

Novel Captodative Methylene Compounds. Spontaneous Oxidation of 1-Alkyl-4(3)-(azolylmethyl)pyridinium Salts

Ermitas Alcalde,* Maria Gisbert and Lluïsa Pérez-García

Laboratorio de Química Orgánica, Facultad de Farmacia, Universidad de Barcelona, E-08028 Barcelona, Spain

For several examples of the title compounds **4–7** and **12** the nature of the non-classical acceptor and donor heteroaromatic moieties modulates the susceptibility of the methylene spacer towards oxidation.

The background offered by Kauffmann's areno-analogy principle,¹ both for classification and generation of heteroaromatic systems, permits heteroaromatic fragments† to be related to classical functional groups.^{2,3} Accordingly, the pyridinium salts **1** can be considered a novel class of captodative methylene compounds, containing a methylene interannular linkage bonded to both π -excessive (donor group) and highly π -deficient (acceptor group) moieties. Hence, the synthetic utility of the captodative effect⁴ should facilitate entry from these structures **1** to the analogues **2** (oxomethyl) and **3** (thiomethyl).

We report that several selected examples‡ of 2-substituted benzimidazoles **4–6** and the 1,2,4-triazole **7** undergo spontaneous oxidation, leading to their oxomethyl counterparts **8–11**. In contrast, the pyridinium salt **12** was found to be very stable in the air.

The pyridinium tetrafluoroborate **4** was known to be unstable in solution,⁶ and we found that air was also sufficient as oxidant in the solid state. Thus, compound **4** was quantitatively converted into its oxomethyl analogue **8**, whereas its positively charged benzimidazolium counterpart **13**‡ was found to be very stable (Scheme 1).

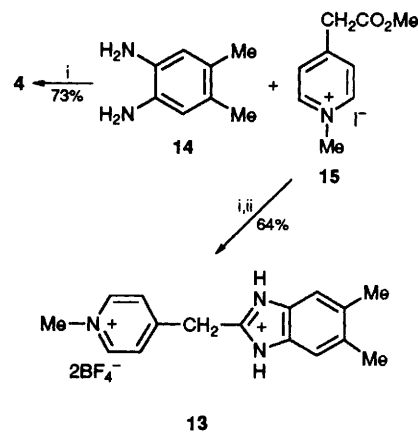
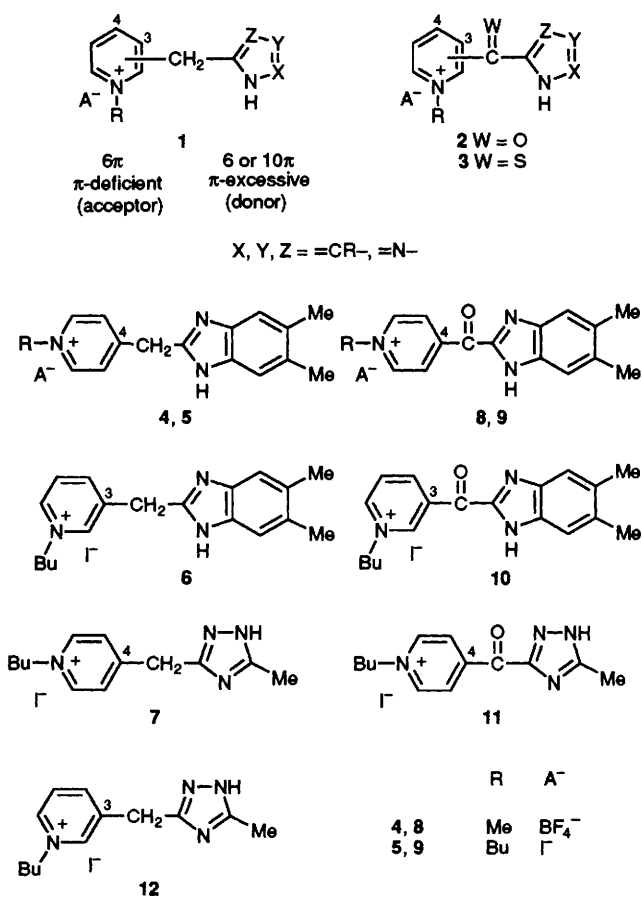
The pyridinium salt **5** was synthesized by an approach conveniently applicable to other homologues,⁷ by quaternization of the previously reported⁶ key intermediate **16** using iodobutane§ as an alkylating agent under neutral conditions

(Menschutkin reaction conditions). Compound **5** underwent spontaneous oxidation affording its corresponding oxomethylene derivative **9** (Scheme 2).

We examined the course of the quaternization reaction of the benzimidazole **16** with rigorous exclusion of air, and also the degree of oxidation of the title salt **5** in the presence of classical free-radical inhibitors (*e.g.* galvinoxyl) or sulfur. Experiments were carried out as shown in Scheme 2, (Methods B–D), and the distribution of products is listed in Table 1. These results suggest that oxidation of compound **5** leads to **9** through the captodative effect. Treatment of compound **5** with sulfur produced the thiomethylene analogue **17** (Scheme 2, method D), along with **9**.

Simple molecular modifications, carried out in both the pyridinium and azole moieties,†‡ led to compounds **6**, **7** and **12**. Quaternization of the benzimidazolylpyridylmethanes **18**⁶ with iodobutane was then examined using standard conditions (method A, Scheme 2). The structural features within the pyridinium salt **6** favoured oxidation through the captodative effect, and it was easily transformed into its analogue **10**.

Different behaviour was observed in the quaternary pyridi-



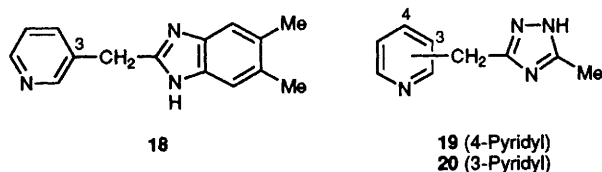
Scheme 1. Reagents and conditions: i, as ref. 6, with polyphosphoric acid; ii, 50% HBF_4-H_2O , pH 4

Scheme 2. Reagents and conditions: (A) BuI (5 equiv.), anhyd. MeCN, reflux under N_2 ; (B) BuI (5 equiv.) degassed anhyd. MeCN, reflux under Ar; (C) as (B), cat. galvinoxyl; (D) as (B), S (2 equiv.)

Table 1 Reactions of compound 16

Method ^a	t/h	Product Distribution ^b (%)		
		5	9	17
A	36	41	59 (58)	—
B	96	86 (64)	14	—
C	24	100 (83)	—	—
D	72	28	4	68 (54)

^a Scheme 2. ^b Ratio determined by ¹H NMR of reaction mixture. Numbers in parentheses are the unoptimized isolated yield of analytical samples. Satisfactory elemental analysis were obtained for compounds 5, 9 and 17.



nium salts 7 and 12. On quaternization of the triazole 19[¶] by standard conditions, its corresponding pyridinium salt 11 was obtained *via* the air-sensitive salt 7, whereas the triazole 20[¶] led to the pyridinium salt 12 which was very stable. New compounds were unambiguously characterized by IR, ¹H NMR and ¹³C NMR spectroscopy^{||} and all the isolated products gave satisfactory elemental analyses.

Our thanks are due to DGICYT, MEC-Spain, through grants PB 89-0214 and PB-92-0792 for support. M. G. thanks CIRIT (Catalonia) for a BQUIFI fellowship.

Received, 7th December 1993; Com. 3/07246K

Footnotes

[†] The electronic effects of heterocyclic fragments as substituents,^{2a} the quantitative analysis of steric effects in heteroaromatics,^{2b} and the basicity and acidity of azoles^{2c} have been reviewed.

[‡] The electronic effects of the heteroaromatic moieties[†] can have a dominant influence upon the ease of oxidation of the methylene spacer. The decreasing π -excessive nature of the azole nucleus⁵ can modulate the chemical behaviour of the interannular linker in substrates of type 1. In compound 13, both rings bonded to the methylene centre are highly π -deficient.

[§] Freshly distilled iodobutane was used. Bromobutane can also be used, but the reaction times are much longer. Iodomethane was not used in the experiments carried out with intermediate 16 to avoid, as far as possible, polymethylation.

[¶] The triazoles 19 and 20 were obtained by standard methods.⁸

^{||} The IR spectra (KBr) of the derivatives 8–11 showed a very strong characteristic absorption band in the range 1670–1655 cm⁻¹ ($\nu_{C=O}$) and the ¹³C NMR (CD₃)₂SO spectra showed a signal δ *ca.* 180

References

- 1 T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 1.
- 2 (a) V. P. Mamaev, P. O. Shkurko and S. G. Baram, *Adv. Heterocycl. Chem.*, 1987, **42**, 1; (b) R. Gallo and Ch. Roussel, *Adv. Heterocycl. Chem.*, 1988, **43**, 173; (c) J. Catalán, J. L. M. Abboud and J. Elguero, *Adv. Heterocycl. Chem.*, 1987, **41**, 187.
- 3 (a) J. Elguero, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 5, pp. 158, 168 and 268; (b) C. Marzin, M. E. Peek, J. Elguero, H. P. Figey and N. Defay, *Heterocycles*, 1977, **6**, 911.
- 4 (a) H. G. Viehe, R. Merényi and Z. Janousek, *Pure Appl. Chem.*, 1988, **60**, 1635; (b) R. Sutschmann and H.-G. Korth, *Adv. Phys. Org. Chem.*, 1990, **26**, 131.
- 5 G. B. Barlin, *J. Chem. Soc. B*, 1967, 641; *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 5.
- 6 E. Alcalde, I. Dinarés, Ll. Pérez-García and T. Roca, *Synthesis*, 1992, 395.
- 7 E. Alcalde, I. Dinarés, J. Frigola, C. Jaime, J.-P. Fayet, M.-C. Vertut, C. Miravittles and J. Rius, *J. Org. Chem.*, 1991, **56**, 4223.
- 8 I. Ya. Postovkii and N. N. Vereshchagina, *J. Gen. Chem., USSR*, 1959, **29**, 2105.