Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Sep 2007.

SYNTHETIC COMMUNICATIONS, 29(2), 289-294 (1999)

A NEW ROUTE FOR THE SYNTHESIS OF 2-MERCAPTO BENZIMIDAZOLES

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Abstract : Benzenes 1,2-bis-(3-methyl-2-thioureido) are refluxed in nonpolar solvents to get the title compounds and N,N'-dimethyl thiourea.

2-Mercapto benzimidazoles were found to be useful starting materials in the synthesis of pharmaceutical agents such as Lansoprazole,[1] an antiulcerative agent.[2] Its 5-OMe analogues served as a starting material in Omeprazole[3] which was used in the treatment of Zoolinger Ellison Syndrome.[4] These mercapto benzimidazoles were generally prepared[5] by the reaction of 1,2-diamino benzene with an equimolar quantity of potassium ethyl xanthate, heated at 60°C using aq. AcOH as solvent.

Now we wish to present an efficacious process for the synthesis of substituted 2-mercaptobenzimidazoles and a useful side product N,N'-dimethyl thiourea,[6] from the 1,2-diamino benzene and methyl isothiocyanate (MiTC).

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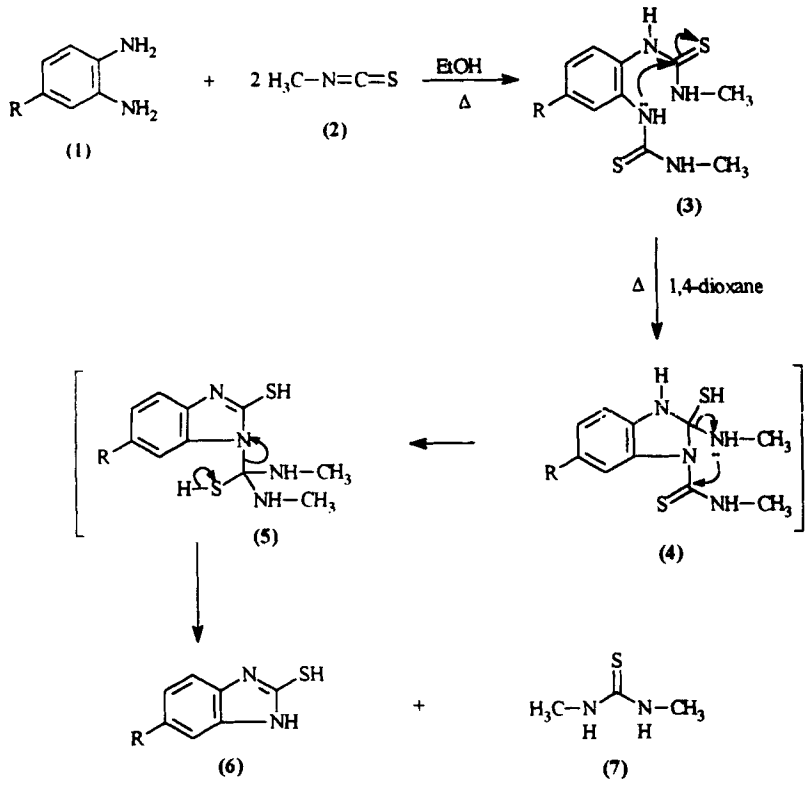
The reaction of 1,2-diaminobenzene (1a) with methyl isothiocyanate (2) has been carried out in dry EtOH at reflux temperature for 2 hrs. The residue obtained on removal of the solvent under reduced pressure has been poured into coold water to yield crude product purified by using column chromatography (EtOAc:Benzene, 1:9) to a colourless crystalline compounds m.p. 165-167°C.

The mass spectrum of the compound recorded the molecular ion peak at m/z 254 corresponding to a molecular formula of $C_{10}H_{14}H_4S_2$. IR spectrum (KBR) showed absorptions at 3273, 3052 and 1140 cm^{-1} attributed by the $-\overset{S}{\overset{\|}{C}}-\underline{NH}$, $\underline{HN}-CH_3$ and C=S functions respectively. The ^1H NMR spectrum (DMSO-d_6) revealed signals at δ 2.8-2.9 (d, 6H, 2NH-$\underline{CH_3}$), δ 7.2-7.4 (m, 4H, arom), δ 7.5 (br, 2H, NH of 2$\underline{NH}$-CH_3), δ 9.0 (br, 2H, NH of $2\underline{NH}-\overset{S}{\overset{\|}{C}}-$). These spectral data suggest the compound has the benzene 1,2-bis-(3-methyl-2-thioureido) structure (3a, scheme-1).

Reaction of benzene 1,2-bis-(3-methyl-2-thioureido) in 1,4-dioxane at reflux temperature for 2 hrs gave, after removal of the solvent under reduced pressure, a crude solid. Purification of the solid through column chromatography over neutral alumina using 9:1, benzene:EtOAc mixture yielded two colourless crystalline compounds. The compound-I (m.p. 69°C) gave absorptions in the IR spectrum (KBr) at 3270 (NH), 1140 cm^{-1} (C=S) functions. The ^1H NMR spectrum ($CDCl_3$ exhibited the signals at δ 2.8 (d, 6H, 2NH-$\underline{CH_3}$) δ 6.5 (br, 2H, 2$\underline{NH}$-CH_3, D_2O exchangeable). The spectral data and the super imposable IR with the

Scheme-1



	a	b	c	d	e
R	H	CH_3	OCH_3	Cl	NO_2

known compound[6] it has been assigned as N,N'-dimethyl thiourea structure (7, Scheme-1).

The other compound-II (m.p. 302°C) gave IR (KBr) absorptions at 3153, 1510 cm^{-1} assignable for NH, SH functions respectively. The ^1H NMR spectrum (DMSO-d_6) exhibited the signals at δ 7.2-7.3 (s, 4H, arom), δ 12.2 (br, 2H, NH and SH, D_2O exchangeable). The spectral data and the IR super imposable with the known compound[5] has suggested the compound-II has 2-mercapto benzimidazole structure (6a, Scheme-1).

Formation of the two produts can be explained by the initial nucleophilic attack of primary amino group of diamine (1) on the electrophilic carbon atom of the thiocarbonyl moieties of MITC (2) to give intermediate (3). After cyclisation on heating, nucleophilic attack of 2-methyl amino group on the thiocarbonyl carbon as in (4) lead to intermediate (5), which can collapse with exhusion of N,N'-dimethyl thiourea (7) gives the final compound 2-mercapto benzimidazole (6).

Similar cyclization of the compounds (3a,3b,3c) in refluxing 1,4-dioxane. or xylene gave as expected the corresponding 2-mercaptobenzimidazoles (6a,6b,6c) and N,N'-dimethyl thiourea (7). However. the compounds (3d,3e) on refluxing in 1,4-dioxane, xylene or in high boiling solvents like decaline, diphenyl ether remain unchanged even after prolonged reaction times.

Characterisation data of 3a-d:

3a : R=H, m.p. 165°C, yield 89%, ^{1}H NMR (δ ppm)
2.8-2.9 (6H, d), 7.2-7.5 (4H, m), 7.5 (br, 2H, 2N<u>H</u>-CH_3)
9.0 (br, 2H, 2-NH- C(=S) -); MS m/z 254 (M^+). Anal. Calcd. for $C_{10}H_{14}N_4S_2$: C 47.24, H 5.51, N 22.04. Found : C 47.18, H 5.58, N 22.05.

3b : R=CH_3, m.p. 140°C, yield 79%, ^{1}H NMR (δ ppm)
2.3 (3H, s), 2.8-2.9 (6H, d), 7.2-7.4 (3H, m), 7.5 (br, 2H, 2NH-CH_3)
9.0 (br, 2H, 2N<u>H</u>- C(=S) -); MS m/z 268 (M^+). Anal. Calcd. for $C_{11}H_{16}N_4S_2$: C 49.25, H 5.97, N 20.89. Found : C 49.28, H 5.92, N 20.91.

3c : R=OCH_3, m.p. 175°C, yield 78%, ^{1}H NMR (δ ppm)
2.8-2.9 (6H, d), 3.6 (3H, s), 7.2-7.8 (3H, m), 7.5 (br, 2H, 2N<u>H</u>-CH_3)
9.0 (br, 2H, 2N<u>H</u>- C(=S) -); MS m/z 284 (M^+). Anal. Calcd. for $C_{11}H_{16}N_4OS_2$: C 46.47, H 5.63, N 19.71. Found : C 46.48, H 5.60, N 19.75.

3d : R=Cl, m.p. 152°C, yield 72%, ^{1}H NMR (δ ppm)
2.8-2.9 (6H, d), 7.2-7.4 (3H, m), 7.5 (br, 2H, 2<u>NH</u>-CH_3) 9.0 (br, 2H, 2<u>NH</u>- C(=S) -); MS m/z 288 (M^+). Anal. Calcd. for $C_{10}H_{13}ClN_4S_2$: C 41.66, H 4.51, N 19.44. Found : C 41.65, H 4.53, N 19.43.

3e : R=NO_2, m.p. 172°C, yield 75%, ^{1}H NMR (δ ppm)
2.8-2.9 (6H, d), 7.2-7.8 (3H, m) 7.5 (br, 2H, 2<u>NH</u>-CH_3), 9.0 (br, 2H, 2<u>NH</u>- C(=S) -); MS m/z 299 (M^+). Anal. Calcd. for $C_{10}H_{13}N_5O_2S_2$: C 40.13, H 4.34, N 23.41. Found : C 40.16, H 4.32, N 23.42.

Characterisation data of 6a-c

6a : R=H, m.p. 302°C, yield 90%, ^{1}H NMR (δ ppm)
7.2-7.3 (4H, s), 12.2 (2H, br, D_2O exchangeable)
MS m/z 150 (M^+). Anal. Calcd. for $C_7H_6N_2S_2$: C 56.00, H 4.00, N 18.66. Found : C 56.02, H 4.00, N 18.64.

6b : R=CH_3, m.p. 296°C, yield 92%, ^{1}H NMR (δ ppm)
2.3 (3H, s), 7.2-7.5 (3H, m)
12.2 (2H, br, D_2O exchangable), MS m/z 164 (M^+). Anal. Calcd. for $C_8H_8N_2S_2$: C 58.53, H 4.87, N 17.07. Found : C 58.58, H 4.84, N 17 09.

6c : R=OCH3, m.p. 275°C, yield 89%, ^{1}H NMR (δ ppm)
3.6 (3H, s), 7.2-7.5 (3H, m)
12.2 (2H, br, D2O exchangable), MS m/z 180 (M^+). Anal. Calcd. for $C_8H_8N_2OS$: C 53.33, H 4.44, N 15.55. Found : C 53.31, H 4.46, N 15.56.

Acknowledgements : One of the authors (ANB) is thankful to the Head, Department of Chemistry, Osmania University for providing lab facilities.

References:

1. Mullar. P *et al.*, *Arzneimittel - Forseh.*, **1983**, *33*, 1685.
2. Lindberg, P. *et al.*, *J. Med. Chem.*, **1986**, *29*, 1327.
3. Satoh, H. *et al.*, *J. Pharmacol. Exp. Ther.* **1989**, *806*, 248.
4. Mullar. P. *et al.*, *Aliment, Pharmacol. Ther.* **1989**, *3*, 193.
5. Van allan, Deacon, *Org. Syn. Coll. Vol. IV*, **1963**, 569.
6. Chattopadhyaya, J.B. et al., *Synthesis*, **1974**, 289.

(Received in the USA 14 July 1998)