Tetrahedron Letters No.31, pp. 2103-2107, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE MICHAEL-ALKYLATION RING SYNTHESIS: PIPERIDINE AND PYRROLIDINE CONSTRUCTION

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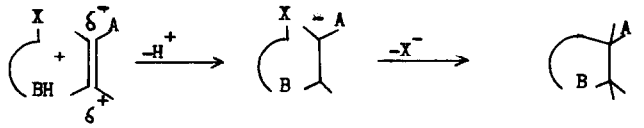
(Received 6 June 1964)

The Michael-alkylation sequence may be fundamentally visuallized as a two step process, involving a bifunctional molecule (I) containing both nucleophilic and electrophilic groups and a typical polarized olefin molecule (II; A=CN, CO_2R, NO_2 etc.), taking place as follows:



(I) (II) (III)

The nucleophilic group, B, may typically be amino, carbanion, mercapto, etc. The leaving group, X, is typically halide or tosylate. The product (III) of such a two step process, i.e., the formation of a Michael anion followed by intramolecular alkylation of the anion, may be either a homo or hetero-cyclic compound, depending on the nature of -BH.

Corollary to the alkylation sequence is what may be termed the Michael-acylation sequence in which a carbonyl function serves as the electrophilic cyclization prompter. This method has been attracting a number of chemists since its inception at the hands of Kuhn and Osswald

in 1956 who utilized N-carboethoxy ethyl glycine (nitrogen anion) and several unsaturated esters with the obtention of substituted pyrrolidones.[1]

A synthesis of 1,2-cyclopropane dicarboxylic esters by Buchman and Deutsch who allowed chloroacetic ester anion to react with acrylate esters may be categorized as a Michael-alkylation reaction.[2]

The potential scope implicit in the sequence under discussion cannot be ignored; the permutations rapidly become obvious and varied. We have, to an extent, studied the implementation of the sequence for piperidine and pyrrolidine ring systems. In particular the reactivity of various 2-haloethylamines and 3-halopropylamines towards unsaturated acceptors has been investigated.

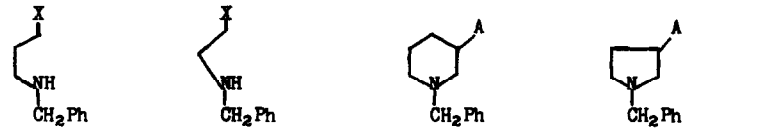
Attempts to condense 2-bromoethylamine or 3-bromopropylamine (prepared from the hydrobromides in situ by potassium carbonate) with methylvinylketone in ethanol or t-butanol effected the preferential intramolecular deterioration of the substrate amines by cyclization and/or fragmentation avenues. However substitution of the amines, conveniently performed with benzyl groups in this exploratory work, enhanced the stability of the haloamines considerably.

N-benzyl-2-bromoethylamine hydrobromide[3] (Va·HBr) and its homologue, N-benzyl-3-bromopropylamine hydrobromide (IVa·HBr), m.p. 184-186°C(Anal:% Found: C, 39.00; H, 4.59; N, 4.64) were prepared by the procedure of Cortese.[4] The free amines were obtained by benzene extraction of basified aqueous solutions of the salts.

When a benzene solution containing equivalent amounts of N-benzyl 3-bromopropylamine (IVa) and methyl vinyl ketone was refluxed for one hour and subsequently treated at reflux with an equivalent of potassium

t-butoxide a gratifying 50% yield of 3-acetyl-1-benzylpiperidine (VIa) b.p. 103-105°C/0.15 mm. (Anal:% Found: C, 77.73; H, 8.92; N, 6.20) was formed. Similar reaction of N-benzyl-2-bromoethyl amine (Va) produced a 20% yield of 3-acetyl-1-benzylpyrrolidine (VIIa), b.p. 98-99°C/0.15 mm. (Anal:% Found: C, 76.49; H, 8.46; N, 6.99).

Encouraged by these results we prepared the chloro congeners, N-benzyl-3-chloropropylamine (IVb) and N-benzyl-2-chloroethylamine (Vb) as their hydrochlorides. This was done by treatment of the corresponding hydroxyamines with two equivalents of thionyl chloride in chloroform at 0°C followed by heating until gas evolution ceased. Compound IVb·HCl possessed m.p. 203°C (sealed tube) (Anal:% Found: C, 54.35; H, 6.69; Cl, 32.04; N, 6.39); compound Vb·HCl was previously known.[5]



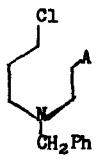
IV a; X = Br V a, X = Br VI a, A = $-\overset{O}{\overset{\|}{C}}CH_3$ VII a, A = $-\overset{O}{\overset{\|}{C}}CH_3$

b; X = Cl b, X = Cl b, A = -CN b, A = -CN

c, A = $-CO_2Et$ c, A = $-CO_2Et$

The free amines IVb and Vb, enjoying even greater stability than their bromo predecessors, reacted nicely in the Michael-alkylation sequence with methyl vinyl ketone in benzene producing, respectively, 80% and 50% yields of VIa and VIIa.

Reaction of IVb with acrylonitrile proceeded not at all in benzene and modestly in t-butyl alcohol, the intermediate, VIIIa, a liquid, b.p. 140-142°C/0.2 mm. (Anal: Found:% C, 66.29; H, 7.50; N, 12.01)



VIII a, A = CN

b, A = CO_2Et

being produced which could be cyclized without isolation by diluting the intermediate reaction mixture with dimethyl sulfoxide and treatment with potassium t-butoxide. The 3-cyano-1-benzylpiperidine (VIb) was obtained in 42% yield as an oil, b.p. 121-124°C/0.3 mm. (Anal: % Found: C, 77.93; H, 8.04; N, 13.81).

Preparation of 3-carboethoxy-1-benzylpiperidine (VIc) was achieved best in two steps. The chloroamine (IVb) was heated with two equivalents ethyl acrylate at reflux in t-butyl alcohol to produce an 83% yield of the acylic compound, VIIIb, b.p. 135-145°C/0.30 mm., characterized as the hydrobromide, m.p. 113.5-115°C (from isopropanol) (Anal:% Found: C, 49.31; H, 6.43; N, 4.08). Cyclization of VIIIb by potassium t-butoxide in dimethyl sulfoxide gave the aminoester (VIc) in 52% yield as a liquid, b.p. 113-117°C (Anal: Found:% C, 72.51; N, 8.27; N, 5.84).

Attempts to prepare the related pyrrolidines VIIb and VIIc using these procedures and the chloroethylamine Vb were unsuccessful. Evidently the chlorine atom inductively deactivates the nitrogen of the amine in question to an extent which essentially precludes addition of the amine to most unsaturated compounds. In 3-chloropropylamines this effect is diminished due to the interpolation of an additional methylene group.

It seems then that this particular application of the Michael-alkylation reaction is capable of producing a variety of piperidine compounds and will be limited to the preparation of pyrrolidine compounds in which only very electrophilic olefinic materials such as alkyl vinyl ketones, nitro ethylenes and acroleins can be employed.

We are continuing to examine these and other aspects of the conceptually general Michael-alkylation sequence.

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