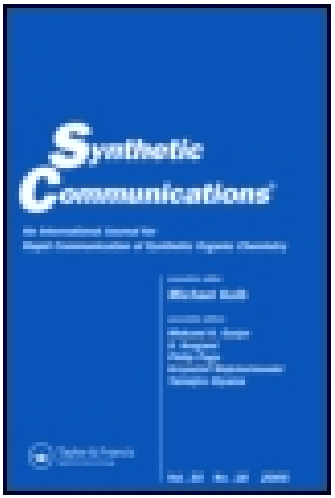

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Benzotriazole Mediated Synthesis of Some 5-Alkyl-Dihydro-4H-1,3,5-Dithiazines

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BENZOTRIAZOLE MEDIATED SYNTHESIS OF SOME 5-ALKYL-DIHYDRO-4H-1,3,5-DITHIAZINES

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Abstract: An efficient synthesis of N-substituted dihydro-4H-1,3,5-dithiazines is described. N,N-Bis(benzotriazolylmethyl)alkylamines **1** smoothly under go cyclisation reaction in the presence of formaldehyde and hydrogen sulfide to give 5-substituted dihydro-4H-1,3,5-dithiazines **2**.

The 5,6-dihydro-4H-1,3,5-dithiazines play an important role in food flavours and particularly in heated food product [1-5]. An important route to 5,6-dihydro-4H-1,3,5-dithiazines system is from formaldehyde, ammonia or alkylamines and hydrogen sulfide. Examples include (i) formation of a mixture of product containing 5-alkyl-1,3,5-dithiazines and 3,5-dialkyldithiazines[6], (ii) use of thioformaldehyde with alkyl amines[7],(iii) use of dichloromethane with sodium sulfide, alkylamines using polyethyleneglycol (PEG) as a catalyst to give a mixture

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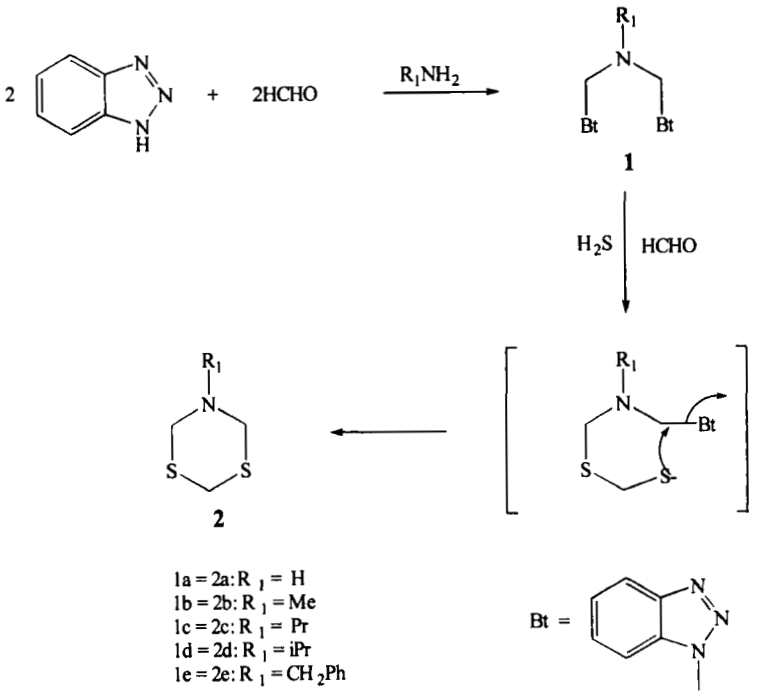
of 5-alkyl-1,3,5 dithiazinane, 3,5-dialkyl-1,3,5-thiadiazinane, 1,3,5-alkyl-1,3,5-triazinane and polymethylsulfide[6]. Howes has synthesised dithiazines and bis-dithiazines via Mannich reaction by treating a variety of dithiolates with formaldehyde and primary amines[8]. Most of these reactions have limited application as they generally give a mixture of product, produce low yield, and lack of control on ring substitution.

Katritzky has previously reported that benzotriazoyl group is both a good anion stablising group and a good leaving group[9]. We have recently shown that benzotriazolyl group could be successfully used as a leaving group for a variety of cyclisation reactions for the synthesis of 1,2,3,4-tetrahydroisoquinolines and its derivatives[10]. Due to these unique properties of the benzotriazolyl group, N,N-bis(benzotriazolylmethyl)alkylamines have been shown to be an excellent precursor for the synthesis of susbtituted dihydro-4H-dithiazines. This investigation describes an efficient synthesis of N-substituted dihydro-4H-1,3,5-dithiazines from N,N-bis(benzotriazolylmethyl)alkylamines which smoothly under go cyclisation reactions in the presence of hydrogen sulfide. This methodology for the synthesis of dithiazines possesses several advantages over the existing strategies. The stable solid intermediates, N,N-bis(benzotriazolylmethyl)alkylamines (**1**) are readily available in high yield, it provides a mild reaction conditions and a control of ring substitution. Benzotriazole could also be recovered at the completion of the reaction. The overall conversion is achieved in one step synthesis, with the isolated yield of dithiazines (based on the N,N-bis(benzotriazolylmethyl)alkylamines being high.

Benzotriazole reacts with primary and secondary aliphatic amines in the presence of an aldehyde (formaldehyde or acetaldehyde) in various ratio to form 1-(α–aminoalkyl)benzotriazoles and N,N-bis(benzotriazolylmethyl)alkylamines, using formaldehyde as the aldehyde[11]. This reaction can be carried out in an ethanolic, hydrocarbon or water solution. Studies have shown that the use of an aqueous solution greatly improves the yields of these adducts and their purity[11]. The work done in these studies concentrated on primary amines with bulky substituents. Initially we prepared a series of N-substituted N,N-bis(benzotriazolylmethyl)alkylamines adducts (**1a-e**) by reacting formaldehyde, amine and benzotriazole in a ratio of 2:1:2 in ethanol as shown in (Scheme 1). The yield of most of the adduct formed were high and the products were identified by literature melting points and NMR data (Table 1).

The cyclisation step to dithiazines was carried out in the presence of sodium sulfide or hydrogen sulfide and formaldehyde. Normally, the N,N-bis(benzotriazolylmethyl)alkylamines were dissolved in dichloromethane and solution chilled at 0°C. To the chilled solution formaldehyde and sodium sulfide solution or hydrogen sulfide was added in excess. The solution was brought to room temperature and stirring continued for six hours. The solvent was removed under reduced pressure and product purified by flash chromatography (Table 2). Dithiazines, generally were very volatile and decomposed easily[6]. 5,6-Dihydro-4H-1,3,5-Dithiazine (**2a**) was not isolated and efforts to purify it by TLC or flash chromatography proved difficult. This compounds was highly volatile and was present in the crude reaction mixture but in low yields. The crude mixture of this reaction was analysed by GC-MS and gave two molecular ion peaks of mass charge



Scheme 1

ratio m/z 121 and m/z 75. The molecular ion m/z 75 compound was the result of late addition of the formaldehyde to the reaction mixture N,N-Bis(benzotriazolylmethyl)alkylamines and sodium sulfide or hydrogen sulfide were mixed for 5 minutes before the addition of formaldehyde. A possible reaction mechanism for the formation of molecular ion compound m/z 75 is suggested in (Scheme 2).

In conclusion, a facile route to dithiazines have been developed via N,N-bis(benzotriazolylmethyl)alkylamines compared with the analogous methods previously developed using amine, formaldehyde, hydrogen sulfide or sodium

Table 1

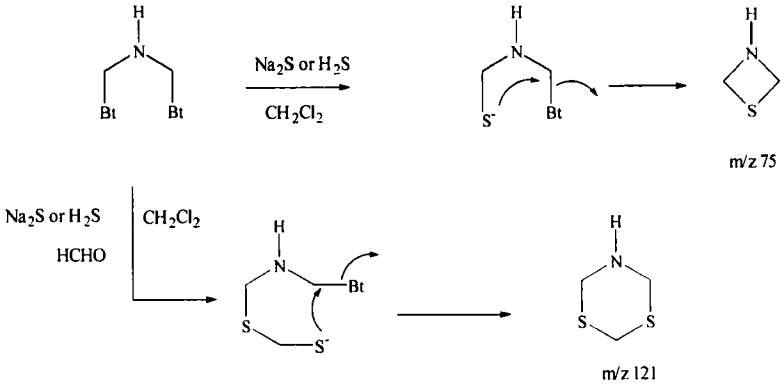
Preparation of N,N-bis(benzotriazolylmethyl)alkylamines **1**

Cpd, No	R_2	Adduct Yield %	Recryst. Solvent	MP °C (lit. mp)[11]	NMR ppm ($CDCl_3$) N-CH_2-N
1a	H	50	EtOH	173-174 (177-178)	5.69 (d)
1b	Methyl	70	EtOH	86-88 (88-90)	5.62 (s)
1c	Propyl	50	MeOH	105-107 (106-108)	5.63 (s)
1d	Isopropyl	75	Ethylacetate /Hexane (1:1)	79-81 (78-79)	5.69 (s)
1e	Benzyl	50	Ethylacetate /Hexane (1:1)	106-108 (108-109)	5.63 (s)

Table 2

Preparation of 5-Substituted-5,6-dihydro-4H-1,3,5-dithiazines **2**

Cpd, No	R_2	Adduct Yield %	MP °C (lit. mp)	NMR ppm ($CDCl_3$) N-CH_2-N	S-CH2-S
2b	Methyl	60	61-62 (63-65)[12]	4.40 (s)	4.06 (s)
2c	Propyl	73	30-32 (30-31)[6]	4.57 (s)	3.97 (s)
2d	Isopropyl	73	33-35 (32-35)[6]	4.50 (s)	4.10 (s)
2e	Benzyl	33	103-104	4.40 (s)	4.10 (s)



Scheme 2

sulfide, our approach complements them by taking advantage of the easy introduction of benzotriazole functionality and successful cyclisation to dithiazines.

EXPERIMENTAL:

Melting points were determined by Electrothermal apparatus and are reported uncorrected. All alkylamines were obtained from Aldrich and used after distillation. All reagent and solvent were of commercial grade. All reactions were carried out under nitrogen atmosphere. Column chromatography was conducted with silica gel 230-400 mesh. Infrared spectra (KBr) were recorded by using Perkin-Elmer Model 580 spectrometer. NMR spectra were obtained with Varian Gemini-200 spectrometer at 50 MHz for ^{13}C and 200 MHz for ^{1}H. Both ^{13}C and ^{1}H NMR spectra were obtained in chloroform-d, chemical shift values are reported as δ downfield from tetramethylsilane (Me_4Si) as the internal standard. Mass spectra were determined at 70eV with Varian Saturn-3 GC-MS.

Typical Procedure for preparation of N,N-bis(benzotriazolylmethyl)-propylamine 1c.

1-Hydroxymethylbenzotriazole (2.98g, 20mmol), glacial acetic acid (0.57mL, 10mmol), absolute ethanol (30mL) and *n*-propyl amine (0.71g, 12mmol) were refluxed together for 2 minutes. The solution was then poured onto ice and extracted with dichloromethane (2 x 50mL). The extracts were washed with 10% sodium carbonate solution (1 x 30mL), water (2 x 30mL), then a saturated brine solution before being dried over anhydrous magnesium sulfate. Evaporation under vacuum at 50°C yielded a brown oil, which on sitting at 4°C for 6 hours crystallised to give the crude adduct (1.81g). The crude product was recrystallised from absolute methanol (1.61g, 50 %), mp. 105-107°, lit[11] 106-108°. ^{1}H NMR ($CDCl_3$) : δ 0.79 (t, J= 7.2Hz, 3H), 1.61 (m, J= 7.4Hz, 2H), 2.82 (t, J= 8Hz, 2H), 5.63 (s, 2H), 7.44 (t, J= 7.2Hz, 1H), 7.531 (t, J= 6.8Hz, 1H), 7.69 (d, J=8.2Hz , 1H), 8.10 (d, J= 8.2Hz, 1H). ^{13}C NMR ($CDCl_3$): δ11.11, 20.54, 52.35, 64.23, 109.83, 118.34, 120.10, 124.28, 127.95, 133.33, 146.16.

5-propyl-5,6-dihydro-4H-1,3,5-dithiazines (2c). General Procedure: N,N-Bis(benzotriazolylmethyl)propylamine (1.61g, 5mmol) was suspended in 30mL of chilled dichloromethane, to this solution was added 0.21g of formaldehyde (7mmol, 0.56mL of 37% formaldehyde). The solution was cooled to approximately 0°C in a salt/ice bath and hydrogen sulfide was introduced in to the solution with stirring. Addition of hydrogen sulfide at 0°C was continued for approximately 4 hours. After which time the reaction vessel was sealed and allowed to return to room temperature. Stirring was continued for 6 hours. The organic layer was washed and

dried, then the solvent was removed under reduced pressure to yield a pale yellow oil which was purified by flash chromatography (0.60g, 73%), lit 30-31[7]. ^{1}H NMR ($CDCl_3$) : δ 4.57 (s, 4H, S-CH_2-N), 3.97 (s, 2H, S-CH_2-S), 3.50 (t, 2H, CH_2), 1.69 (m, 2H, CH_2), 1.03 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 58.29, 50.73, 33.67 , 20.4, 11.68. MS (EI) m/z (%):163 (35, M^+),117 (27), 84 (100), 70 (44), 56 (36), 42 (76).

Anal. Calcd. for $C_6H_{13}NS_2$: C, 44.13; H, 8.02; N, 8.58.

Found: C, 44.12; H, 8.18; N, 8.45.

5-Methyl-5,6-dihydro-4H-1,3,5-dithiazine (2b): obtained as a colourless solid (0.45g, 59%), mp. 61-62 lit[12] 63-65°. ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H), 4.06(s, 2H), 4.4(s, 4H). MS (EI) m/z (%): 135 (34, M^+), 89 (28),70 (20),57 (100), 44 (85).

Anal. Calcd. for $C_4H_9NS_2$: C, 35.52; H, 6.71; N, 10.36

Found: C, 35.55; H, 6.68; N, 10.20

5-Isopropyl-5,6-dihydro-4H-1,3,5-dithiazine (2d): obtained as a colourless oil (0.60g, 73%), mp lit[13] 33-35. ^{1}H NMR ($CDCl_3$): δ 4.5 (s, 4H), 4.1 (s, 2H), 3.75 (q, 1H, J_{HH} = 6.4Hz), 1.2 (d, 6H, J_{HH} = 6.4Hz), 1.15 (d, J_{HH} = 6.4Hz). ^{13}C NMR ($CDCl_3$): δ 56.2, 44.9, 33.6, 20.4. MS (EI) m/z (%):163 (35, M^+),117 (27), 85 (59), 84 (100), 70 (44), 56 (36), 42 (76).

Anal. Calcd. for $C_6H_{13}NS_2$: C, 44.12; H, 8.18; N, 8.45.

Found: C, 44.13; H, 8.02; N, 8.58.

5-Benzyl-5,6-dihydro-4H-1,3,5-dithiazine (2e): obtained as a colourless solid (0.34g, 33%), mp 103-104. ^{1}H NMR ($CDCl_3$): δ 7.30-7.41 (m, 5H), 4.41 (s, 4H),

4.10 (s, 2H), 4.20 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 137.3, 129.3, 128.6, 127.6, 57.7, 53.1, 33.8. MS (EI) m/z (%): 211 (53 M^+), 178 (8), 165 (39), 133 (100), 118 (52), 91 (74), 65 (24), 42 (98).

Anal. Calcd. for $C_{10}H_{13}NS_2$ C: 56.87; H: 6.16; N: 6.63.

Found: C: 56.52; H: 5.81; N: 6.60

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References

1. Farakas, P; Sadecka, J; Kovac, M; Siegmund, B; Leitner, E and Pfannhauser, W. *Food Chemistry* **1997,** *60* (4), 617-621.
2. Suzuki, T and Shibata, N. *Food Rev. Int.* **1990,** *6* (1), 119.
3. Kubota, K; Shijimaya, H and Kobayashi, A. *Agric. Biol. Chem.* **1986**, *50* (11), 2867.
4. Kawai, T; Ishida Y; Hakiuchi, N; Ikeda, T; Higashida, T and Nakamura, S. *J. Agric. Food Chem.* **1991**, *39*, 770.
5. Noleau, I; Richard, H and Peyroux,A. S. *J. Ess. Oil Res.* **1991**, *3*, 241.
6. Torres, M and Vega, J. C. *Phosphorous, Sulfur, and Silicon.* **1995**, *106*, 125-130.
7. Okajima, N and Okada, Y. *J Heterocyclic Chem.* **1990**, *27*, 567-574.

8. Howes, P. D; Paynes, J. J and Pianka, M. *J. Chem Society Perkin* Trans.1. **1980**,1038-1044.

9. Katritzky, A. R; Lan, X; Yang, J. Z and Denisko, O. *Chem., Rev.* **1998**, *98*, 409-548.

10. Locher, C and Peerzada, N. *J. Chem. Society Perkin Trans.* 1 **1999**, (002) 179-184.

11. Katritzky, A. R; Rachwal, S and Rachwal, B. *J. Chem. Society Perkin Trans.* 1. **1987**, 799-804.

12. Juaresti, E; Gonzalez, E. A; Pinto, B. M and Johnson, B. Nalgelkerke, R. *J. Am. Chem. Society*, **1989**. *111*, 6745-6749.

13. Cadenas-Pliego, G; Rozales ;Contreras, R and Flores-Parra, A. *Tetrahedron Asymmetry* **1994**, *5* (4), 633-640.

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