

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

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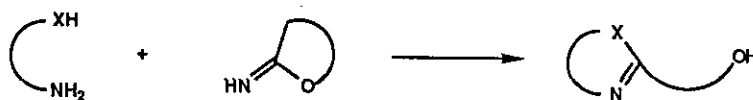
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**Abstract** - The reaction of the title cyclic imidate with *o*-phenylene dinucleophiles affords the 2-substituted benzazoles (**3a-c**). Thermal cyclization of **3** via *N*-azolum salt to saturated benzazole-azines is also described.

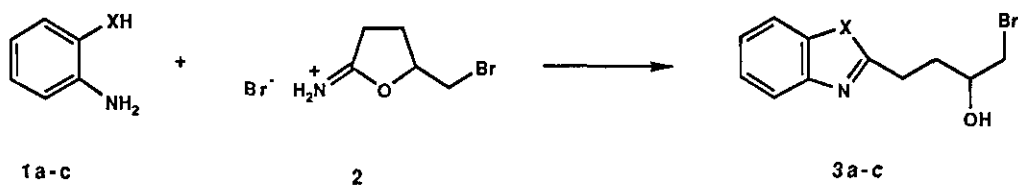
It is wellknown that the imidates cyclize with dinucleophiles through intramolecular condensation reactions to give various aza-heterocyclic rings.<sup>1</sup> In this field, however, the cyclic imidates are slightly employed although their use can lead to suitable functionalized azoles<sup>2</sup> (Scheme 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**)<sup>3</sup>, generated *in situ* from 4-pentenoic carboxamide and bromine in  $\text{CH}_2\text{Cl}_2$ ,<sup>4</sup> 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-butanol (**3**)<sup>5</sup> in moderate yields (**3a**, 48%; **3b**, 50%; **3c**, 53% respectively).

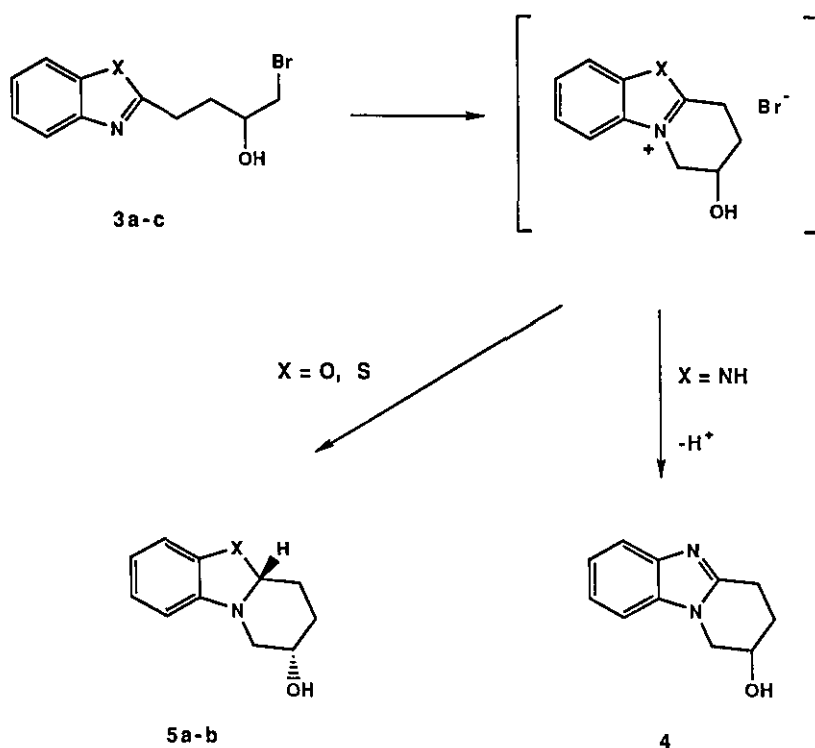


a, X = S; b, X = O; c, X = NH

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  $\gamma$ -position; iii) the bromomethyl substituent gives an electrophilic character to the carbon in  $\delta$ -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<sub>3</sub>CN for 30 min gives the fused benzimidazole-tetrahydropyridine (4)<sup>6</sup> (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<sub>3</sub>CN and reduction with sodium borohydride (2 equivalents at room temperature in CH<sub>3</sub>OH), the corresponding fused benzothiazoline-tetrahydropyridine (5a)<sup>7</sup> (83% yield) and benzoxazoline-tetrahydropyridine (5b)<sup>8</sup> (72% yield) as single isomer. The complete assignment of the <sup>1</sup>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  $\Delta_{6a,5a} = 11.1$  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); <sup>1</sup>H-nmr (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.53 (m, 1 H), 1.92 (m, 1 H), 2.67 (m, 2 H), 3.32 (dd,  $\Delta = 11.5$  and 6.3 Hz, 1 H), 3.41 (dd,  $\Delta = 11.5$  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<sup>-1</sup>; <sup>1</sup>H-nmr (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.16 (m, 2 H), 3.32 (t,  $\Delta = 6.9$  Hz, 2 H), 3.47 (dd,  $\Delta = 10.2$  and 6.3 Hz, 1 H), 3.54 (dd,  $\Delta = 10.2$  and 4.3 Hz, 1 H), 3.74 (br, 1 H), 3.97 (m, 1 H), 7.40 (m, 2 H), 7.84 (d,  $\Delta = 7.7$  Hz, 1 H), 7.96 (d,  $\Delta = 7.7$  Hz, 1 H); <sup>13</sup>C-nmr (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  30.07, 33.60, 38.90, 70.05, 121.70, 122.70, 125.20, 126.30, 153.30, 171.70.  
Compound 3b: mp 63-65°C (from chloroform-cyclohexane); ir (nujol) 3250, 1600, 1560 cm<sup>-1</sup>; <sup>1</sup>H-nmr (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.18 (m, 2 H), 3.16 (t,  $\Delta = 7.1$  Hz, 2 H), 3.35 (br, 1 H), 3.48 (dd,  $\Delta = 10.4$  and 6.5 Hz, 1 H), 3.57 (dd,  $\Delta = 10.4$  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<sup>-1</sup>; <sup>1</sup>H-nmr (300 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>O), 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<sup>-1</sup>; <sup>1</sup>H-nmr (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.13 (m, 2 H), 2.81 (br, 1 H), 3.20 (dt,  $\Delta = 17.6$  and 6.1 Hz, 1 H), 3.26 (ddd,  $\Delta = 17.6$ , 8.6, and 6.1 Hz, 1 H), 4.03 (dd,  $\Delta = 12.3$  and 4.8 Hz, 1 H), 4.17 (dd,  $\Delta = 12.3$  and 4.2 Hz, 1 H), 4.50 (m, 1 H), 7.18-7.30 (m, 3 H), 7.66 (m, 1 H); <sup>13</sup>C-nmr (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.68 (m, 1 H), 2.07 (m, 2 H), 2.36 (m, 1 H), 2.52 (br, 1 H, exchange with  $\text{D}_2\text{O}$ ), 2.83 (dd,  $J = 12.3$  and 2.1 Hz, 1 H,  $\text{C}_2\text{-H}$ ), 3.76 (ddd,  $J = 12.3$ , 2.4, and 2.4 Hz, 1 H,  $\text{C}_2\text{-H}$ ), 4.10 (br s, 1 H,  $\text{C}_3\text{-H}$ ), 4.85 (dd,  $J = 11.1$  and 2.7 Hz, 1 H,  $\text{C}_6\text{-H}$ ), 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);  $^{13}\text{C-nmr}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{CHCl}_3$ ) 3400, 1590, 1500  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C-nmr}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  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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