Pak J Sci Ind Res 2000 43 (3) 168-170

TETRACYCLIC HETEROAROMATIC SYSTEMS. *PART-II.* BENZIMIDAZO [1, 2-a] BENZIMIDAZOLES

Misbahul Ain Khan*[ab] and Vera Lucia Teixeira Ribeiro[c]

[a]*PCSIR Chairman's Secretariat Plot 16, H-9, Islamabad, Pakistan*

[b]*Laboratorio de Quimica Medicinal, Faculdade de Farmacia, Universidade Federal Fluminense, Rua MarioViana 23, Santa Rosa, Niteroi, RJ, Brasil, CEP 24230-000, (M.A.K.)*

[c]*Secao de Quimica Instituto Mititar de Engenharia Praia, Vermelha, Rio de Janeiro, RJ, Brasil (V.L.T.R.)*

(Received 2 February 2000; accepted 14 April 2000)

Benzimidazo [**1**, 2-a] benzimadozoles (**1**, R=H) were synthesized by the trialkylphosphite-induced deoxygenation and thermolysis of 1-*o*-nitrophenyl and 1-*o*-azidophenyl benzimidazole. Spectral and other properties of the product and the intermediate compounds are reported.

Key words: Benzimidazoles, Multicyclic heteroaromatic, Deoxygenation, Thermolysis.

Introduction

The title ring system benzimidazo [1, 2-a] benzimidazole (1, R=H) is of much interest since it may be considered to arise from the fusion of two bezimidazole rings. It contains an amidine moiety (--C(=N)-N)of considerable pharmacological importance. Recently much interest has been shown in benzimidazole and systems containing an intrinsic amidine functionality (Lombardy *et al* 1996; Trent *et al* 1996; Wexler *et al* 1996; Yamada *et al* 1996). Not much work has been reported about **1**. Some years ago the synthesis of **1** was reported by the thermolysis (Hubert and Reimlinger 1970) or photolysis (Hubert and Reimlinger 1970; De Mondoza and Eleguero 1974) of some derivaties of 1-(benzi-madazol-2-yl) benzotriazole. Other derivatives of the titlering system have been prepared from1-*o*-nitro-phenylbenzimidazole-2-one by reduction with stannous chloride (Achour and Zniber 1987), by the intramolecular cyclization of N_1, N_2, N_3-pentafluoro-phenyl guanidine with potassium carbonate in N, N-dimethyl formamide and by the Wittig type reaction of *bis* [phosphoranylidene) amino]-diphenylamine with isocyanate (Molina *et al* 1994).

Our interest in the synthesis of multicyclic hetero-aromatic systems (Khan and Ribeiro 1983; Khan and Rolim 1983; Khan and Caldas 1986-87) led to alternative synthesis of **1** by the trialkylphosphite-induced deoxygenation and thermolysis of 1-*o*-nitrophenyl (**4**) and I-*o*-azidophenylbenzimidazole (**5**) respectively.

Experimental

The PMR spectra were recorded on a Hitachi Perkin-Elmer model R-20B spectrometer operating at 60 MHz with TMS as internal reference. The IR absorption spectra were measured as potassium bromide discs on a Perkin-Elmer 180 spectrophotometer. Melting points were determined with a Fisher-John melting point apparatus and are uncorrected, elemental analyses were carried out on a Perkin-Elmer model 240 apparatus. Mass spectra were recorded on a Varian model CH5.

Thermolysis. A mixture of 0.3g of **5** (obtained in 70% yield from 1-*o*-aminophenylbenzimidazole by successive diazotization and reaction with sodium azide, IR: 2120 cm^{-1} (N_3)), and 6 ml of *o*-dichlorobenzene was heated under reflux for 3 h. On cooling the crystallized material was washed with benzene and dried to give **1**, yield 0.07g (25%), m.p. 336-8° (lit m.p. 310° and 330°) picrate m.p. 310° (EtOH).

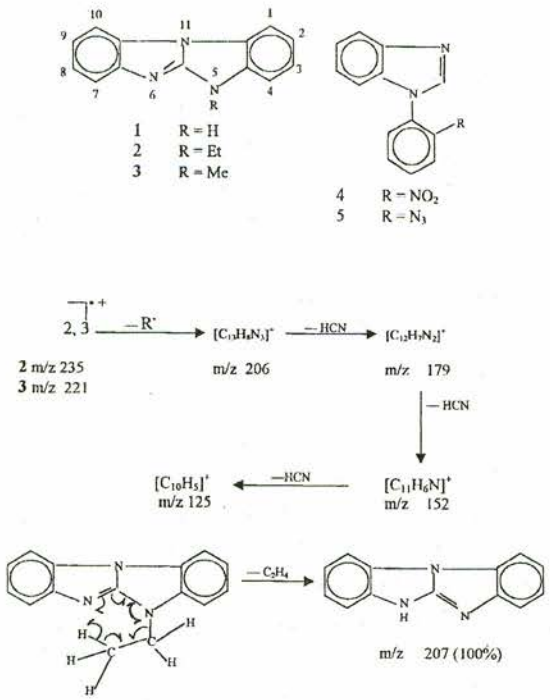
Analysis: For $C_{19}H_{12}N_6O_7$ - Calcd: 52.3%C, 2.8%H, 19.3%N
Found: 52.2%C, 2.8%H, 19.0%N

IR.cm^{-1}: 2700(br.), 1650, 1570, 1500, 1440, 1220, 730 and 715. (Hubert and Reimlinger 1970): 2701(br.),1647,1574,1501,1219 and 736.

UV(EtOH) nm: 304, 284, 236 (Hubert and Reimlinger 1970): 304, 285, 238).

Deoxygenations. (a) A mixture of 2g of **4,** 10 ml of triethylphosphite and 20 ml of xylene was heated under reflux with agitation and under nitrogen for 4 h. The solvent and excess of the reagent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel with benzene as the eluting solvent. Crystallization from petroleum ether (b.p.40-60°) to afford **2**, m.p. 104° (it seems to be hygroscopic as evidenced by the elemental analysis and IR).

* Author for correspondence, [a] Present address



Scheme 1

Analysis:For $C_{15}H_{13}N_3.H_2O$-Calcd: 71.1%C, 5.9% H, 16.6%N;
Found:71.3%C, 5.5%H, 16.5%N.

PMR ($CDCl_3$), d: 1.58 (t, 3H, J=7.5Hz, CH_3), 4.65 (q, 2H, J=7.5Hz, CH_2), 7.20-7.90 (m, 8H, arom.); UV (EtOH)nm: 306, 286, 238. MS m/z (%): 236 (10), 235(54), 220(11), 208(15), 207 (100), 206(17), 185(6), 180(2), 179(7), 152(5), 129(5), 125(2), 118(5), 104(5), 103(11), 102(11), 92(8), 90(6), 78(6), 77(7), 76(7), 75(7), 65(6), 63(6), 51(9), 50(5), 44(7), 42(5), 40(5), 38(16), 35(42).

Repeating the reaction over a reflux periods of 2 h, 8.5 h and 10 h, **2** was isolated in somewhat similar yields.

(b) A reaction of **4** with trimethyl phosphite over a reaction period of **5** h gave after chromatography on neutral alumin (benzene/pet. ether, 1:1), 0.3% of **3**, m.p. 149-51° (Hubert and Reimlinger 1970) 154°) IR. cm^{-1}: 1650, 1570, 1510 and 730 (Hubert and Reimlinger 1970): 1647, 1569, 1505, 739, 728 and 709). PMR ($CDCl_3$) d, 3.84 (s,3H, CH_3), 7.04-7.84 (m. 8H, arom); UV (EtOH) nm: 305, 286 and 237 (Hubert and Reimlinger 1970); 304, 288 and 238). MS, m/z (%): 222 (16), 221 (100), 220 (38), 207 (7), 206 (32), 179 (8), 152(5), 129(5) 125(2) 111(18), 109 (5), 103 (5), 102(11), 92(8), 90(6), 78(7), 77(7), 76(6), 75(6), 65(5), 63(5), 51(9), 50(9) 44(5).

Results and Discussion

1-*o*-nitrophenylbenzimidazole (**4**) was obtained by the Ullmann condensation of benzimidazole with *o*-chloro-or *o*-bromonitrobenzene (Khan and Polya 1970). When **4** was heated with triethyl phosphite under an atmosphere of nitrogen, the product isolated was not the expected **1**, but its *N*-ethyl derivative **2**.Which was identified through its infra-red spectra (IR: absence of an NH stretching), proton magnetic spectra (PMR): the presence of *N*-ethyl protons (1.58 d a triplet and 4.65 d a quartet with a coupling constant of 7.5 Hz) and the mass spectra (MS) (molecular peak at m/z 235). In four different runs of this reaction, varying the reaction time from two to ten hours neither improved the yield (3%) nor afforded the desired **1**. Replacing triethyl phosphite with trimethyl phosphite still gave the N-alkylated product **3** (identical in all respects m.p. IR, and UV spectra with that reported by Hubert and Reimlinger (1970), albeit in even lower yield (0.13%). There seems to be much decomposition of the material, a characteristic of nitro compounds when heated with alkyl phosphite (Kametani *et al* 1975) or without the deoxygnating reagents (Janzen 1965). Heating **4** alone in p-dichlorobenzene revealed four reaction products in its thin layer chromatogram pointing at the possible destruction of **4** under the reaction condition, however, no attempts at this stage were made to isolate and identify these products.

Exclusive *N*-alkylation during the deoxygenation reaction has been reported in the literature (Kurihara *et al* 1972) and triethyl phosphate- a by-product in these reactions is known to be a good alkylating agent for heterocyclic compound (Yamauchi and Kinoshita 1973) may be responsible for the *N*-alkylated product **2** and **3**.

In another attempt to synthesize **1** from **4** via reduction and conversion to the corresponding azide (**5**) followed by its thermolysis gave **1** in 25% yield. It was found to be identical (mp, IR & UV spectrum) to the **1** as already reported by Hubert and Reimlinger (1970), De Mendoza and Elguero (1974).

The mass spectra of **2** and **3** were very simple in their fragmentation (Scheme 1). Both these compounds underwent fragmentation by first loss of the N-alkyl group followed by a successive loss of 3 fragments of HCN as expected in the mass spectra of benzimidazoles (Lawesson *et al* 1968; Lalezari and Nabahi 1980). The main feature of the fragmentation of **2** was the loss of C_2H_4 by a "Mclaferty type" rearrangement to produce the parent peak at 207.

Acknowledgements

The support from the Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq) and Financia-dora de Estudos e Projetos (FINEP) is gratefully acknowledged. Vera L.T. Ribeiro thanks Coordenacao de Aperfeicoamento de Nivel Superior (CAPES) for fellowship. We would also like to thank Centro de Pesquisa de Petrobras (CENPES) for the mass spectra.

References

Achour R, Zniber R 1987 *Bull Soc Chim Belg* **96** 787.

Carboni R A, Kauer J C, Hatchard 1967 Aromatic azapentalenes II reactions of monobenzo and dibenzo 1, 3a 46a, tetraazo pentalenes. *J Amer Chem Soc* **89** 2626.

De Mendoza J, Elguero 1974 *Bull Soc Chim Fr* 2987.

Harapanhalli, Mc Laughlin L W, Howell R W, Rao D V, Adelstein S J, Kassis A I 1996 *J Med Chem* **39** 4804.

Hubert A J, Reimlinger H 1970 *Chem Ber* **103** 2828.

Janzen E G 1965 Spontaneous free radical formation in the pyrolysis of nitro aromatic compound. *J Amer Chem Soc* **87** 3 531.

Kametani T, Ebetino F F, Fukumoto K 1975 *Tetrahedron* **31** 1241.

Khan M A, Polya J B 1970 Synthesis of heterocyclic compounds. Part II. N Arylazoles by Ullmann condensation. *J Chem Soc* 85.

Khan M A, Ribeiro V L T 1983 IH-pyrazolo [3-4d] thieno [2, 3-6] pyridine and its derivatives. *Monatsch Chem* **114** 425.

Khan M A, Rolim A M C 1983 Monatsh Chem **114** 1079.

Khan M A, Caldas E C 1986 *Bull Korean Chem Soc* **7** 412.

Khan M A, Caldas E C 1987 *Chem Scr* **27** 269.

Kurihara T, Okada E, Akagi M 1972 *Yakugaku Zasshi* **92** 1557.

Lalezari I, Nabahi S 1980 Reaction of M-cyanofurmimidol with some heterocyclic compound, a new synthesis of 5 azaadenon and related compound (1). *J Heterocycl Chem* **17** 1121.

Lawesson SO, Schroll G, Bowie J H, Cooks R G 1968 *Tetrahedron* **24** 1875.

Lombardy R L, Tanious F A, Ramachandrank, Tidwell R R, Wilson W D 1996 *J Med Chem* **39** 1452.

Molina P, Lidon M J, Tarraga A 1994 *Tetrahedron* **50** 10029.

Trent J O, Clark G R, Kumar A, Wilson W D, Boykin W D, Boykin D W, Hall J E, Tidwell R R, Blagburn B L, Neidle S 1996 *J Med Chem* **39** 4554.

Wexler R R, Greenlee W J, Irvin J D, Goldberg M R, Prendergast K, Smith R D 1996 *J Med Chem* **39** 625.

Yamada M, Yura T, Morimoto M, Harada T, Yamada K, Honma Y, Kinoshita M, Sugiura M 1996 *J Med Chem* **39** 559.

Yamauchi K, Kinoshita M 1973 *J Chem Soc Perkin* I 2506.