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SYNTHESIS AND REACTIONS OF AN AZETIDIN-3-ONE

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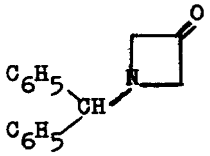
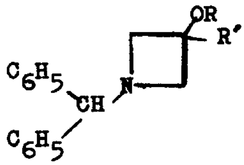
Despite current interest in the synthesis and chemistry of azetidins, there have been particularly few reports on those derivatives which have functional groups directly attached to the ring (1). Most of the methods available for the synthesis of substituted azetidins (2) seem to be limited by the availability of the starting materials required and the methods themselves cannot claim wide applicability. Recently, however, an elegant method of preparing 1-alkyl-azetidin-3-ols has been described (3). This communication is concerned with a convenient method for the conversion of azetidin-3-ols to the corresponding -3-ones together with e few reactions of the ketone which will provide an entree into various funtionally substituted azetidins.

1-Benzhydryl-azetidin-3-ol (4) was oxidised with chromic acid in acetic acid under carefully controled conditions (0 to 5°). The oxidation was complete in about six hours and the ketone (I) was extracted from the reaction mixture after making it alkaline with NH_4OH. It was recrystallised from hexane (mp. 82°; 65 % yield). The ketone (I) is unstable at room temperature and develops a faint yellow colour. It could be stored in cold (0 to 5°) for a couple of weeks.



(I)



(II)

(a) $R = -\overset{O}{\overset{\|}{C}}-C_6H_5$
$R' = -CN$

(b) $R = -H$
$R' = -C_6H_5$

(c) $R = -H$
$R' = -CH_3$

Assigment of structure (I) was supported by correct elemental analysis and further confirmed by mass spectrometry which gave a molecular formula $C_{16}H_{15}NO$ $[M^+, 237;$ m/e M-28 $(C_{15}H_{15}N)$; m/e M-70 $(C_{13}H_{11})]$. The infrared spectrum showed a strong ν_{max} (KBr) 1820 (strained ring ketone) and 1885 cm^{-1} (m) (aromatic) and the N.M.R. spectrum (in $CDCl_3$) (Me_4Si reference) showed a four proton singlet at τ6,0 assignable to the ring methylene protons of (I) and a one proton singlet at τ5,4 assignable to the benzylic proton, in addition to the signals expected for the aromatic protons. The structure was further confirmed by its

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+Present address: Chemische Werke Albert AG, 6202 Wiesbaden-Biebrich, W-Germany reduction with $NaBH_4$ in methanol to the parent azetidinol.

The ketone (I) gave a cyanohydrin-benzoate (IIa) (mp. 215°) on treatment with potassium cyanide and benzoyl chloride in benzene. It gave a satisfactory analysis and its ir [ν_{max}(KBr) 2240 (w) and 1720 cm^{-1} (s)] and n.m.r. [τ5.9-6.5 (m, 8H), 5.5 (s. 1H) 1.8-2.7 (m, 15 H)] were in agreement with the structure (IIa). Treatment of the ketone (I) with phenyl lithium in ether at room temperature gives 1-benzhydryl-3-phenyl-azetidin-3-ol (IIb) (mp. of the hydrochloride; 195°) in 95 % yield. Its structure was proved unequivocally from its correct analysis, ir [ν_{max} 3400(s) 1585 (m)] and n.m.r. [τ7.3 (broad hump, exchangeable with D by D_2O shake, O$\underline{H}$), 6.2-6.5 (m, 4H), 5.5 (s, 1H), 2.2-2.8 (m,15H)]. (IIb) is a fairly stable compound and attempted dehydrations did not succeed. Similarly, the ketone (I) on treatment with equimolar ammounts of methyl-lithium or methylmagnesium-bromide gave 1-benzhydryl-3-methyl-azetidin-3-ol (m.p. 120° d).

Additional examples of azetidin-3-ones which can be prepared by this method and their utility in the synthesis of various functionally substituted azetidins is under investigation and will be reported in a full paper.

Acknowledgements

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