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Graphical Abstract

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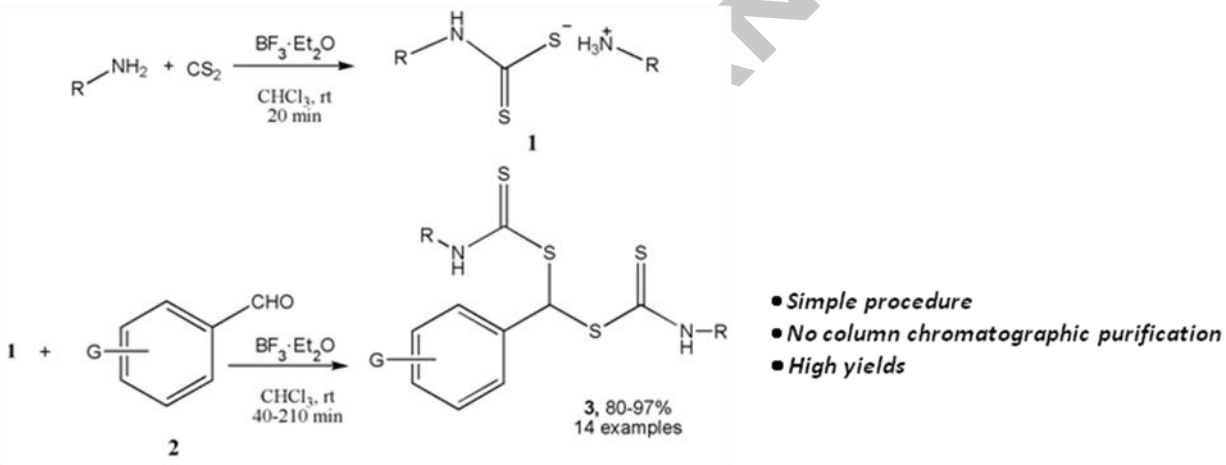

A rapid and convenient synthesis of *gem*-bis(dithiocarbamate) derivatives from primary aliphatic amines, carbon disulfide and aromatic aldehydes using boron trifluoride-diethyl etherate

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Abstract

An efficient route for the synthesis of *gem*-bis(dithiocarbamate) derivatives is developed using dithiocarbamic acid salts generated from primary aliphatic amines and CS_2. The method offers high yields, employs mild reaction conditions, and demonstrates excellent functional group compatibility. The structures of the products were confirmed spectroscopically and by X-ray analysis.

Keywords: Dithocarbamic acid salt; Primary aliphatic amine; Carbon disulfide; Boron triflouride –diethyl etherate.

Organic dithiocarbamates are valuable synthetic intermediates that are found in a variety of biological compounds (Figure 1).[1,2] They have received considerable attention because of their pivotal role in agriculture and as linkers in solid phase organic synthesis.[3-7] They are also used in the rubber industry as vulcanization accelerators and as inhibitors of enzymes.[8,9] One area that has been intensely studied is their activity against cancer.[10-13]

Figure 1.

Dithiocarbamates represent a versatile class of ligands with the ability to stabilize transition metals in a wide range of oxidation states.[14] They have also been widely used in the synthesis of amino-1,3,4-thiadiazoles,[15] thioureas,[16-19] aminobenzimidazoles,[20] isothiocyanates,[21-23] alkoxyamines,[24] 2-imino-1,3-dithiolane,[25] and for the total syntheses of natural compounds.[26, 27] These compounds exhibit good nucleophilic reactivity with electrophiles such as alkyl halides, epoxides, and α,β-unsaturated carbonyl compounds to give products that can be exploited easily in functional group transformations and have applications in organic synthesis and industry.[28-33] Ziyaei-Halimehjani *et al*. previously reported the reaction of dithiocarbamic acid salts with aryl aldehydes in the presence of $BF_3.Et_2O$. The reaction is temperature-dependent and gives *gem*-bis(dithiocarbamates) and 2-iminium-1,3-dithietane as the only products at 35-45 °C and 15-20 °C, respectively. They indicated that the reaction does not give the desired products with primary aliphatic amines.[34] It should be noted that their method was conducted with secondary aliphatic amines, which are more nucleophilic than their primary equivalents.

Most reports on these compounds have dealt solely with the properties of dialkyldithiocarbamates, and little mention has been made of the properties of

monoalkyldithiocarbamates.[35-38] The synthesis of derivatives of monoalkyldithiocarbamates is therefore of interest. This study examines the reactions of primary aliphatic amines, CS_2, and aromatic aldehydes in the presence of $BF_3{\cdot}OEt_2$ as the catalyst.

Considering the above reports and in order to investigate the possibility of a one-pot synthesis of the target compounds, the reaction conditions were initially optimized using *n*-propylamine, CS_2, and 4-chlorobenzaldehyde as model substrates in the presence of $BF_3{\cdot}OEt_2$. Different solvents and temperatures were examined, but, unfortunately, no product was obtained under these conditions. As an alternative, the dithiocarbamic acid salt was prepared in a different vessel and was added to a solution of 4-chlorobenzaldehyde and $BF_3{\cdot}OEt_2$ in chloroform at room temperature. These conditions led to the formation of the *gem*-bis(dithiocarbamate) product **(3a)** in high yield and in a short reaction time (Scheme 1).

Scheme 1.

In an effort to improve the reaction conditions and to scrutinize the possibility of the formation of a 2-imino-1,3-dithietane ring (**4a**), different amounts of $BF_3{\cdot}OEt_2$ and varying the reaction temperature (-10 to 80 °C) were investigated. Lowering or raising the temperature or amount of $BF_3{\cdot}OEt_2$ did not lead to production of 2-imino-1,3-dithietane **4a**; only *gem*-bis(dithiocarbamate) **3a** was obtained. Other reaction parameters were subsequently examined, such as the addition of stronger bases including triethylamine and NaOH and changing the reagent ratios in the model reaction. These efforts also failed to give 2-imino-1,3-dithietane. Accordingly, 1.7 mL of $BF_3.OEt_2$ was found to be the optimum amount of catalyst for obtaining the *gem*-bis(dithiocarbamate) at room temperature in chloroform. Incremental changes in the amount of $BF_3.OEt_2$ or the temperature did not produce useful increases in the product yield. The most suitable mole ratio of CS_2:amine:aldehyde was 5:10:2.

Using the optimized reaction conditions, the scope and limitations of this process were explored with a range of aromatic aldehydes and primary aliphatic amines. As can be seen from Table 1, aromatic aldehydes containing either electron-donating or electron-withdrawing groups reacted efficiently, giving high yields of the *gem*-bis(dithiocarbamate) derivatives. This protocol proved to be clean and fast. Pure products were isolated in yields of 80-97% after 25-210 min following a simple work-up (Table 1). Notably, thiophene-2-carbaldehyde successfully produced the desired products, which are useful for synthetic elaboration (Table 2, entries 5 and 6). Unfortunately, benzylamine and an aryl aldehyde with an NO_2 functional group produced unstable products that decomposed immediately after work-up (Table 1, entries 13 and 14).

Table 1.

The deprotection of synthetic *gem*-bis(dithiocarbamate) derivatives in the presence of dilute nitric acid returned the corresponding aldehydes in excellent yields after 10-15 minutes with the evolution of NO_2 gas. This procedure can be used for the protection of a carbonyl group in aldehydes, since deprotection of *gem*-bis(dithiocarbamates) can be carried out in aqueous nitric acid.[39-41]

The structures of products **3a-l** were characterized using FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analyses. For example, the FTIR spectrum of compound **3b** revealed characteristic absorptions at 3238 cm^{-1} for N-H and 1175 cm^{-1} for C=S stretching vibrations. The ^{1}H NMR spectrum of **3b** showed a singlet for the benzylic hydrogen at δ 6.99. The resonance appearing low field at δ 8.0 (N-H), supported the formation of a thioamide functional group. The ^{1}H-decoupled ^{13}C NMR spectrum of **3b** showed nine distinct resonances in agreement with the

suggested structure. We were also able to obtain suitable crystals of **3c** for X-ray crystallography to confirm the structure of the product.[43] The ORTEP view of the single crystal X-ray analysis of **3c** with atomic numbering is shown in Figure 2.

Figure 2.

A plausible mechanism for this conversion is illustrated in Scheme 2. The reaction commences with the coordination of the aldehyde to BF_3. The activated carbonyl group is then attacked by the dithiocarbamic acid salt to form intermediate **A**. In turn, intermediate **A** reacts with a second equivalent of the dithiocarbamic acid salt to yield the *gem*-bis(dithiocarbamates) after dehydration. The interaction of non-bonding electrons of nitrogen with BF_3 and the lower basicity of primary aliphatic amines is thought to prevent the synthesis of a 2-imino-1,3-dithietane.

Scheme 2

To summarize, we have reported an efficient, safe and experimentally simple method for the synthesis of *gem*-bis(dithiocarbamate) derivatives. These reactions were carried out using primary aliphatic amines, CS_2 and aromatic aldehydes in the presence of $BF_3.OEt_2$ as an acid catalyst. The significant features of this reaction include short reaction times, no column chromatographic purification, high yields of products and readily available starting materials.

Acknowledgements

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References and Notes

1. Dhooghe, M.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 513–535.

2. Fernandez, J. M. G.; Mellet, C. O.; Blanco, J. L. J.; Mota, J. F.; Gadelle, A.; Coste-Sarguet, A.; Defaye, J. *Carbohydr. Res.* **1995**, *268*, 57–71.

3. Mizuno, T.; Nishiguchi, I.; Okushi, T.; Hirashima, T. *Tetrahedron Lett.* **1991**, *32*, 6867–6868.

4. Rafin, C.; Veignie, E.; Sancholle, M.; Postal, D.; Len, C.; Villa, P.; Ronco, G. *J. Agric. Food Chem.* **2000**, *48*, 5283–5287.

5. Morf, P.; Raimondi, F.; Nothofer, H. G.; Schnyder, B.; Yasuda, A.; Wessels, J. M.; Jung, T. A. *Langmuir* **2006**, *22*, 658–663.

6. McClain, A.; Hsieh, Y. L. *J. Appl. Polym. Sci.* **2004**, *92*, 218–225.

7. Bongar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *J. Chem. Res.* **2004**, *9*, 450-451.

8. Nieuwenhuizen, P. J.; Ehlers, A. W.; Haasnoot, J. G.; Janse, S. R.; Reedijk, J.; Baerends, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 163–168.

9. Thorn, G. D.; Ludwig, R. A. *The Dithiocarbamates and Related Compounds*; Elsevier: Amsterdam, New York, 1962.

10. Ge, Z. M.; Li, R. T.; Cheng, T. M.; Cui, T. M. *Arch. Pharm. Med. Chem.* **2001**, *334*, 173–176.

11. Hou, X. L.; Ge, Z. M.; Wang, T. M.; Guo, W.; Cui, J. R.; Cheng, T. M.; Lai, C. S.; Li, R. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4214–4219.

12. Cui, J. L.; Ge, Z. M.; Cheng, T. M.; Li, R. T. *Synth. Commun.* **2003**, *33*, 1969–1976.

13. Wang, Y. Q.; Ge, Z. M.; Hou, X. L.; Cheng, T. M.; Li, R. T. *Synthesis.* **2004**, 675–678.

14. Hogarth, G. *Prog. Inorg. Chem.* **2005**, *53*, 71-561.

15. Aryanasab F.; Ziyaei-Halimehjani A.; Saidi M. R. *Tetrahedron Lett.* **2010**, *51*, 790–792.

16. Ziyaei-Halimehjani, A.; Porshojaei, Y.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 32–34.

17. Sugimoto, H.; Makino, I.; Hirai, K. *J. Org. Chem.* **1988**, *53*, 2263–2267.

18. Ranu, B. C.; Dey, S. S.; Bag, S. *ARKIVOC* **2003**, *ix*, 14–20.

19. Maddani, M.; Prabhu, K. R. *Tetrahedron Lett.* **2007**, *48*, 7151–7154.

20. Das, P.; Kumar, C. K.; Kumar, K. N.; Innus, M. D.; Iqbal, J.; Srinivas, N. *Tetrahedron Lett.* **2008**, *49*, 992–995.

21. Liu, P.; Li, C.; Zhang, J.; Xu, X. *Synth. Commun.* **2013**, *43*, 3342–3351.

22. Munch, H.; Hansen, J. S.; Pittelkow, M.; Christensen, J. B.; Boas, U. *Tetrahedron Lett.* **2008**, *49*, 3117–3119.

23. Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969–3971.

24. Guillaneuf, Y.; Couturier, J. L.; Gigmes, D.; Marque, S. R. A.; Tordo P.; Bertin, D. *J. Org. Chem.* **2008**, *73*, 4728–4731.

25. Ziyaei-Halimehjani, A.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747–2749 and references therein.

26. Grainger, R. S.; Welsh, E. J. *Angew. Chem. Int. Ed.* **2007**, 46, 5377–5380.

27. Kapanda, C. N.; Masquelier, J.; Labar, Geoffray.; Muccioli, G. G.; Poupaert, J. H.; Lambert, D. M. *J. Med. Chem.* **2012**, *55*, 5774−5783.

28. Ziyaei-Halimehjani, A.; Marjani, K.; Ashouri, A. *Green Chem.* **2010**, *12*, 1306–1310.

29. Zubarev, A. A.; Shestopalov, A. M.; Larionova, N. A.; Rodinovskaya, L. A.; Shestopalov, A. A. *Tetrahedron* **2013**, *69*, 9648-9655.

30. Azizi, N.; Gholibeglo, E.; Maryami, M.; Dehghan, S. N.; Bolourtchian, S. M. *C. R. Chimie* **2013**, *16*, 412–418.

31. Yavari, I.; Hosseini, N.; Moradi, L.; Mirzaei, A. *Tetrahedron Lett*. **2008**, *49*, 4239–4241.

32. Ziyaei-Halimehjani, A.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747–2749.

33. Chatterjee, T.; Bhadra, S.; Ranu, B. C. *Green Chem*. **2011**, *13*, 1837–1842.

34. Ziyaei-Halimehjani A.; Shayegan, M. H.; Hashemi, M. M.; Notash, B. *Org Lett*. **2012**, *14*, 3838–3841.

35. Barzen, R.; Schunack, W. *Arch. Pharm.* **1980**, *313*, 544–549.

36. Ahlbrecht, H.; Kornetzky, D. *Synthesis* **1988**, 775-778.

37. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Bull. Soc. Chim. Fr*. **1995**, *132*, 808–814.

38. Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 1973–1991.

39. Carmeli, M.; Rozen, O. *Tetrahedron Lett*. **2006**, *47*, 763–766.

40. Ren, Y.-M.; Cai, C. *Tetrahedron Lett*. **2008**, *49*, 7110–7112.

41. Srivastava, P.; Srivastava, R. *Catal. Commun*. **2008**, *9*, 645–649.

42. *Typical procedure for the synthesis of gem-bis(dithiocarbamate)* ***3c****:*

To a stirred solution of 4-chlorobenzaldehyde (0.28 g, 2 mmol) and $BF_3{\cdot}OEt_2$ (1.7-2 mL) in $CHCl_3$ (10 mL) was gradually added freshly prepared dithiocarbamic acid salt. [The dithiocarbamic acid salt was prepared in a separate vessel by the reaction of *sec*-butylamine (1.02 g, 14 mmol) and CS_2 (0.5 g, 7 mmol) in $CHCl_3$ (10 mL) for 20 min]. The mixture was stirred at room temperature for 45 min (Table 1). After completion of the reaction as monitored by TLC, $CHCl_3$ (20 mL) was added to the mixture, which was then washed with H_2O (3×60 mL). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent and washing the residue with *n*-hexane (20 mL) gave the pure product **3c** (0.38 g, 92%) as a white solid.

Compound **3b:** IR (KBr, cm^{-1}): ν 3238, 1175; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (6H, t, *J*= 7.5 Hz), 1.63-1.76 (4H, m), 3.65-3.71 (4H, m), 6.99 (1H, s), 7.27 (2H, d, *J*=8.7 Hz), 7.46 (2H, d,

J=8.7 Hz), 8.00 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4, 21.8, 48.9, 59.2, 122.9, 129.5, 132.1, 136, 193.1; Anal. Calcd for $C_{15}H_{21}N_2S_4Br$: C, 41.18; H, 4.80; N, 6.40; Found: C, 41.30; H, 4.99; N, 6.19.

Compound **3c:** IR (KBr, cm^{-1}): ν 3238, 1165; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91-0.97 (6H, m), 1.22-1.28 (6H, m), 1.57-1.66 (4H, m), 4.59 (2H, m), 7.21 (s, 1H), 7.31-7.42 (4H, m), 8.01 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.3, 20.6, 29.9, 55.8, 57.2, 128.9, 129.1, 132.6, 140.1, 195.3; Anal. Calcd for $C_{17}H_{25}N_2S_4Cl$: C, 48.51; H, 5.94; N, 6.65; Found: C, 48.71; H, 6.17; N, 6.51.

43. X-ray data for **3c:** $C_{34}H_{50}Cl_2N_4S_8$ (2 molecules in the unit cell), M = 842.16, triclinic system, space group $P\bar{1}$, a = 12.114(2), b = 13.267(3), c = 14.974(3) Å; α = 95.75(3), β = 110.80(3), γ = 102.12(3)º; V = 2159.0(10) Å^3, Z = 2, Dcalcd = 1.295 g cm^{-3}, μ(Mo-Kα)= 0.566 mm^{-1}, crystal dimensions of 0.40×0.32×0.22 mm. The X-ray diffraction measurement was made on a STOE IPDS 2T diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved using SHELXS. The data reduction and structure refinement was carried out with SHELXL using the X-STEP32 crystallographic software package.[44] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.0873, wR_2 = 0.2053 and S = 1.032 with 463 parameters using 11596 independent reflections (θ range = 2.33-29.20º). Hydrogen atoms attached to nitrogen atoms were located in the difference Fourier map and refined isotropically. All other hydrogen atoms were added in idealized positions. The crystallographic information file has been deposited with the Cambridge Crystallographic Data Centre, CCDC 985711.

44. *X-STEP32 Version 1.07b*, *Crystallographic Package*; Stoe & Cie GmbH: Darmstadt, Germany, 2000.

Table 1. Synthesis of *gem*-bis(dithiocarbamate) derivatives.[42]

Entry	ArCHO	RNH_2	Product	Time (min)	Yield (%)[a]	M.p (°C)
1	4-ClC_6H_4CHO	*n*-$PrNH_2$	**3a**	40	90	81-83
2	4-BrC_6H_4CHO	*n*-$PrNH_2$	**3b**	60	80	88-89
3	4-ClC_6H_4CHO	*s*-$BuNH_2$	**3c**	45	92	96-97
4	2-ClC_6H_4CHO	*s*-$BuNH_2$	**3d**	210	87	104-105
5	thiophene-2-carbaldehyde	*s*-$BuNH_2$	**3e**	30	90	99-100
6	thiophene-2-carbaldehyde	*n*-$PrNH_2$	**3f**	30	92	84-85
7	2-naphthaldehyde	*n*-$PrNH_2$	**3g**	70	95	94-95
8	2-naphthaldehyde	*s*-$BuNH_2$	**3h**	70	97	109-110
9	4-$MeOC_6H_4CHO$	*s*-$BuNH_2$	**3i**	45	87	98-99
10	4-FC_6H_4CHO	*n*-$PrNH_2$	**3j**	25	91	68-70
11	4-FC_6H_4CHO	*s*-$BuNH_2$	**3k**	210	88	107-108
12	4-MeC_6H_4CHO	*n*-$PrNH_2$	**3l**	30	95	90-91
13	4-$NO_2C_6H_4CHO$	*s*-$BuNH_2$	**3m**[b]	210	85	92-94
14	4-ClC_6H_4CHO	$PhCH_2NH_2$	**3n**[b]	70	85	-

[a]Yield of isolated product.

[b]These compounds decomposed within one day.

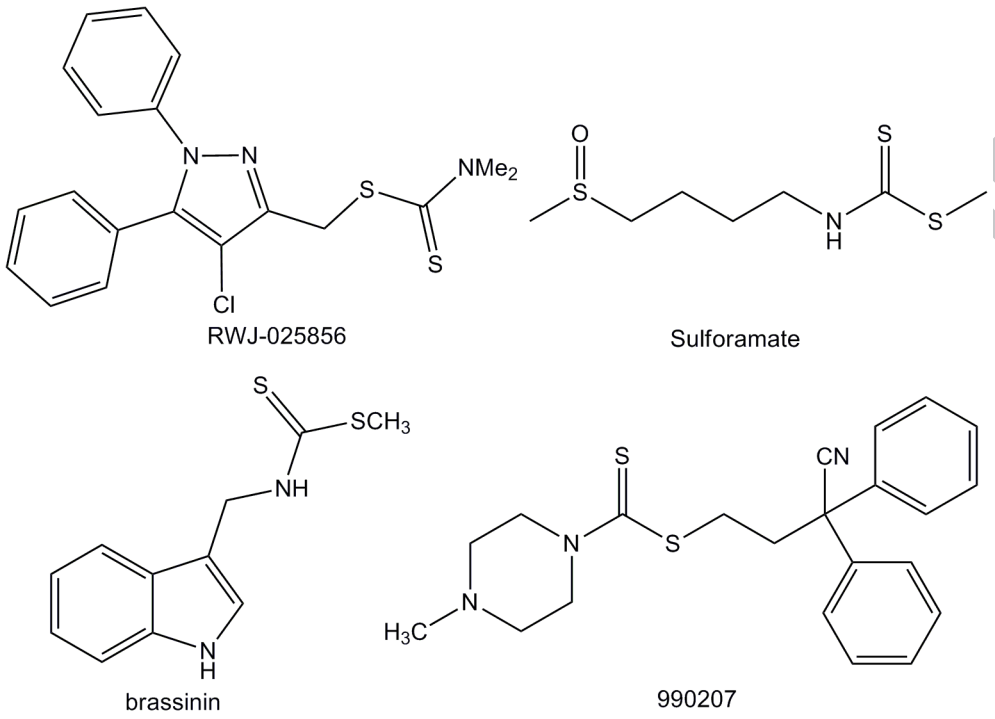


Figure 1. Examples of bioactive dithiocarbamate derivatives.

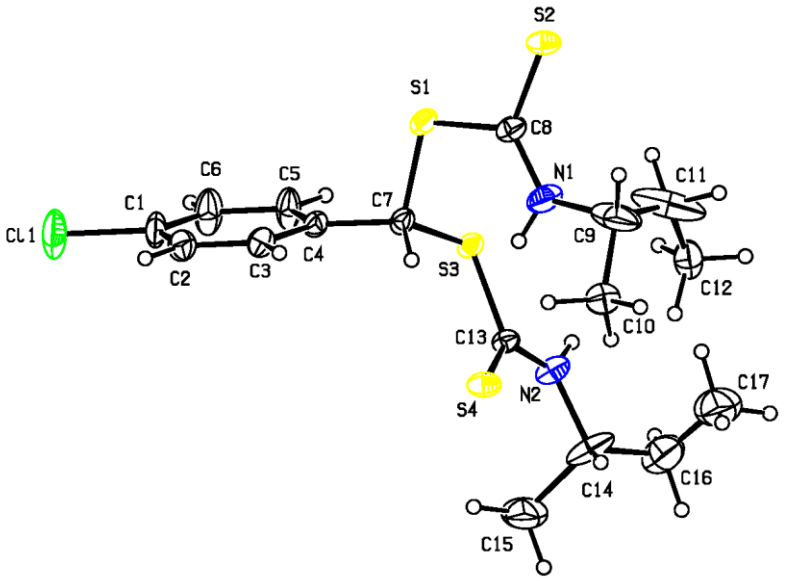
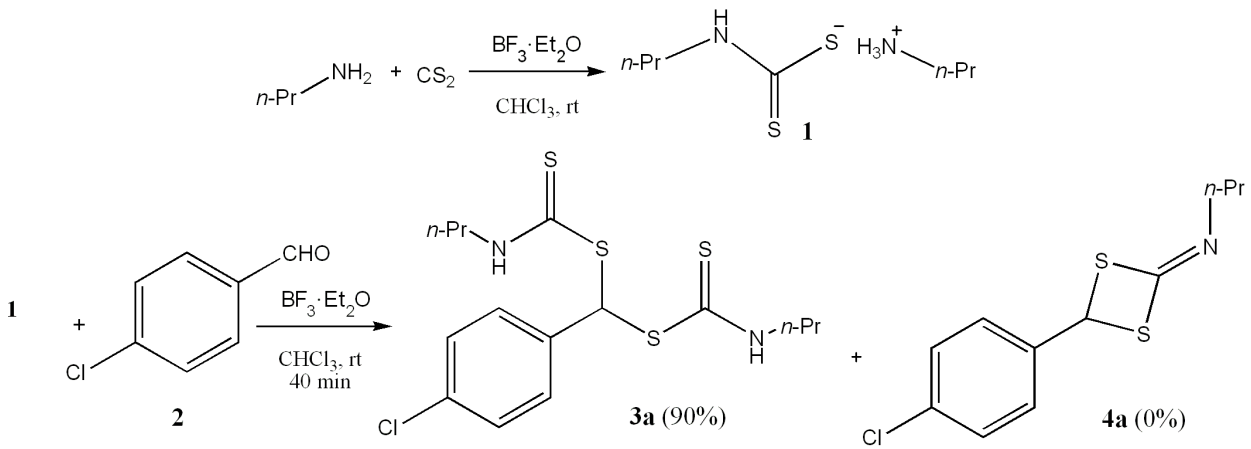
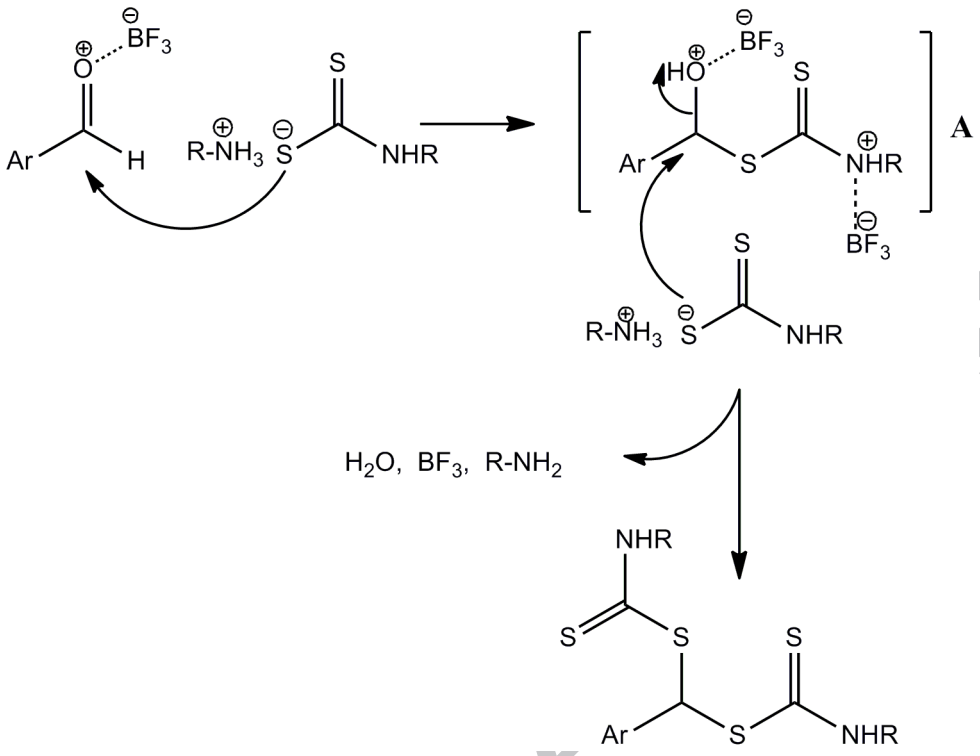


Figure 2. The ORTEP diagram of **3c**. Thermal ellipsoids are at 30% probability level.



Scheme 1. Preliminary studies



Scheme 2. A plausible mechanism.

Figures and Schemes Captions

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Scheme 1. Preliminary studies.

Scheme 2. A plausible mechanism.