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3 - KETOPIPERIDINE RING CONSTRUCTION THROUGH TRANSPOSITIONS OF AMINOMETHYL CYCLOPROPYL KETONES

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It is well documented that nucleophilic cleavage of cyclopropane rings is most facile when the ring bears two geminal electron-withdrowing groups[1].

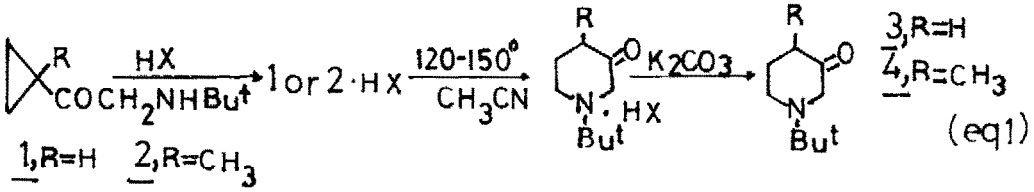
In this note we wish to report that only one electronegative group may provide sufficient driving force for facile cyclopropane ring opening by an internal nucleophile. Thus, on heating the solutions of hydrochloride or hydrobromide salts of aminoketones 1 and 2 in acetonitrile these give corresponding salts of 3-ketopiperidines 3 and 4 in excellent yields (eq.1). As to the mechanism of this rearrangement the following experimental evidence is of implication: i. The free bases 1 or 2 are quite stable at the reaction conditions.ii. The ease of rearrangement for hydrobromides is greater than for hydrochlorides; potassium iodide considerably enhances the reaction.iii. No rearrangement is detectable for salts of HBF_4.iv. The end-product 3 (HBr) was obtained with 70% yield directly by cristallisation of the evaporate.

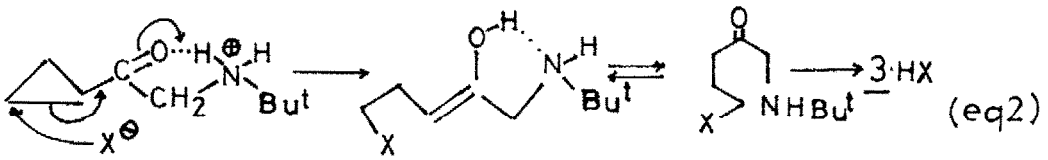
Thus, the following sequence of transformations is probably involved (see eq.2): i. Nucleophilic opening of activated cyclopropane ring by $I^{\ominus}$, $Br^{\ominus}$ or $Cl^{\ominus}$.ii. Intramolecular cyclisation of thus formed haloaminoketones into 3-ketopiperidines.

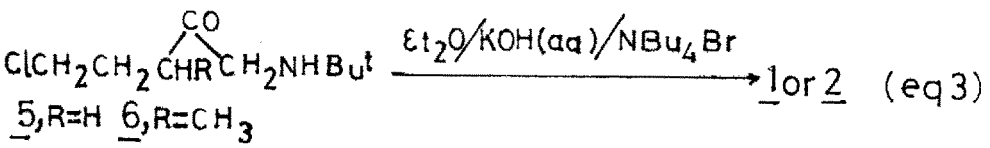
The above outlined 3-ketopiperidine ring formation through transposition of salts of α-aminoacyl cyclopropanes constitutes a useful practical synthesis of such compounds with bulky substituent on nitrogen (e.g., Bu^t). The starting cyclopropyl ketones were prepared in high yields as follows (eq.3): a solution of chloroketone 5 or 6 in ether was stirred under argon with the excess of 50% aqueous KOH and some phase-transfer catalyst (NBu_4Br).

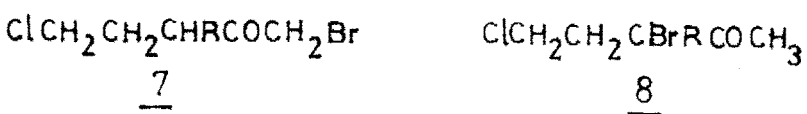
At room temperature the reaction is complete in 2 or 3 hrs (control by v.p. or t.l.c.). It is worthwhile to note that pure 5 or 6 may be prepared by the controlled amination of mixture of isomeric bromo-chloro ketones 7 and 8 as it is obtained by bromination of γ-chloro ketones in methanol (R = H, 7:8 as 1:1; R = CH_3, 7:8 as 9:1).

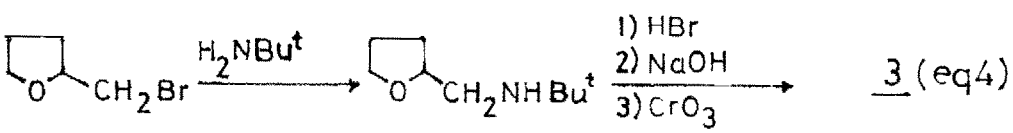
The piperidones 3 and 4 were identified by i.r. - and p.m.r. - data and were also synthesized by an independent way as shown in eq. 3 and 4.

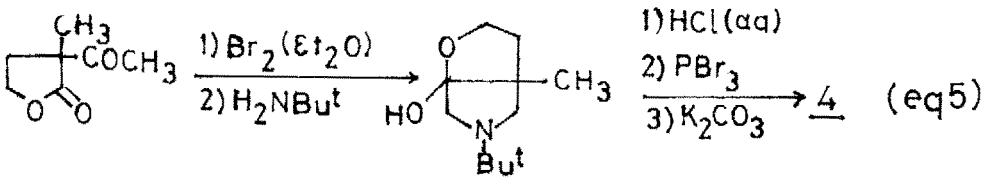












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