CHEMISTRY LETTERS, pp. 967-970, 1974. Published by the Chemical Society of Japan

SYNTHESIS OF PYRIMIDINE-FUSED 1,4-BENZODIAZEPINES

Shigeru KOBAYASHI

Medicinal Research Laboratories, Central Research Division,
Takeda Chemical Industries, Ltd., Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532

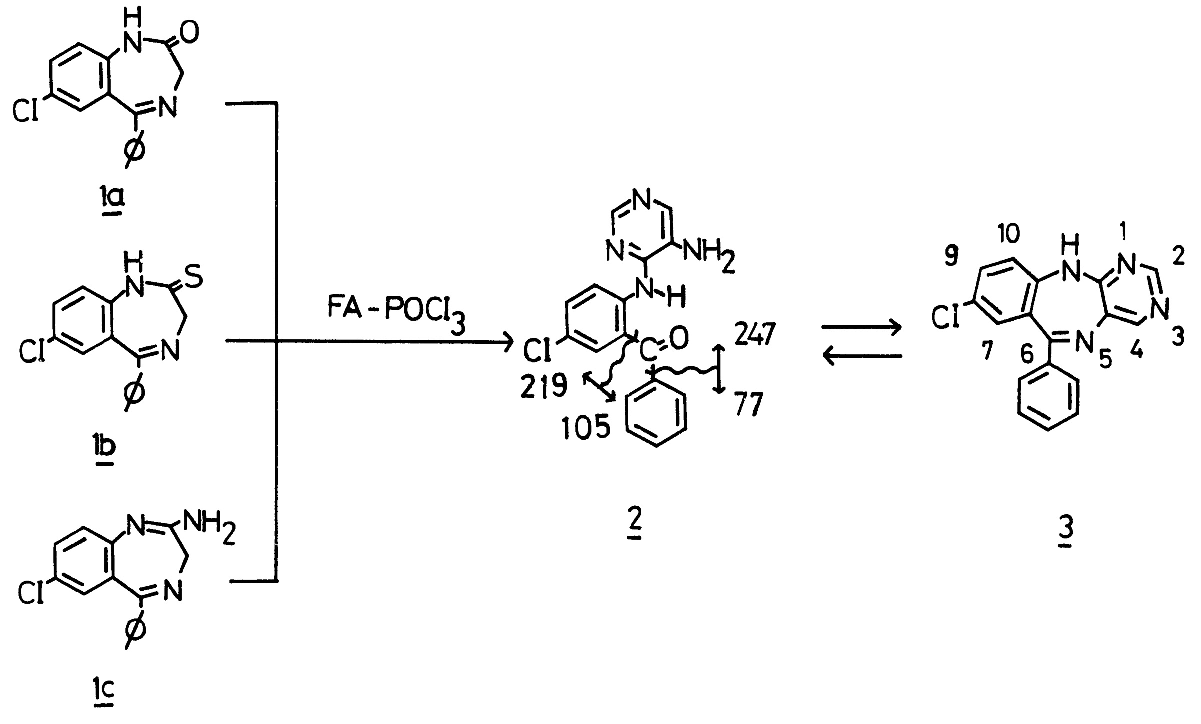
Synthesis of new pyrimidine-fused 1,4-benzodiazepines (3 and 4) was achieved by heating the corresponding 1,4-benzodiazepines (1) with formamide in the presence of phosphoryl chloride.

Previously, we reported that carboxamides containing a methylene group alpha to the carbamoyl group react with formamide (FA) in the presence of phosphoryl chloride ($POCl_3$) to give pyrimidine compounds.1) Further extention of this reaction to the synthesis of some pharmacologically important 1,4-benzodiazepines2) was attempted and compounds with a tricyclic ring system were synthesized.

This paper describes a synthesis of 11H-pyrimido[4,5-b][1,4]benzodiazepines (3 and 4) starting from 1,4-benzodiazepines (1).

A mixture of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (1a),3) FA, and $POCl_3$ (1:2:3 mole ratio) was heated at 110°C in a sealed vessel for 11 hr. The reaction mixture was dissolved in ethyl acetate and the solution was washed carefully with ice-cooled 4N NaOH until the aqueous layer remained basic. After the usual work-up, the residue was chromatographed on a column of silica gel using $CHCl_3$-acetone (4:1, v/v) as solvent. The product thus obtained was pale yellow crystals showing the correct analysis for $C_{17}H_{13}N_4OCl$. It was identified as 5-amino-4-(2-benzoyl-4-chloroanilino)pyrimidine (2; yield, 23%) on the basis of its mass spectrum, which displays intense peaks at m/e 247 (11%), 219 (43%), 105 (63%), and 77 (100%), all of which can be reasonably accounted for by the fragments shown in Scheme 1. In addition, 2 produces strong ion peaks at m/e 324, 306, and 271. These are best rationalized by loss of a water molecule from the molecular ion (M^+ 324, 23%) to generate 8-chloro-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine (3; M^+ 306, 9%), followed by loss of Cl (m/e 271, 9%). This strongly suggested that the cyclization of 2 should take place to give 3 under appropriate conditions.

In fact, cyclization of 2 to 3 was smoothly effected by treatment with p-toluenesulfonic acid in EtOAc-EtOH (2:1, v/v) at a refluxing temperature for 30 min (yield, 96%). Heating of 2 in dimethyl sulfoxide at 70°C for 3 hr also produced 3.



Scheme 1

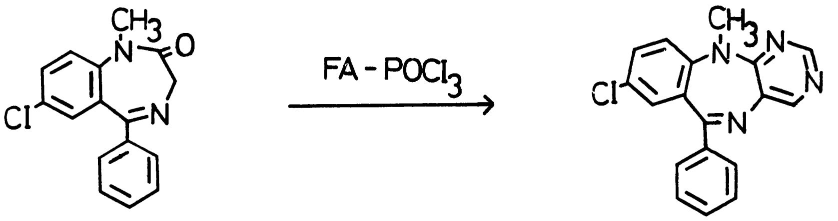
The mass spectrum of 3 was much simpler than that of 2, and showed the molecular ion peak as base peak and loss of Cl as indicated in the mass spectrum of 2. In view of the fused-ring structure of 3 the high abundance of the parent molecular ion was reasonable.

The nmr spectrum (d_6-DMSO) of 3 shows a doublet at δ 6.80 (1H, J=2.5 Hz, C_7-H), a doublet at 7.21 (1H, J=8.5 Hz, C_{10}-H), a double doublet at 7.45 (1H, J=2.5 and 8.5 Hz, C_9-H), a singlet at 7.55 (5H, phenyl moiety), a singlet at 8.36 (1H, C_4-H), a singlet at 8.46 (1H, C_2-H), and a singlet at 8.70 (1H, NH). All these nmr data were accounted for by the proposed structure 3.

Similarly, 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thione (1b),[4] and 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine (1c)[5] were treated with FA and POCl$_3$ under the same conditions, and produced 2 in both cases in yields of 10% and 25%, respectively, as shown in Scheme 1.

Hydrolysis of 3 to 2 was easily carried out when an ethyl acetate solution of 3 was treated with 1N HCl for a few minutes (yield, 94%).

When 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1d)[3] was used as starting material, 8-chloro-11-methyl-6-phenyl-11H-pyrimido[4,5-b][1,4]-benzodiazepine (4) was obtained in a single step (Scheme 2). Its mass spectrum produces a strong molecular ion at m/e 320 (100%) and the phenyl radical ion at m/e 77 (56%). Other important avenues of fragmentation included loss of Cl (m/e 285, 24%), and loss of the phenyl moiety (m/e 243, 36%) followed by loss of HCN (m/e 216, 44%). The structure (4) was further confirmed by its nmr spectrum (CDCl$_3$): δ 3.31 (3H, s, N-CH$_3$), 6.93-7.87 (8H, m, aromatic), 8.53 (1H, bs, C$_4$-H), and 8.66 (1H, s, C$_2$-H). Thus, the hydrolytic cleavage of the C=N bond in diazepinone ring 1d was not observed in this case. The reaction proceeded somewhat sluggishly and the starting material was not consumed completely under the conditions employed and the yield of this reaction was 21% on the basis of the material consumed.



1d 4

Scheme 2

The reaction described in this communication seems to be applicable to a variety of 1,4-benzodiazepines to obtain 11H-pyrimido[4,5-b][1,4]benzodiazepines. Studies on the synthesis of a series of 1,4-benzodiazepines along this line and their pharmacological evaluation are now in progress in these laboratories.

Acknowledgement

The author is grateful to Drs. K. Morita, Y. Kuwada, and K. Meguro of this division for their valuable discussions in this study.

References

1) K. Morita, S. Kobayashi, H. Shimadzu, and M. Ochiai, Tetrahedron Letters, **1970**, 861; S. Kobayashi, Bull. Chem. Soc. Japan, **46**, 2835 (1973).

2) Recent review: L. H. Sternbach, Angew. Chem. Int. Ed. Eng., **10**, 34 (1971).

3) L. H. Sternbach and E. Reeder, J. Org. Chem., **26**, 4936 (1961); L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

4) G. A. Archer and L. H. Sternbach, *ibid.*, **29**, 231 (1964).

5) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, J. Org. Chem., **26**, 4488 (1961); K. Meguro, H. Tawada, and Y. Kuwada, Yakugaku Zasshi, **93**, 1253 (1973).

(Received July 3, 1974)