5-BROMOMETHYL-2-IMINOTETRAHYDROFURAN HYDROBROMIDE: A USEFUL CYCLIC IMIDATE IN THE SYNTHESIS OF BENZAZOLE-FUSED HETEROCYCLES

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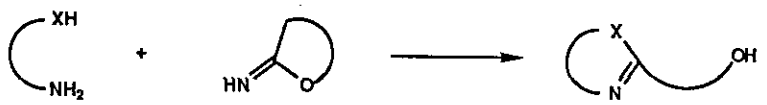
Abstract - The reaction of the title cyclic imidate with *o*-phenylene dinucleophiles affords the 2-substituted benzazoles (**3a-c**). Thermal cyclization of **3** via *N*-azolium salt to saturated benzazole-azines is also described.

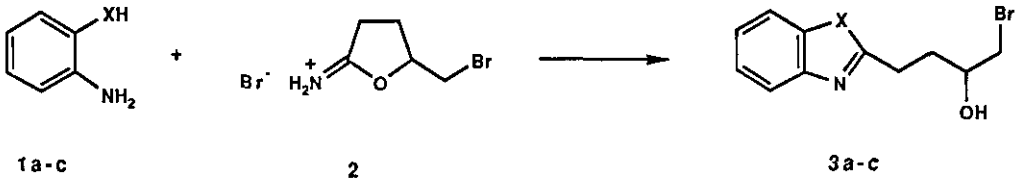
It is wellknown that the imidates cyclize with dinucleophiles through intramolecular condensation reactions to give various aza-heterocyclic rings.[1] In this field, however, the cyclic imidates are slightly employed although their use can lead to suitable functionalized azoles[2] (Scheme 1). This reaction can be viewed as a transformation of a cyclic imidate with an exocyclic imino-nitrogen into a compound in which the imidate function lies completely within the ring.



Scheme 1

In the present work we describe the reaction of *o*-phenylene dinucleophiles (**1a-c**) with 5-bromomethyl-2-iminotetrahydrofuran hydrobromide (**2**) (Scheme 2).

The cyclic imidate (**2**)[3], generated *in situ* from 4-pentenoic carboxamide and bromine in CH_2Cl_2,[4] reacts with the appropriate *o*-phenylene dinucleophiles (**1a-c**) (1.1 equivalents) to give, after 4 h at room temperature, the corresponding 4-(1,3-benzazol-2-yl)-1-bromo-2-butanols (**3**)[5] in moderate yields (**3a**, 48%; **3b**, 50%; **3c**, 53% respectively).



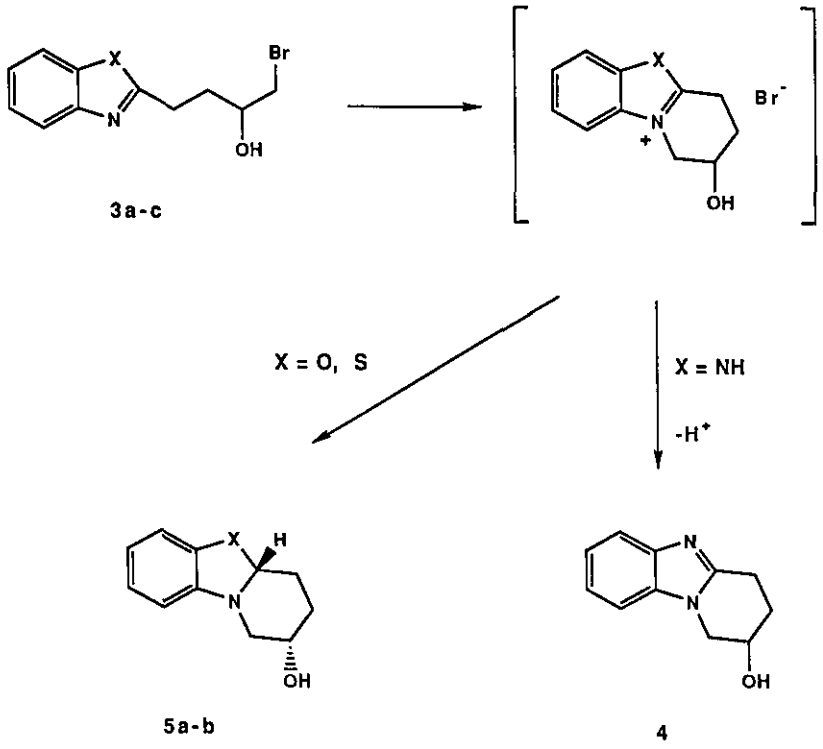
1a-c 2 3a-c

a, X = S; b, X = O; c, X = NH

Scheme 2

The choice of the cyclic imidate (2) has been made on the basis of its structure. In fact, the synthesis of 2 *via* a formal halo-lactonization affords a cyclic imidate with three distinct properties: i) the imidate function reacts under mild conditions with nucleophiles in condensation reactions; ii) the imidate-opening allows to the retention of the hydroxy function in γ-position; iii) the bromomethyl substituent gives an electrophilic character to the carbon in δ-position.

On the basis of these characteristics 2-substituted benzazoles (3) easily give the annulation products (4) and (5) (Scheme 3).



Scheme 3

The heating of the benzimidazole (**3c**) in CH_3CN for 30 min gives the fused benzimidazole-tetrahydropyridine (**4**)[6] (90% yield). This behaviour is due to the easy intramolecular *N*-quaternization followed by hydrogen loss from the NH group and subsequent aromatization. The analogous formation of the *N*-azolium salt with benzothiazole (**3a**) and benzoxazole (**3b**) produces, after removing of CH_3CN and reduction with sodium borohydride (2 equivalents at room temperature in CH_3OH), the corresponding fused benzothiazoline-tetrahydropyridine (**5a**)[7] (83% yield) and benzoxazoline-tetrahydropyridine (**5b**)[8] (72% yield) as single isomer. The complete assignment of the ^{1}H-nmr signals of **5a** allows a straightforward identification of its stereochemistry. The trans-diaxial orientation of the OH group and C6-hydrogen in the azine ring is substantiated by the large vicinal coupling constant $J_{6a,5a}$ = 11.1 Hz and by the absence of the trans-diaxial relationship between the protons at C2 and C3. The structure of **5b** was assigned by analogy with **5a**.

The use of this reagent with ethylene dinucleophiles and further elaboration of the alkyl chain will be the subject of a future paper.

REFERENCES AND NOTES

1 R. Roger and D. G Neilson, Chem. Rev., **1961**, 61,169. D. G. Neilson, "The Chemistry of Amidines and Imidates", ed. by S. Patai, Wiley Interscience, London, 1975, Chapt. 9.

2 A. I. Meyers, Y. Yamamoto, E. D. Mihelich, and R. A. Bell, J. Org. Chem., **1980**, 45, 2792.

3 Cyclic imidate **2**: mp 127-130° C (from acetone); ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.53 (m, 1 H), 1.92 (m, 1 H), 2.67 (m, 2 H), 3.32 (dd, J = 11.5 and 6.3 Hz, 1 H), 3.41 (dd, J = 11.5 and 3.5 Hz, 1 H), 4.77 (m, 1 H), 10.70 (s, 2 H).

4 P. N. Craig, J. Am. Chem. Soc., **1952**, 74, 129.

5 Compound **3a**: mp 94-96° C (from chloroform-cyclohexane) ; ir (nujol) 3250, 1500 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.16 (m, 2 H), 3.32 (t, J = 6.9 Hz, 2 H), 3.47 (dd, J = 10.2 and 6.3 Hz, 1 H), 3.54 (dd, J = 10.2 and 4.3 Hz, 1 H), 3.74 (br, 1 H), 3.97 (m, 1 H), 7.40 (m, 2 H), 7.84 (d, J = 7.7 Hz, 1 H), 7.96 (d, J = 7.7 Hz, 1 H); ^{13}C-nmr (75.5 MHz, $CDCl_3$) δ 30.07, 33.60, 38.90, 70.05, 121.70, 122.70, 125.20, 126.30, 153.30, 171.70.

Compund **3b**: mp 63-65°C (from chloroform-cyclohexane); ir (nujol) 3250, 1600, 1560 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$), δ 2.18 (m, 2 H), 3.16 (t, J = 7.1 Hz, 2 H), 3.35 (br, 1 H), 3.48 (dd, J = 10.4 and 6.5 Hz, 1 H), 3.57 (dd, J = 10.4 and 4.4 Hz, 1 H), 3.98 (m, 1 H), 7.32 (m, 2 H), 7.68 (m, 1 H).

Compound **3c**: mp 105-107° C (decomp.) (from chloroform-cyclohexane); ir (nujol) 3400, 3200, 1520 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.08 (m, 1 H), 2.20 (m, 1 H), 3.15 (m, 2 H), 3.43 (m, 2 H), 3.94 (m, 1 H), 5.30 (br, 2 H, exchange with D_2O), 7.23 (m, 2 H), 7.54 (m, 2 H).

6 Compound **4**: mp 179-181° C (decomp.) (from chloroform-cyclohexane); ir (nujol) 3150, 1605, 1500 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.13 (m, 2 H), 2.81 (br, 1 H), 3.20 (dt, J = 17.6 and 6.1 Hz, 1 H), 3.26 (ddd, J = 17.6, 8.6, and 6.1 Hz, 1 H), 4.03 (dd, J = 12.3 and 4.8 Hz, 1 H), 4.17 (dd, J = 12.3 and 4.2 Hz, 1 H), 4.50 (m, 1 H), 7.18-7.30 (m, 3 H), 7.66 (m, 1 H); ^{13}C-nmr (75.5 MHz, $CDCl_3$) δ 20.34, 27.65, 48.87, 63.04, 109.10, 118.36, 122.24, 122.70, 134.62, 142.37, 151.35.

7 Compound **5a**: mp 113-115° C (from chloroform-cyclohexane); ir (nujol) 3500, 1580, 1470 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.68 (m, 1 H), 2.07 (m, 2 H), 2.36 (m, 1 H), 2.52 (br, 1 H, exchange with D_2O), 2.83 (dd, J= 12.3 and 2.1 Hz, 1 H, C_2-H), 3.76 (ddd, J = 12.3, 2.4, and 2.4 Hz, 1 H, C_2-H), 4.10 (br s, 1 H, C_3-H), 4.85 (dd, J = 11.1 and 2.7 Hz, 1 H, C_6-H), 6.48 (d, J = 7.7 Hz, 1 H), 6.74 (t, J= 7.7 Hz, 1 H), 7.0 (t, J = 7.7 Hz, 1 H), 7.10 (d, J= 7.7 Hz, 1 H); ^{13}C-nmr (75.5 MHz, $CDCl_3$) δ 25.52, 30.35, 52.02, 63.69, 71.84, 107.61, 120.43, 122.73, 125.80, 126.73, 148.33.

8 Compound **5b**: mp 61-63° C (from chloroform-cyclohexane); ir ($CHCl_3$) 3400, 1590, 1500 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.65 (m, 2 H), 1.93 (m, 2 H), 2.80 (m, 2 H), 3.0 (dd, J = 11.1 and 3.0 Hz, 1 H), 3.98 (m, 1 H), 6.90 (m, 2 H), 7.08 (m, 2 H); ^{13}C-nmr (75.5 MHz, $CDCl_3$) δ 22.66, 31.54, 52.89, 59.58, 66.84, 114.47, 120.23, 121.36, 126.30, 139.65, 151.56.

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