J. Sci. I. R. Iran

Vol.10 No.1
Winter 1999

Research Note

SELECTIVE CYCLIZATION AND ISOMERIZATION OF 3-PROPARGYLTHIO-1,2,4-BENZOTRIAZINE TO THIAZOLO [2,3-c] [1,2,4] BENZOTRIAZINE

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Abstract

The method cited in the literature for synthesis of 1,2-dihydro 3-thioxo -1,2,4-benzotriazine **1** was improved. **1** was condensed with propargyl bromide to afford 3-propargylthio -1,2,4-benzotriazine **5**. Transformation of this compound to 9H-3-methylthiazolo [2,3-c] [1,2,4] benzotriazine (3, R=Me) was performed in the presence of $Na^{+}O^{-}Me/MeOH$. Orientation of this selective cyclization was ascertained by (N.O.E.) NMR experiment.

The cyclization of 3-propargylthio and propargylseleno -1,2,4-triazine as routes to thiazolo -1,2,4-triazines [1-5] and selenazolo -1,2,4-triazines [6,7], respectively, is well documented. However, the related thiazolo -1,2,4-benzotriazine has been largely overlooked. Pujari and his co-workers [8] correctly reported that 1,2-dihydro 3-thioxo-1,2,4-benzotriazine **1** on condensation with α-halogenoketones yielded ketones **2** which on treatment with polyphosphoric acid underwent cyclization giving a single compound (TLC). They have assigned structure **3** on the basis of analogy. However, cyclization of **2** can afford the other regioisomer **4**. Spectral data were not much help in deciding in favour of either angular product **3** or linear product **4**.

Keywords: Selective cyclization; Isomerization; Benzotriazine; N.O.F; Propargylthiobenzotriazine

In continuation of our earlier studies on the orientation of cyclization in a reaction of unsymmetrical triazines with bifunctional group [2-7], we wish to report in the present communication our work on the reaction of 3-thioxo-1,2,4-benzotriazine with propargyl bromide.

1,2-Dihydro-3-thioxo-1,2,4-benzotriazine **1** was obtained by the fusion of thiosemicarbazide with o-phenylenediamine. The procedure which will be given here is an improvement on the method cited in the literature [8] and has proved to be the most convenient and to produce a much better yield.

When **1** was condensed with propargyl bromide in the presence of sodium methoxide at ambient temperature, 1,2-dihydro-3-propargylthio-1,2,4-benzotriazine **5** was obtained. In the ^{1}H NMR spectrum of this compound, methylene protons appear as a doublet and the acetylenic

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*To whom all correspondence should be addressed proton as a triplet showing a long range coupling (J= 2.60 Hz).

When **5** was refluxed in sodium methoxide in MeOH for 4 h, a solid was isolated that was crystallized from ethanol to give a single white crystalline compound. The compound was identified as either 9H-3-methylthiazolo [2,3-c] 1,2,4-benzotriazine (**3**, R=Me) or 4H-3-methylthiazolo [3,2-b] [1,2,4] benzotriazine (**4**, R= Me). In the 1H NMR spectrum of this compound, CH of thiazole ring appeared as a quartet (J=1.34 Hz) and CH_3 attached to thiazole ring appeared as a doublet (J=1.34 Hz) showing long range coupling between CH of thiazole ring and CH_3 attached to thiazole ring.

Transformation of **5** to either (**3**, R= Me) or (**4**, R= Me) could not be undertaken either in protic or aprotic solvent at their refluxing temperature even for a long period of time. Activation of triple bond by Pd(II) salt [9] for cyclization was not selective and satisfactory.

Since benzotriazine **5** is unsymmetrical, it can be assumed that the base (Na^+O^-Me/MeOH) abstracts a hydrogen from either nitrogen 4 or nitrogen 2 of **5**. The nitrogen then attacks the acetylenic group to give a single cyclized intermediate 6 or 7.

Isomerization and aromatization of this intermediate produces selectively either (3, R=Me) or (4, R=Me) respectively. The structure of (3, R= Me) has been assigned to the TLC-pure product on the basis of (N.O.E.) NMR experiment. The N.O.E. spectrum of this compound gave N.O.E.s between methyl group and H_a on the benzene ring and methyl group and CH of thiazole ring. Observation of mutual N.O.E. enhancement between methyl group on thiazole ring and Ha on the benzene ring and CH of thiazole ring led us to assign structure 3 for the obtained compound. This effect is expected in 3 whereas N.O.E. effect between methyl group and H_a of the benzene ring in 4 is quite improbable.

This result showed that in spite of the α-effect and steric considerations of this system and the existence of a vast amount of literature [10] on the reactivity of N-2 in 1,2,4-triazine, the base abstracts hydrogen from nitrogen 4 of 1,2,4- benzotriazine selectively resulting in intermediate 6 and hence compound (3, R=Me). The reaction mechanism is given in Scheme 1. This behavior has been observed for two step cyclization and isomerization of 1,2,4-triazines [3-7].

The concentration of the base was decreased and time was cut in an unsuccessful attempt to isolate **6**. Sodium hydroxide solution, in different concentrations, and triethylamine were also used as a base, but the same result was obtained.

Work is continuing in this area to isolate the intermediate and implement cyclization around b bond by making use of nitrogen 2 selectively.

Experimental Section

Melting points were obtained on a Buchi 530 and are uncorrected. ^1H NMR spectra were recorded on a Brucker AC 80 spectrometer in (DMSO-d_6) as solvent and internal standard. IR spectra were recorded on a Perkin-Elmer model 883 using KBr disc, and mass spectra were obtained on a Finnigan Mat model 8430.

1,2-Dihydro-3-thioxo-1,2,4-benzotriazine 1

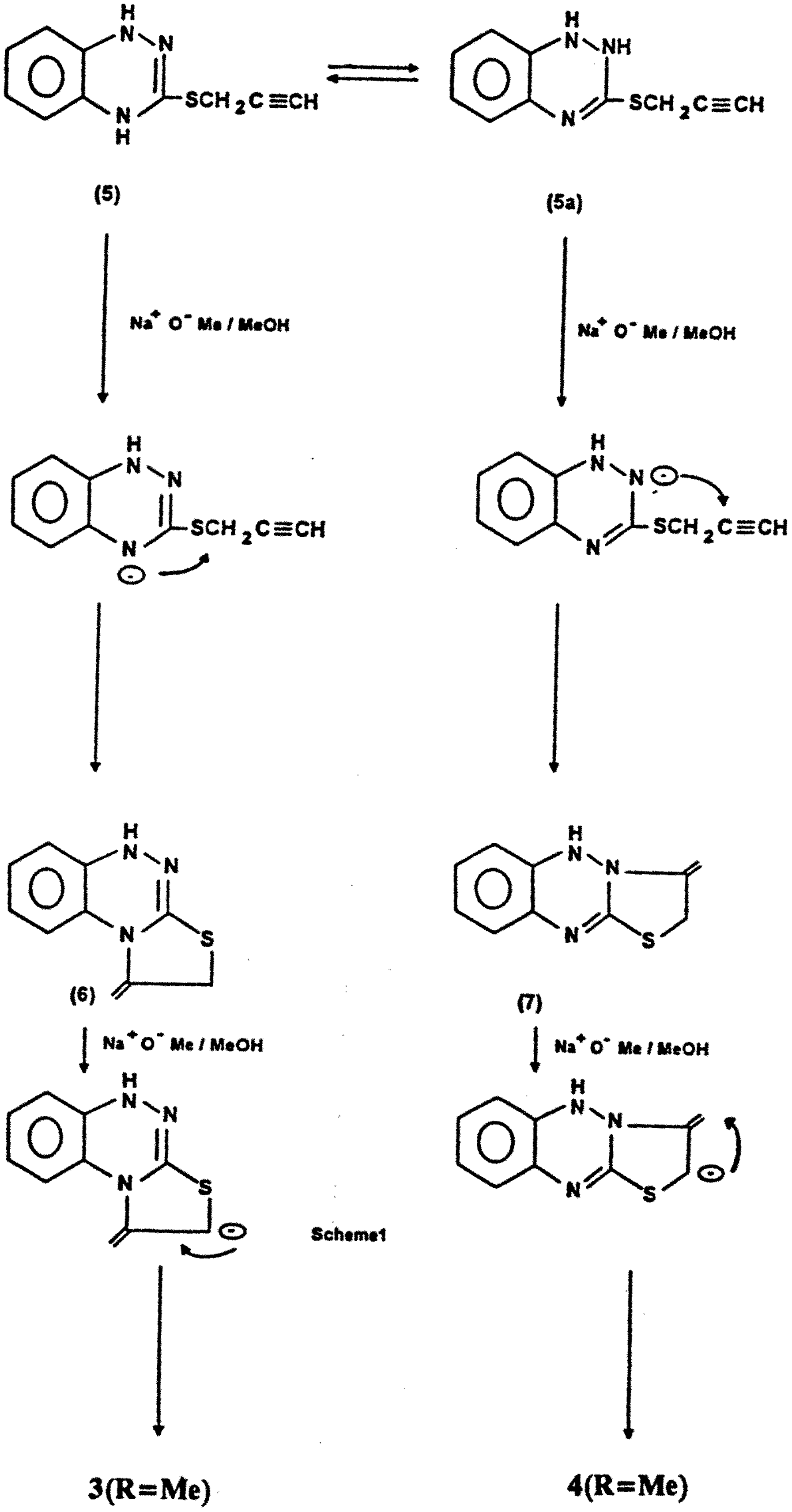
As an improvement on the method cited in the literature [8], the following procedure was the most convenient: o-phenylenediamine (0.8 g, 0.01 mol) and thiosomecarbazide (0.92 g, 0.01 mol) were mixed thoroughly in a test tube. This mixture was gradually heated in an oil bath for 4 h at 180°C. After cooling of melted material, it was solidified. This solid was extracted four times with MeOH (100 ml). The combined extracts were evaporated off and the residue was crystallized from MeOH to afford the title compound, (yield 75%, lit. [8], 48%, m.p. 289-290°C, lit. [8], 290°C. ν(KBr disc)/cm^{-1}, 3050-3060 (NH broad), 1216 (C= S stretching), ms: m/z 165 (M^+, 12), 164 (62), 76 (100).

3-Propargylthio-1,2,4-benzotriazine 5

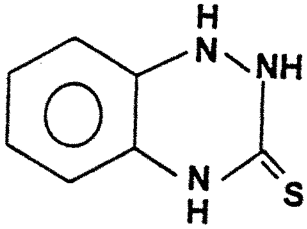
Sodium methoxide (0.5 g, 0.092 mol) was dissolved in MeOH (50 mL). To this solution compound **1** (0.82 g, 0.05 mol) was added. Under nitrogen propargyl bromide (0.6 g, 0.0504 mol) was added dropwise at room temperature. The reaction mixture was stirred at ambient temperature for 4 h. The solvent was evaporated off and the solid was washed with water thoroughly and recrystallized from MeOH to afford **2**, (0.908 g, 90% yield), m.p. 143-145°C; ν(KBr disc)/cm^{-1}, 3285(≡C-H), 1679, 1621, 1506, 1440, 927, 826, 743; ^1H NMR, 3.1 (t, J= 2.60, 1H, C≡CH) 4.1 (d, J= 2.60, 2H, CH_2), 7.01-7.25 (m, 2H, C_6H_4), 7.31-7.58 (m, 2H, C_6H_4); NH protons are not exhibited in the normal chart, ms: m/z, 205 (M^+, 8), 188 (100), 155 (9), 143 (18), 102 (10).

9H-3-Methylthiazolo [2,3-c] [1,2,4] benzotriazine (3)

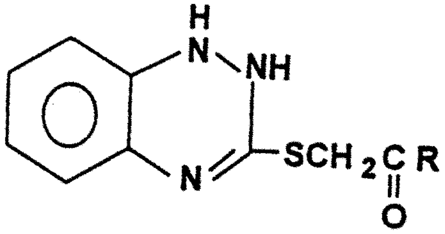
Compound **5** (0.5 g, 0.024 mol) was refluxed in a solution of Na^+O^-Me (1 g, 0.045 mol) in MeOH (50 mL) for 5 h. The solvent was evaporated off, the obtained solid was washed with water thoroughly and recrystallized from MeOH to afford (3, R=Me), (yield 0.44 g, 88%), m.p. 130-132°C; ν, (KBr disc)/cm^{-1}, 3419, 2950, 1931, 1625, 1308, 809, 735. ^1H NMR, δ 2.35 (d, J=1.34, 3H, Me), 6.83 (q, J=1.34, 1H, CH of thiazole ring), 7.10-7.39 (m, 2H, C_6H_4), 7.58-7.76 (m, 1H, C_6H_4), 7.86, 8.03 (M, 1H, orthoproton, C_6H_4); NH proton is not exhibited in the normal chart. N.O.E. experiment: Sample was degassed prior to experiment; N.O.E. spectra were measured by irradiation of Me at δ 2.35. The enhancement of N.O.E. signals at δ 6.83 and 7.86-8.03 was observed. Ms: m/z,



Scheme1



(1)



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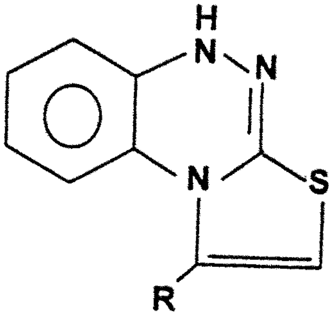
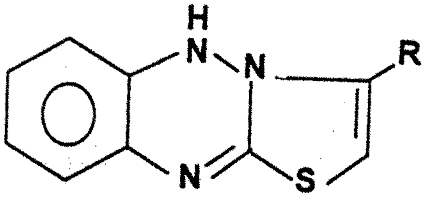


(3)

R=Me



(4)

203 (5), 187 (100), 155 (42), 149 (45), 122 (50), 41 (35).

References

1. Mizutani, M., Sanemitsu, Y., Tamaru, Y. and Ichi Yoshida, Z. *Tetrahedron*, **42**, 305, (1986).
2. Heravi, M.M. *Iran. J. Chem & Chem Eng.*, **11** (2), 8, (1992); *Chem. Abstr.*, **120**, 323500d, (1992).
3. Heravi, M.M. and Bakavoli, M. *J. Chem. Research*, **11**, 480, (1995).
4. Heravi, M.M. and Shafaie, M. *Indian J. Heterocyclic Chem.*, **5**, (1), 83, (1995).
5. Heravi, M.M., Shafaie, M., Bakavoli, M., Sadeghi, M.M. and Khoshdast, A.R. *Indian J. Chem.*, Section B, **35 (B)**, 1260, (1996).
6. Heravi, M.M. and Bakavoli, M. *J. Chem. Soc Pak.*, **17**, (2), 118, (1995).
7. Heravi, M.M., Bakavoli, M., Tajbakhsh, M. and Beheshtiha, Y.Sh. *Indian J. Heterocyclic Chem.*, **5**, (1), 77, (1995).
8. Bala, S., Sachdeva, M.L., Handa, R.N. and Pujari, H.K. *Heterocycles*, **14**, (2), 149, (1980).
9. Tsuji, T. and Mandai, T. *Synthesis*, **1**, 1, (1996), and the references therein.
10. Neuenhoeffer, H. and Wiley, P.F. *Chemistry of 1,2,3-triazines and 1,2,4-triazines, tetrazines and pentazines.* Wiley Interscience, New York, (1978), and references therein.