Tetrahedron Letters No. 51/52, pp 4539 - 4542, 1974. Pergamon Press. Printed in Great Britain.

PRODUCTS OF ABNORMAL SUBSTITUTION OF s-TRIAZOLO(1,5-a)PYRAZINES

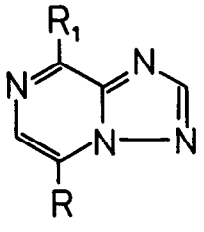
B.Verček, B.Stanovnik, and M.Tišler

Department of Chemistry, University of Ljubljana
61000 Ljubljana, Yugoslavia

(Received in UK 4 November 1974; accepted for publication 13 November 1974)

We have recently reported that s-triazolo(1,5-a)pyrazine is successfully prepared from aminopyrazine in a relatively simple reaction sequence [1]. The lack of knowledge of reactivity of this little explored heterocyclic system [2] prompted us to investigate this bicyclic system in more detail.

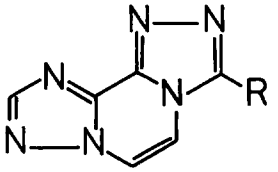
s-Triazolo(1,5-a)pyrazine is easily brominated with bromine in methylene chloride to give the 5-bromo derivative (I, R = Br, R_1 = H, mp 143-145°). The bromine atom can be readily displaced with different nucleophiles and in this manner the 5-mercapto compound (I, R = SH, R_1 = H, mp over 250°, dec.) was obtained with an ethanolic KHS solution at room temperature. At moderate elevated temperature other substituents could be introduced at position 5 and the corresponding methylthio (I, R = MeS, R_1 = H, mp 147-148°), phenylthio (I, R = C_6H_5S, R_1 = H, mp 95°), ethoxy (I, R = OEt, R_1 = H, mp 90-91°) or hydrazino derivatives were prepared. The hydrazino compound (I, R = $NHNH_2$, R_1 = H, mp 217° dec., τ (DMSO-d_6) 1.57 (s, H_2), 1.48 (s, H_8), 2.24 (s, H_6), 5.34 (broad s, NH)) could be transformed into the corresponding azido derivative (I, R = N_3, R_1 = H, mp 95-96°) with nitrous acid and further reduction of the azide with hydrogen sulfide afforded the 5-amino compound (I, R = NH_2, R_1 = H, mp over 250°), which could not be obtained in a direct displacement reaction from the 5-bromo compound with ammonia.



I

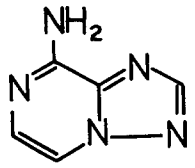
However, if an ethanolic solution of the 5-bromo compound was treated with hydrazine hydrate and the reaction mixture left to stand at room temperature overnight another hydrazino derivative was formed and on hand of nmr spectra correlation it could be established that 8-hydrazino-s-triazolo(1,5-a)pyrazine (I, R = H, R_1 = $NHNH_2$, mp 248-250°, τ (DMSO-d_6) 1.72 (s, H_2), 2.10 (d, H_5), 2.56 (d, H_6), $J_{5,6}$ = 5 Hz) was formed. Similarly, treatment of the 5-bromo compound with hydroxylamine at room temperature afforded the 8-hydroxyamino compound (I, R = H, R_1 = NHOH, mp 242-244°) and with liquid ammonia the 8-amino derivative (I, R = H, R_1 = NH_2, mp 218-219°) was obtained. To the best of our knowledge, the above transformations are the first example of abnormal substitution in the azoloazine series with bridgehead nitrogen atoms. Abnormal nucleophilic substitutions have been observed with some pyrazine derivatives [3,4], but only if a dichloromethyl group was attached to the pyrazine ring. Substitutions which afford isomeric products are known also with other heterocyclic systems [5-8], the reactions being associated with the presence of a halomethyl group.

The 8-hydrazino compound could be transformed with a hot aqueous solution of $CuSO_4$ into the parent compound (I, R = R_1 = H) and it was used as staring material for the preparation of



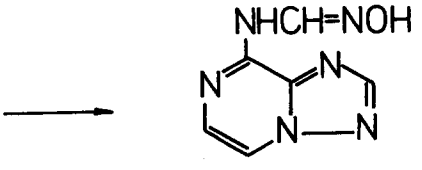
II

some tricyclic systems. With triethyl orthoformate the 8-hydrazino compound afforded II (R = H, mp over 290°) and alternatively, the 3-phenyl derivative (II, R = C_6H_5, mp 270-271°) was obtained by

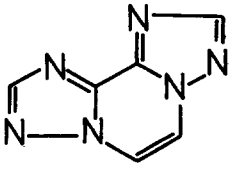


III

IV



V

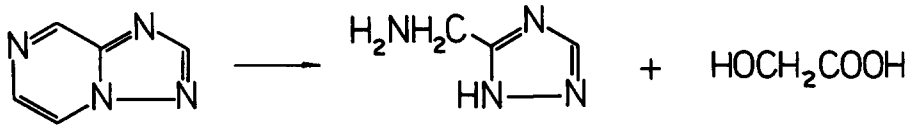


VI

oxdiative cyclization of the corresponding benzylidene derivative (I, R = H, R_1 = NHN=CHC$_6$H$_5$, mp 209-210°) with lead tetraacetate. In a similar manner, the isomeric tricyclic system VI (mp over 260°) could be prepared from III via the dimethylaminomethyleneamino derivative (IV) and compound V [9] which was cyclized to VI with polyphosphoric acid.

The nmr spectrum of this highly symmetric system (VI) revealed only two singlets at τ 1.31 and 1.34, corresponding to $H_{2'}H_9$ and $H_{5'}H_6$, respectively. The nonequivalence of H_3 and H_9 (τ 0.79 (s) and 1.56 (s)) in the isomeric tricyclic system II (R = H) and an observed $J_{5,6} \cong 6$ Hz in II (R = C_6H_5) fully support the proposed structures. Moreover, all these observations indicate that during the abnormal substitution of 5-bromo-s-triazolo(1,5-a)pyrazine which afforded the 8-substituted derivatives no isomerization of the bicyclic system (Dimroth rearrangement) took place.

However, the s-triazolo(1,5-a)pyrazine ring is destroyed under the influence of hot 50 % aqueous sodium hydroxide and 3-aminomethyl-1,2,4-triazole [10] (VII) and glycolic acid (VIII) were identified as decomposition products.



VII VIII

This indicates that the attack of the base on the parent bicyclic system takes place at position 5.

The ready nucleophilic attack at position 5 of s-triazolo(1,5-a)pyrazine is also in accord with the observed hydrogen deuterium exchange under base catalyzed conditions. The following order of reactivity could be established: $H_5 \gg H_2 \geq H_8 > H_6$.

Further investigation of the mechanism of the abnormal substitution is proceeding.

All the new compounds gave proper analysis and appropriate IR, NMR and mass spectra.

Acknowledgement The authors wish to thank the Boris Kidrič Found for financial support of this work.

NOTES AND REFERENCES

1. S.Polanc, B.Verček, B.Šek, B.Stanovnik, and M.Tišler, J.Org.Chem., 39, 2143 (1974).
2. T.Okamoto, Y.Torigoe, M.Sato, and Y.Isagai, Chem.Pharm.Bull. (Tokyo), 16, 1154 (1968).

3. E.J.J.Grabowski, E.W.Tristram, R.Tull, and P.I.Pollak, Tetrahedron Letters, 1968, 5931.
4. US Pat. 3.501.472; Chem.Abstr., 72, 111508 (1970).
5. G.Durant, M.E.Foottit, C.R.Ganellin, J.M.Loynes, E.S.Pepper, and A.M.Roe, Chem.Commun., 1968, 108.
6. F.G.Bordwell, F.Ross, and J.Weinstock, J.Amer.Chem.Soc., 82, 2878 (1960).
7. F.G.Bordwell, P.E.Sokol, and J.D.Spainhour, J.Amer.Chem.Soc., 82, 2881 (1960).
8. A.R.Katritzky and J.M.Lagowski: The Principles of Heterocyclic Chemistry, Methuen & Co., London, 1967, p. 122.
9. For structure assignment of this potentially tautomeric type of compounds see: S.Polanc, B.Verček, B.Stanovnik, and M.Tišler, J.Heterocycl.Chem., 11, 103 (1974).
10. The compound was found to be identical with and authentic specimen. See: C.Ainsworth and R.G. Jones, J.Amer.Chem.Soc., 76, 5651 (1954); P.Westermann, H.Paul, and G.Hilgetag, Chem.Ber., 97, 528 (1964).