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A NEW SYNTHESIS OF N-ARYLAZETIDINES

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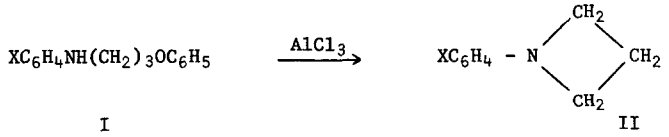
Low yields of N-phenylazetidine have been obtained previously[1,2] by alkaline cyclisation of N-(3-bromopropyl)aniline. We now describe a new synthesis of N-arylazetidines which gives considerably greater yields without concomitant formation of N-allylanilines.[1]

We showed[3] earlier that 1,3-diaryloxypropanes are decomposed smoothly by aluminium chloride to give chromans in good yields, but found that N,N'-diaryl-1,3-diaminopropanes[4] are unaffected by this reagent. Treatment of N-aryl-3-aminopropyl phenyl ethers (I) with aluminium chloride causes cleavage at the ether linkage only and leads to formation of the corresponding N-arylazetidines (II) together with small amounts of substituted tetrahydroquinolines and 3-chloropropylanilines.



I II

This type of cyclisation depends[3,4] on the availability of the lone pair of electrons on the nitrogen. The ability of the aluminium chloride to complex with this nitrogen atom tends to prevent reaction and this is reflected in the low overall yield of azetidines and tetrahydroquinolines. The optimum amount of aluminium chloride was found to be 1.3 moles per mole of I. A considerable quantity of unchanged starting material could be recovered under these conditions and the yields shown in Table I are based on the amount of I consumed. An increase in the

proportion of aluminium chloride used led to an increase in the amount of tetrahydroquinoline and 3-chloropropylaniline formed without greatly increasing the overall yield of cyclisation products.

TABLE I

Yields of N-(X-phenyl)-3-aminopropyl phenyl ethers (I) and N-(X-phenyl)azetidines (II)

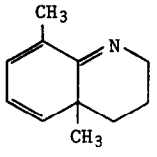
X	I		II	
	% yield	bp(ca 1mm) °C	%[f] yield	bp(ca 1mm) °C
H	82	163-7[b]	30	70
2-CH_3	83	170[a]	22	58[a]
3-CH_3	80	175[a,c]	29	80[a]
4-CH_3	77	170[a,d]	25	85[g]
2-Cl	75	180[a]	20	85[a]
3-Cl	77	185[a]	20	85[a]
4-Cl	78	185[a]	22	80[a,h]
4-CH_3O	72	175[a,e]	5	80[a]
2,6-$DiCH_3$	85	185[a]	j	a
2,4,6-$TriCH_3$	85	190[a]	6	78[a]

a - new compound; b - mp 32° (pet. ether) (lit.[5] 32°);
c - mp 38.5° (MeOH); d - mp 73° (MeOH); e - mp 62° (MeOH);
f - based on unrecovered starting material;
g - mp 38-39° (MeOH) (lit.[1] 37°); h - mp 40° (MeOH);
j - obtained in low yield by preparative VPC.

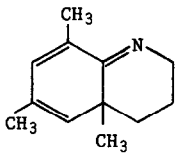
The N-aryl-3-aminopropyl phenyl ethers (I) listed in Table I were prepared by heating an excess of the appropriate amine in toluene with 3-bromopropyl phenyl ether.[5] The reaction mixture was made alkaline, extracted with ether and the product obtained by distillation. These compounds (0.1 mole) were warmed, cautiously, with aluminium chloride (0.13 mole) in anhydrous benzene

(300 ml) and refluxed for 2.5 hours (1.5-2 hr for ortho- chloro or ortho- dimethyl substituted anilines). The resulting mixture was cooled, diluted with ether (50-100 ml) and shaken with ice and concentrated hydrochloric acid. Unchanged starting material precipitated as its hydrochloride and was filtered off. The organic layer of the filtrate was extracted with acid and the combined aqueous extracts were made alkaline and extracted with ether. The solvent was evaporated and fractionation of the residue through an 18" spinning-band column readily separated the required azetidine as the most volatile product in all but the two cases mentioned below. The corresponding tetrahydroquinolines were generally present in much smaller quantities. Compounds were identified and shown to be pure by analysis, VPC retention measurements, and infrared and NMR spectra. For example, the infrared spectra of the azetidines showed out-of-plane C-H vibrations typical of the appropriately substituted benzene, an absorption in the range 1230-1240 cm^{-1} characteristic[6] of azetidines, and no N-H stretching vibration.

The decomposition of N-(2,6-dimethylphenyl)- and N-(2,4,6-trimethylphenyl)-3-aminopropyl phenyl ethers gave 2,3,4,10-tetrahydro-8,10-dimethylquinoline (III) and 2,3,4,10-tetrahydro-6,8,10-trimethylquinoline (IV) respectively in quantities comparable with the corresponding azetidines. These compounds are analogous to the dienones formed[7] from reaction of 2,4,6-trisubstituted phenols with electrophilic reagents.



III



IV

The quinoline derivatives were separated from the corresponding azetidine by preparative VPC (III), or fractionation through the spinning-band column (IV), the quinoline derivative having the lower boiling point in each case. The structures of these compounds were assigned by analysis and the following physical measurements.

2,3,4,10-Tetrahydro-8,10-dimethylquinoline (III): UV, λ max 299 mμ, ξ max 2,230, consistent with a conjugated non-aromatic system; IR (smear), bands at 1670 cm^{-1}, 1610 cm^{-1} (C=C, C=N), 735 cm^{-1} (alkene C-H bend), no absorption corresponding to an N-H stretching mode; NMR (CCl_4 - δ in ppm downfield from TMS), 1.13 (singlet, 3H), 1.35-2.0 (1.85 strong) (multiplet,

7H), 3.80 (triplet, 2H, J = 5.0 cps), and 5.67-5.93 (multiplet, 3H).

Corresponding figures for IV were: UV, λ max 307 mμ, ξ max 3,420; IR, 1670, 1620, 810 cm^{-1}; NMR, 1.08 (singlet, 3H, 1.33-2.25 (1.73, 1.83 strong) (multiplet, 10H), 3.77 (triplet, 2H, J = 5.0 cps), 5.30 (singlet, 1H), 5.87 (singlet, 1H).

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