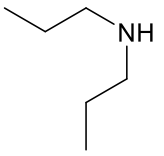
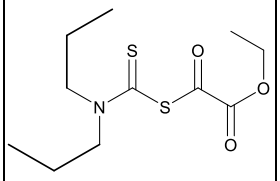
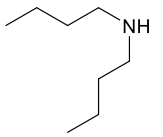
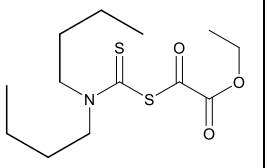
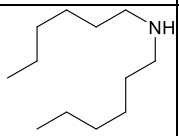
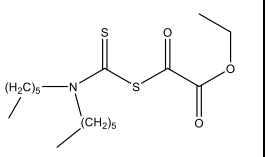
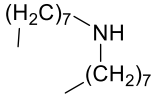
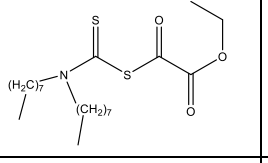
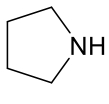
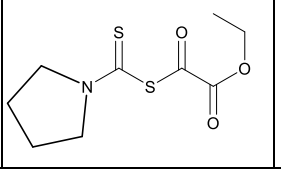
Results and discussion

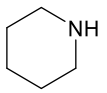
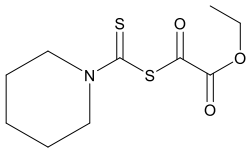
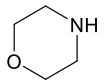
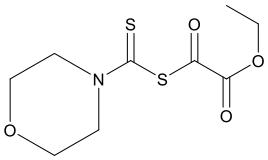
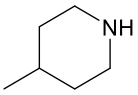
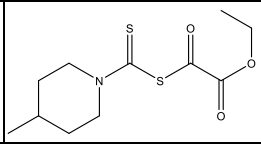
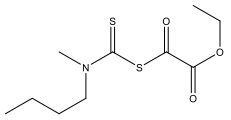
In our progressing efforts to employ harmless solvents as an environmentally friendly medium for organic transformation, herein, we developed a facile and mild process for the convenient synthesis of oxalyl functionalized dithiocarbamate without utilizing any catalyst at room temperature with good to excellent yields. Firstly, to optimize reaction conditions, the various conditions such as reaction time, temperature and solvent were tested on a one-pot reaction of carbon disulfide, secondary aliphatic, and ethyl oxalyl chloride as the modal reaction. The model reaction was performed in different organic solvents, including water, acetone, tetrahydrofuran, ethyl acetate, ethanol, methanol, and ionic liquids. As illustrated in Table 1, the highest yields were obtained in ethyl acetate, and other solvents like THF and acetone also have shown acceptable results. The lowest yields belonged to the protic solvent. After optimizing the solvent, the reaction temperature was optimized. Three different temperatures, from room temperature to 60^{0}C, were tested. The highest yield was observed at room temperature because the exothermic reaction between ethyl oxalyl chloride and in-situ prepared dithiocarbamate produced enough heat to drive the reaction to the desired product.

Based on the obtained optimum conditions on modal reaction, a range of reactions using secondary aliphatic amines were performed to evaluate the limitations and scope of the proposed procedure. The obtained outcomes are shown in Table 2. The highest yield was given from morpholine (**4i**) (97%), other aliphatic amines like dibutylamine (**4d**) and (**4f**) also have shown acceptable yields. The lowest yield was attributed to dioctylamine (4e) (78%). In addition, primary aliphatic amines like benzyl amine were also tested, giving the mixture of products.

Table. 2. Different prepared products based on optimized conditions



Entry	Diamine	Code	Product chemical structure	Yield (%)
1		4a		87
2		4b		95
3		4c		82
4		4d		90
5		4e		78
6		4f		76
7		4g		85

8		4h		94
9		4i		97
10		4j		96
11		4k		88

Conclusions

In summary, we have reported a facile, highly effective, and green approach for synthesizing ethyl oxalyl functionalized dithiocarbamate under mild reaction conditions. The proposed procedure provides facile synthesis work-up, short preparation times, and good to high yields which employed environmentally friendly organic solvent, making this approach a cost-effective and beneficial method from an economic and environmental point of view.

Conflicts of interest

There are no conflicts to declare.

References

1. Liu, P.; Hao, J-W.; Mo, L-P.; Zhang, Z-H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. *RSC Advances*, **2015**, 5(60), 48675-48704.
2. Banerjee, B.; Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles. *Ultrasonics Sonochemistry*, **2017**, 35, 15-35.
3. Kommi, D.N.; Kumar, D.; Chakraborti, A.K.; "All water chemistry" for a concise total synthesis of the novel class anti-anginal drug (RS), (R), and (S)-ranolazine. *Green Chemistry*, **2013**, 15(3), 756-767.
4. Saha, A.; Baig, R.B.N.; Leazer, J.; Varma, R.S. A modular synthesis of dithiocarbamate pendant unnatural α-amino acids. *Chemical Communications*, **2012**, 48(71), 8889-8891.
5. Ruijter, E.; Orru, R.V. Multicomponent reactions–opportunities for the pharmaceutical industry. *Drug Discovery Today Technologies*, **2013**, 10(1), 15-20.
6. Kamali, M.; Ebrahimi, A.; Vatanpour, V. New dithiocarbamate-based polymer (DTCP) as an additive to improve microporous polysulfone membrane efficiency in lead and dye removal. *Journal of Environmental Management*, **2023**, 339, 117925.
7. Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M.R. One-pot synthesis of dithiocarbamates accelerated in water. *The Journal of Organic Chemistry*, **2006**, 71(9), 3634-3635.
8. Chaturvedi, D.; Mishra, N.; Mishra, V. An efficient, one-pot synthesis of S-alkyl thiocarbamates from the corresponding thiols using the Mitsunobu reagent. *Synthesis*, **2008**, 2008(03), 355-357.
9. Li, B.; Zhou, S.; Wang, S.; Sun, X.; Ge, Z.; Li, R. Efficient synthesis of organic sulfonic acid derivatives containing dithiocarbamate side chains. *Tetrahedron*, **2016**, 72(27-28), 3885-3889.
10. Venkatesh, R.; Shankar, G.; Narayanan, A.C.; Modi, G.; Sabiah, S.; Kandasamy, J. Multicomponent Synthesis of S-Benzyl Dithiocarbamates from para-Quinone Methides and Their Biological Evaluation for the Treatment of Alzheimer's Disease. *The Journal of Organic Chemistry*, **2022**, 87(10), 6730-6741.
11. Bala, V.; Gupta, G.L.; Sharma, V. Chemical and medicinal versatility of dithiocarbamates: an overview. *Mini reviews in medicinal chemistry*, **2014**, 14(12), 1021-1032.
12. Jaiswal, S.; Parida, S.K.; Murarka, S.; Singh, P. Development of S-aryl dithiocarbamate derived novel antiproliferative compound exhibiting tubulin bundling. *Bioorganic & Medicinal Chemistry*, **2022**, 68, 116874.
13. Adeyemi, J.O.; Onwudiwe, D.C. The mechanisms of action involving dithiocarbamate complexes in biological systems. *Inorganica Chimica Acta*, **2020**, 511, 119809.
14. Li, B.; Zhou, S.; Wang, S.; Sun, X.; Ge, Z.; Li, R. Efficient synthesis of organic sulfonic acid derivatives containing dithiocarbamate side chains. *Tetrahedron*, **2016**, 72(27), 3885-3889.
15. Menezes, D.; de Lima, G.; de Oliveira, G.; Boas, A.V.; Nascimento, A.; Vieira, F. In vitro antibacterial activity of dithiocarbamate organotin (IV) complexes towards Staphylococcus aureus. *Main Group Metal Chemistry*, **2008**, 31(1-2), 21-28.
16. Jiang, S.; Su, S.; Chen, M.; Peng, F.; Zhou, Q.; Liu, T. Antibacterial activities of novel dithiocarbamate-containing 4 H-chromen-4-one derivatives. *Journal of agricultural and food chemistry*. **2020**, 68(20), 5641-5647.
17. Gao, M.Y.; Xu, W.; Zhang, S.B.; Li, Y.S.; Dong, Z.B. Synthesis of Phenyl Dithiocarbamates Starting from Sodium Dialkyldithiocarbamates and Aryl Boronic Acids: a Copper Catalyzed S-Arylation. *European Journal of Organic Chemistry*, **2018**, 47,6693-6698.
18. Kaul, L.; SŘss, R.; Zannettino, A.; Richter, K. The revival of dithiocarbamates: from pesticides to innovative medical treatments. *IScience*, **2021**, 24(2), 102092.
19. Kumar, R.; Takkar, P. Repositioning of Isatin hybrids as novel anti-tubercular agents overcoming pre-existing antibiotics resistance. *Medicinal Chemistry Research*, **2021**, 30(4), 847-876.
20. Jiao, J.; Zhang, Z. Copper-Catalyzed Direct C (sp2)–H Sulfuration of Aryl Alkenes by Using Tetraalkylthiuram Disulfides for the Synthesis of Alkenyl Dithiocarbamates. *Synthesis*, **2022**, 54(16), 3588-3594.
21. Bhattacharjee, S.; Deswal, S.; Manoj, N.; Jindal, G.; Biju, A.T. Aryne Three-Component Coupling Involving CS2 for

the Synthesis of S-Aryl Dithiocarbamates. *Organic Letters*, **2021**, 23(23), 9083-9088.
22. Anamika, A.; Yadav, C.L; Drew, M.G.; Kumar, K.; Singh, N. Ferrocene-Functionalized Dithiocarbamate Zinc (II) Complexes as Efficient Bifunctional Catalysts for the One-Pot Synthesis of Chromene and Imidazopyrimidine Derivatives via Knoevenagel Condensation Reaction. *Inorganic Chemistry*, **2021**, 60(9), 6446-6462.
23. Azizi, N.; Gholibeglo, E.; A highly efficient synthesis of dithiocarbamates in green reaction media. *RSC advances*, **2012**, 2(19), 7413-7416.
24. Chatterjee, T.; Bhadra, S.; Ranu, B.C. Transition metal-free procedure for the synthesis of S-aryl dithiocarbamates using aryl diazonium fluoroborate in water at room temperature. *Green chemistry*, **2011**, 13(7), 1837-1842.
25. Rudorf, W.D. Reactions of carbon disulfide with N-nucleophiles. *Journal of Sulfur Chemistry*, **2007**, 28(3), 295-339.
26. Azizi, N.; Aryanasab, F.; Saidi, M.R. Straightforward and highly efficient catalyst-free one-pot synthesis of dithiocarbamates under solvent-free conditions. *Organic Letters*, **2006**, 8(23), 5275-5277.
27. Zhou, Y.; Yang, C.L.; Ye. L.; Dong, Z.B. Copper-Catalyzed C-S Formation for the Synthesis of Benzyl Phenyl Sulfides from Dithiocarbamates. *Synthesis*, **2022**, 54, 4104-4110.
28. Saha, A.; Baig, R.N.; Leazer, J.; Varma, R.S. A modular synthesis of dithiocarbamate pendant unnatural α-amino acids. *Chemical Communications*, **2012**, 48(71), 8889-8891.
29. Azizi, N.; Alipour, M. Synthesis of carboxylic dithiocarbamic anhydride and substituted thiourea derivatives in water. *Environmental Chemistry Letters*, **2018**, 16, 1415-1421.