New Synthesis of 2-Formyl-4-methyl-1-phenylimidazole 3-Oxide

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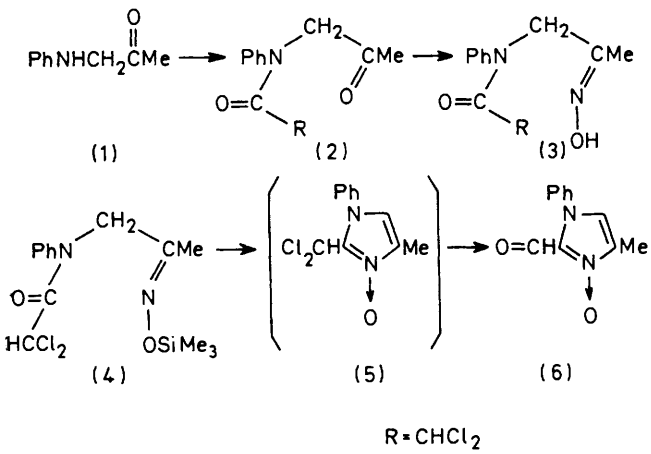
Summary A novel synthesis of 2-formyl-4-methyl-1-phenylimidazole 3-oxide (**6**) involving fluoride ion-promoted cyclization of the trimethylsilyl ether of *N*-dichloroacetyl-*N*-phenylaminopropanone oxime is described.

RECENTLY Sartorelli and his co-workers[1] found that *p*-tosylhydrazones of 2-formylpyridine 1-oxide show potent antitumour activity against mice bearing Sarcoma 180 ascites cells. In order to find a more active agent we plan to prepare *p*-tosylhydrazones of 2-formylazole *N*-oxides. We report here a new synthesis of 1-substituted imidazole 3-oxides bearing a functionalized substituent, the formyl group,[2] on the 2-position.



SCHEME

Acylation of *N*-phenylaminopropanone (**1**)[3] with either $Cl_2CHCOCl$ and $MeCO_2Et$–aqueous 5% KOH or Cl_2CHCO_2H and dicyclohexylcarbodi-imide gave *N*-phenyl-*N*-dichloroacetylaminopropanone (**2**; R = $CHCl_2$), m.p. 86—87 °C,† which (n-hexane, MeCN, EtOH) was converted into the corresponding oxime† (**3**; R = $CHCl_2$), m.p. 138—139 °C, *m/e* 274 and 276 (M^+) in 84% yield (Scheme). Attempts to cyclize (**3**) into (**5**) were unsuccessful. However, fluoride ion-promoted cyclization of its trimethylsilyl derivative (**4**) led to the desired product (**6**) as follows. Compound (**4**) [*m/e* 203, 205, 206, and 207 (M^+)] (588 mg) was treated with an excess of tetraethylammonium fluoride (2·2 g) in anhydrous dioxan (20 ml) with stirring at room temperature for two days. After work-up, recrystallization of the crude product from dioxan–ethanol afforded, in 50% yield‡ [based on (**3**)], 2-formyl-4-methyl-1-phenylimidazole 3-oxide (**6**),† m.p. 180—182 °C (decomp.), δ 2·20 (s, 3H, 4-Me), 7·24 (s, H-5 of the imidazole ring), 7·41 (s, 5H, ArH), and 7·63 (s, 1H, –CHO); *m/e* 202 (M^+), 186 (M^+ — O), and 185 (base peak, M^+ — OH); λ_{max} (MeOH) 291 (ε 10000) and 356 (5070) nm; λ_{min} (ε 2400) and 325 (3700) nm. It is noteworthy that the signal due to the formyl proton appears at exceptionally high field, presumably because of the anisoptropic effect of the 1-phenyl group. This is consistent with the fact that the signal due to phenyl protons appears as a singlet.§

This report represents the first example of the preparation of a 1-substituted 2-formylimidazole 3-oxide and a further example of fluoride ion-promoted reactions of trialkylsilylated derivatives.[4]

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† New compounds gave satisfactory combustion values.

‡ Reaction conditions were not optimized.

§ Phenylazoles which contain another substituent in the azole ring adjacent to the phenyl group (*i.e.*, if steric hindrance to coplanarity is present) give phenyl signals which are essentially a singlet (see ref. 2, p. 22).

[1] A. C. Sartorelli, K. C. Agrawal, B. A. Booth, J. Pittmann, D. G. Bartholomew, and A. D. Broom, *J. Medicin. Chem.*, 1976, **19**, 830.

[2] To our knowledge, the preparation of 2-formylimidazole 3-oxides has never been reported. However, see K. Schofield, M. R. Grimmett, and B. R. Keene, 'Hetero Aromatic Nitrogen Compounds, the Azoles,' Cambridge University Press, Cambridge, 1977, p. 172.

[3] V. Wolf, *Annalen*, 1952, **578**, 83.

[4] For example, see R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Amer. Chem. Soc.*, 1977, **99**, 1265.