A Convenient Preparation of 3-(1*H*-Imidazol-4-yl)propanol

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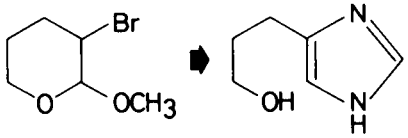
Difficulties in the availability of suitably substituted carbonyl precursors, rather than limitations in heterocyclic ring formation constitute a serious obstacle to the synthesis of simple 4-substituted imidazoles (1). The only synthesis of 3-(1*H*-imidazol-4-yl)propanol (II) reported (2) involves the rather inaccessible 4,5-dioxovaleric acid as a key intermediate.

We wish to report a simple preparation of II based on a bulk chemical, 3,4-dihydro-2*H*-pyran. An addition of bromonium ion to dihydropyran in methanol has been recently shown to furnish (3) 2-methoxy-3-bromotetrahydropyran (I). We have found the latter to be a suitable substrate for Bredereck's method (4). Thus simple treatment of I with formamide yielded directly 3-(1*H*-imidazol-4-yl)propanol (II), which was isolated and characterized as an oxalate.



I II

EXPERIMENTAL

2-Methoxy-3-bromotetrahydropyran (163 g.) was added to stirred formamide (800 ml.) at 165° under nitrogen during 90 minutes. After an additional period of 90 minutes, the reaction mixture was chilled and diluted with water (2 l.). The solution was passed through a Dowex AG 50W-X8 resin (H^+ form, capacity 1.5 eq.), subsequently washed with water and methanol. The free bases were eluted with methanolic ammonia (0.5 mole/l.), evaporated and chromatographed on silica gel (500 g., pretreated with ammonia); an ammonia treated chloroform/1-butanol (5:1) mixture was used as eluent. The residue obtained on evaporation of a uniform fraction was neutralized with hydrochloric acid (0.5 mole/l.) and filtered through an Amberlite IRA-400 resin (oxalate form, capacity 0.5 eq.). Evaporation followed by crystallization from a methanol/acetone mixture afforded the oxalate of II as a white solid (60.5 g.), m.p. 146-147°; pmr: (60 MHz, in deuterium oxide, sodium 2,2,3,3-tetradeutero-3-trimethylsilylpropionate as an internal reference): δ 1.92 (distorted quintet J ~ 7 Hz, CH_2-CH_2OH), δ 2.82 (distorted triplet J ~ 7.5 Hz, CH_2 next to imidazole), δ 3.66 (triplet, J = 6.3 Hz, CH_2OH), δ 7.23 (complex, imidazole $H_{(5)}$), δ 8.67 (doublet, J = 1.3 Hz, imidazole $H_{(2)}$); mass spectrum: m/e (%); 126(32.6, M^+, from dissociated free base), 125(5.0), 108(6.6), 107(12.5), 96(37.5), 95(98.0), 82(90.3), 81(100), 80(13.4), 68(28.8), 54(23.1).

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