A NOVEL ONE STEP APPROACH TO THE SYNTHESIS OF 3H-1,4-BENZODIAZEPIN-(1H,4H)-2,5-DIONES FROM 1,2,3-BENZOTRIAZIN-4-(3H)-ONE.

Renu Gupta, Reenu Sirohi, Sudha Shastri and D. Kishore*
Department of Chemistry, Banasthali Vidyapith- 304022(Rajasthan)
Phone : 91-01438-228316, Fax: 91-01438-228365
E-mail : kishoredharma@yahoo.co.in

ABSTRACT

1,2,3-Benzotriazin-4-(3H)-one(**3**) and its 6-chloro derivative (**4**) on thermal condensation with α-amino acids yielded 3H-1,4-benzodiazepin-(1H,4H)-2,5-diones(**7-12**) in moderate to good yield. The cyclocondensation is believed to proceed through the formation of an iminoketene intermediate (**5**).

INTRODUCTION

1,4-Benzodiazepines and their oxo derivatives represent an active class of compounds possessing a broad spectrum of psychopharmacological properties[1]. Our quest[2] to develop novel one step strategy to 1,4-benzodiazepine synthesis has led us to examine materials with proven synthetic potentials for their application in its synthesis[3]. A search of the literature[4] revealed that 1,2,3-benzotriazin-4-(3H)-one (**3**) has extraordinary facility for the cleavage of its nitrogen containing ring with acids[5],alkalies[6] and in absence of these, under thermal conditions[7] to give an intermediate benzazetone **5** which has been widely used in synthesis[4]. This prompted us to examine its application in 1,4-benzodiazepine synthesis. Excluding only one attempt made by Nesmeyanov and co-workers in 1973[8] to convert **1** to **2** using 30 % phosphoric acid (scheme-1), no other attempt seems to has been made earlier to explore the synthetic potentialities of **3** in 1,4-benzodiazepine synthesis. Under acidic conditions 1,2,3-benzotriazine behaves as a masked diazonium compound whose formation is believed to involve the reversible hydrolytic cleavage of N_2-N_3 bond to give rise to the transient formation of a diazonium compound which in appropriately substituted **3** is amenable further to products through the intra or intermolecular condensations.

RESULTS AND DISCUSSION

1,2,3- Benzotriazin-4-(3H)-ones (**3**) are most intensively studied class of 1,2,3-benzotriazine derivatives and effective method for their synthesis are known. The most frequently used method involved the reaction of nitrous acid on 2-amino arylamide[9]. This method has been applied in the present study for the preparation of **3** and **4** from anthranilamide and 2-amino-5-chlorobenzamide respectively.

Our intial synthetic approach for the preparation of 3H-1,4-benzodiazepin-(1H,4H)-2,5- dione (**7**) from **3** had envisaged that **3** would react in a straight forward manner with glycine in pyridine to give **7**[10] through

the intermediacy of **13**. But contrary to our expectations, this reaction behaved in an entirely different manner and formed a complex mixture of products from which only 2,5-diketopiperazine could be isolated in the pure form . It clearly indicated that **3** failed to react with glycine in pyridine to give the proposed intermediate **13**. When this plan did not succeed to give **7**, this scheme had to be eventually abandoned in favour of a more direct route (scheme-2), that involved the formation of **7**, through the iminoketene intermediate **5**. **5** was formed from **3** on heating in a high boiling solvent 1-methyl naphthalene at 250-260°C. It has been trapped with benzyne[7b], isocyanates[11] and many other nucleophiles[12] and dienophiles[7b,7c].

Authentic samples of **7-12** were prepared according to the literature procedure[10,13]. The physical and spectral data of synthetic products were found to be consistent to the authentic samples.

EXPERIMENTAL

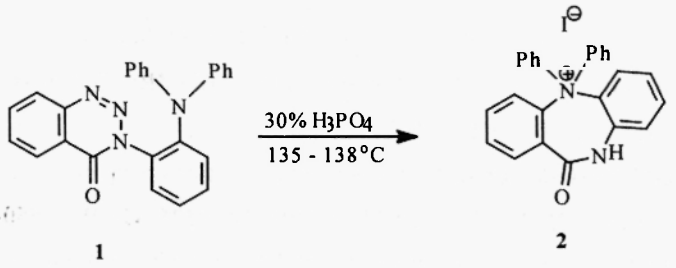
All the melting points are uncorrected. The purity of all the compounds was checked by TLC using the solvent systems (benzene: methanol, 9 : 1 v/v) and silica gel G as adsorbent. IR spectra were recorded on Pye Unicam Model SP3-300 infracord in nujol and on KBr pellets. ^{1}HNMR spectra were recorded on Varian EM 360 L using $CDCl_3$ and DMSO-d_6 as the solvent and TMS as internal reference. Commercial samples of glycine, alanine, phenylalanine and sarcosine were used.

General procedure for the preparation of 3H-1,4-benzodiazepin-(1H,4H)-2,5-diones (7-12) : A mixture of 1,2,3-benzotriazin-4-(3H)-ones (0.01 mole) and the amino acid (glycine/alanine/phenylalanine/sarcosine, 0.01 mole) was heated in 1-methyl naphthalene (10ml) at 250-260 °C for 10 hr. Progress of the reaction was checked through TLC. After completion of the reaction , mixture was cooled and petroleum ether (40-60°) (100ml) was added. The solid which separated out was filtered and dried. The crude product was chromatographed over silica gel 'G' in $CHCl_3$: MeOH (9.5 : 0.5 v/v) as an eluant and was recrystallized from ethanol.

3H-1,4-benzodiazepin-(1H,4H)-2,5-dione (7): Prepared by heating an equimolecular mixture of **3** and glycine in 1-methyl naphthalene. Yield 41%; m.p.325°C (lit[10] 327 °C). IR: 3500-3400(lactimOH), 3170(NH of anilide), 3150(NH of amide), 1690(CO of anilide), 1650(CO of amide)cm^{-1}; ^{1}HNMR: δ7.39(m,4H,ArH), 8.57(s,br,1H, N^4H), 7.8(s, br, N^1H), 3.64(s, 2H, -CH_2-).

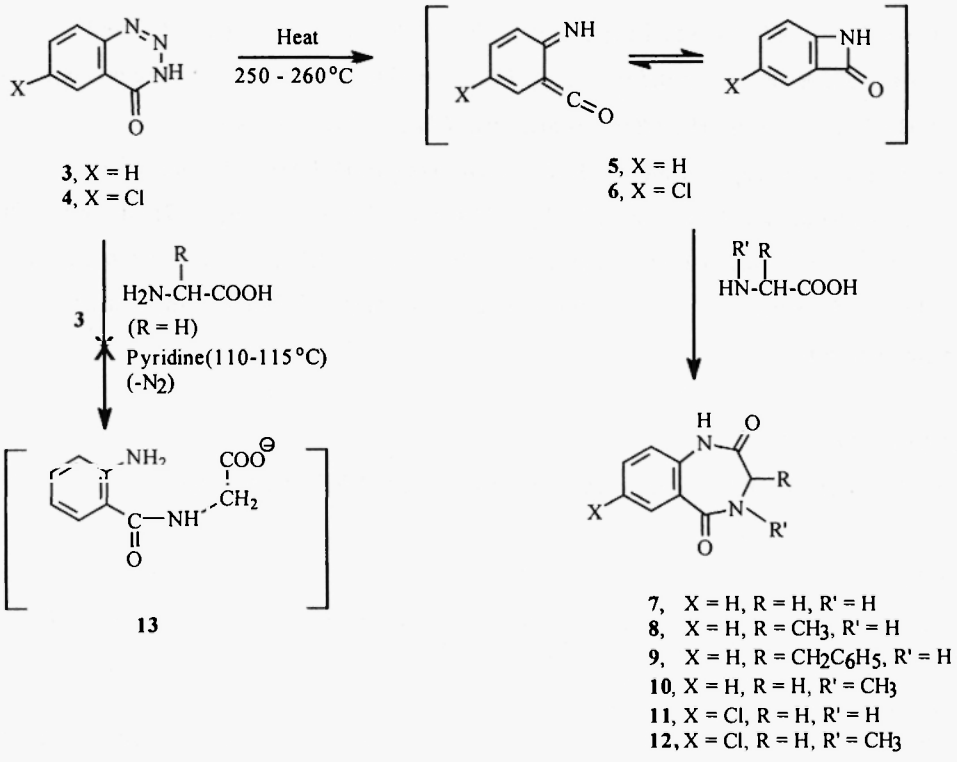
3H-3-Methyl-1,4-benzodiazepin-(1H,4H)-2,5-dione (8): Prepared by heating an equimolecular mixture of **3** and alanine in 1-methyl naphthalene. Yield 42%; m.p.315°C (lit[10] 316 °C). IR: 3540-3380(lactim OH), 3190(NH of anilide), 3045(NH of amide), 1685(CO of anilide), 1650(CO of amide)cm^{-1}; ^{1}HNMR: δ7.6(m,4H,ArH), 8.48 (s,br,1H, N^4H), 7.6(s, br, N^1H), 3.83(q,1H, C^3H),1.22(d, 3H, C^3-CH_3).

3H-3-Benzyl-1,4-benzodiazepin-(1H,4H)-2,5-dione (9): Prepared by heating an equimolecular mixture of **3** and phenyl alanine in 1-methyl naphthalene. Yield 40%; m.p. 248°C (lit[13] 250 °C). IR: 3530-3385(lactim OH), 3270(NH of anilide), 3070(NH of amide), 1675(CO of anilide), 1655(CO of amide)cm^{-1}; ^{1}HNMR: δ7.51(m,9H,ArH), 8.00 (s,br,1H, N^4H), 7.4(s, br, N^1H), 4.1(d, 2H, CH_2 of benzyl),3.80(t, 1H, C^3H).



1 2

Scheme - 1



7, X = H, R = H, R' = H
8, X = H, R = CH_3, R' = H
9, X = H, R = $CH_2C_6H_5$, R' = H
10, X = H, R = H, R' = CH_3
11, X = Cl, R = H, R' = H
12, X = Cl, R = H, R' = CH_3

Scheme - 2

3H-4-Methyl-1,4-benzodiazepin-(1H,4H)-2,5-dione (10): Prepared by heating an equimolecular mixture of **3** and sarcosine in 1-methyl naphthalene . Yield 54%; m.p.244°C (lit[10] 243-246 °C). IR: 3535-3390 (lactim OH), 3170(NH of anilide), 1680(CO of anilide), 1640(CO of amide)cm^{-1}; ^{1}HNMR: δ7.8(m,4H,ArH), 7.7(s, br, 1H, N^1H), 3.84(q, J=6Hz ,2H, $-CH_2$), 3.40(s, 3H, NCH_3).

7-Chloro-3H-1,4-benzodiazepin-(1H,4H)-2,5-dione (11): Prepared by heating an equimolecular mixture of **4** and glycine in 1-methyl naphthalene. Yield 52%; m.p.325°C (lit[10] 323- 325 °C). IR: 3550-3375(lactim OH), 3125(NH of anilide), 3100(NH of amide), 1695(CO of anilide), 1655(CO of amide)cm^{-1}; ^{1}HNMR: δ7.45(m,3H,ArH), 8.59(s, br, 1H, N^4H), 7.9(s, br,1H, N^1H), 3.72(s, 2H, $-CH_2$).

7-Chloro-3H-4-methyl-1,4-benzodiazepin-(1H,4H)-2,5-dione (12): Prepared by heating an equimolecular mixture of **4** and sarcosine in 1-methyl naphthalene. Yield 56%; m.p.259°C (lit[10] 259-262°C). IR: 3525-3390(lactim OH), 3220(NH of anilide), 1685(CO of anilide), 1645(CO of amide)cm^{-1}; ^{1}HNMR: δ7.54(m,3H,ArH), 7.5(s, br,1H, N^1H), 3.85(q, J=6Hz ,2H, $-CH_2$), 3.42(s, 3H, NCH_3).

Attempted method for the preparation of 3H-1,4-benzodiazepin-(1H,4H)-2,5-dione (7):

A mixture of 1,2,3-benzotriazin-4-(3H)-one (**3**) (3g, 0.02mole) and glycine (1.5g, 0.02mole) was refluxed in pyridine (10 ml) for 10 hr. It was then poured in water (100 ml) and acidified with dil HCl to give the product ,0.65g, m.p. 316-317 °C, which was washed with water and identified as 2,5-diketopiperazine by comparison with a commercial sample.

ACKNOWLEDGEMENT

The authors wish to thank CDRI, Lucknow, India, for providing ^{1}HNMR spectral data.

REFERENCES

1. (a) G. Mohiuddin, P.S. Reddy, K. Ahmed and C.V. Ratnam, Heterocycles, **24(12),** 3489,(1986). (b) G.A. Archer and L.H. Sternbach, Chem. Rev., **68**, 747, (1968).
2. A.Singh, R.Sirohi, S.Shastri and D.Kishore, Communicated to Ind. J. Chem. (2003).
3. M. Ogata and Matsumoto, Chem. Ind.(London), 1067,(1976).
4. H. Neunhoeffer, "Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor (Eds.),John Wiley, New York, **33**, 1-188,(1978).
5. M. S. Gibson, J. Chem. Soc., 3539,(1963).
6. (a) M. S. Gibson and M. Green, Tetrahedron, **21**, 2191,(1965). (b) G. Heller and A. Siller, J. Pract. Chem., **116**, 9, (1927), Chem. Abstr., **21**, 2697,(1927).
7. (a) J. G. Archer, A. J. Barrker and R. K. Smalley, J. Chem. Soc. Perkin I,1169, (1973). (b) H. E. Crabtree, R. K. Smalley and H. Suschitzky, J. Chem. Soc. C, 2730,(1968). (c) R. K. Smalley, H. Suschitzky and E. M. Tanner, Tetrahedron Lett., 3465, (1966).
8. A. N. Nesmeyanov, T. P. Tolstaya, A. V. Grib and J. A. Casanova, Izv. Akad. Nank. SSSR, Ser. Khim. , 1096,(1973), Chem. Abstr., 79, 66327z,(1973).
9. Ref. 4, page 17.
10. D. J. Kim, J. Heterocyclic Chem., **12**, 1323,(1975).
11. H. Herlinger, Angew Chem., **76**, 437, (1964), Chem. Abstr., **61**, 4357b, (1964).
12. A. W. Murray and K. Vaughan, J. Chem. Soc. C, 2070,(1970).
13. G. Mohiuddin, P. S. Reddy, K. Ahmed and C. V. Ratnam, Ind. J. chem.., **24B**, 905,(1985).

Received on March 21, 2003