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1,3-DEHYDROHALOGENATION OF α-HALOKETIMINES AS A SYNTHETIC TOOL FOR THE GENERATION OF GEMINALLY FUNCTIONALIZED CYCLOPROPANES.[1]

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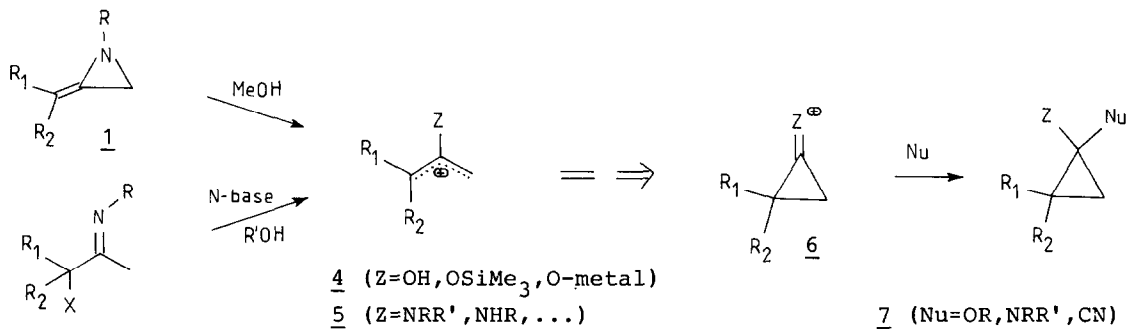
Abstract

1-Alkoxy-1-(N-alkyl)aminocyclopropanes were synthesized by base-assisted alcoholysis of α-haloketimines using tertiary amine bases.

While 2-oxyallylcarbenium ions 4 received considerable attention in the literature,[3] the corresponding nitrogen analogues, i.e. 2-aminoallylcarbenium ions 5, have only been studied to a very limited extent. Their proven potential to be transformed into geminally functionalized cyclopropanes via activated intermediates 6 is of great utility in synthetic organic chemistry. For instance, 2-aminoallylcarbenium ions 5 are precursors for cyclopropaniminium derivatives 6



2 X=Cl, Br; R_1=R_2=Me
3 X=Cl, Br; R_2=H

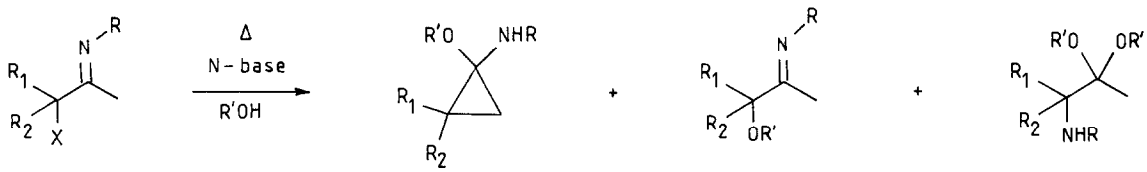
4 (Z=OH,$OSiMe_3$,O-metal)
5 (Z=NRR',NHR,...)

7 (Nu=OR,NRR',CN)

($Z=NR_1R_2$), which readily add nucleophiles, e.g. alcohols,[4] amines,[4a,5] cyanide,[4a,6] etc. to provide 1,1-difunctionalized cyclopropanes 7. The latter are known as synthetic equivalents of cyclopropanes[7] and have been used extensively as synthons in heterocyclic chemistry (including β-lactam syntheses)[7] and natural product syntheses.[6,8] A recent report[9] concerning the generation of such novel delocalized ions 5 from methyleneaziridines 1, prompted us to disclose our preliminary results on the base-induced alcoholysis of α-haloketimines 2 (X=Cl, Br)

to afford functionalized cyclopropanes 8, presumably via 2-aminoallylcarbenium ions 5. It will be demonstrated that the intermediate formation of the latter species via 1[9] or α-haloketimines 2 and subsequent conversion into cyclopropanone adducts 8 is a very related process.

The reaction of secondary α-haloketimines 3[10] with alcohols (methanol or isopropanol) under reflux gave rise to α-(N-alkyl)aminoacetals 10 (R_1=alkyl; R_2=H),[11] while tertiary α-chloroketimines 2[10] under the same conditions yielded mainly α-alkoxyketimines 9. If both reactions were run (reflux 4-20 hrs) in the presence of tertiary amines, e.g. triethylamine or DABCO, secondary α-haloketimines 3 furnished the same α-(N-alkyl)aminoacetals 10 (R_1=alkyl; R_2=H)[11] but tertiary α-haloketimines 2 afforded a mixture of 1-alkoxy-1-(N-alkyl)aminocyclopropanes 8, α-alkoxyketimines 9 and α-(N-alkyl)aminoacetals 10.



2 X=Cl,Br 8 9 10

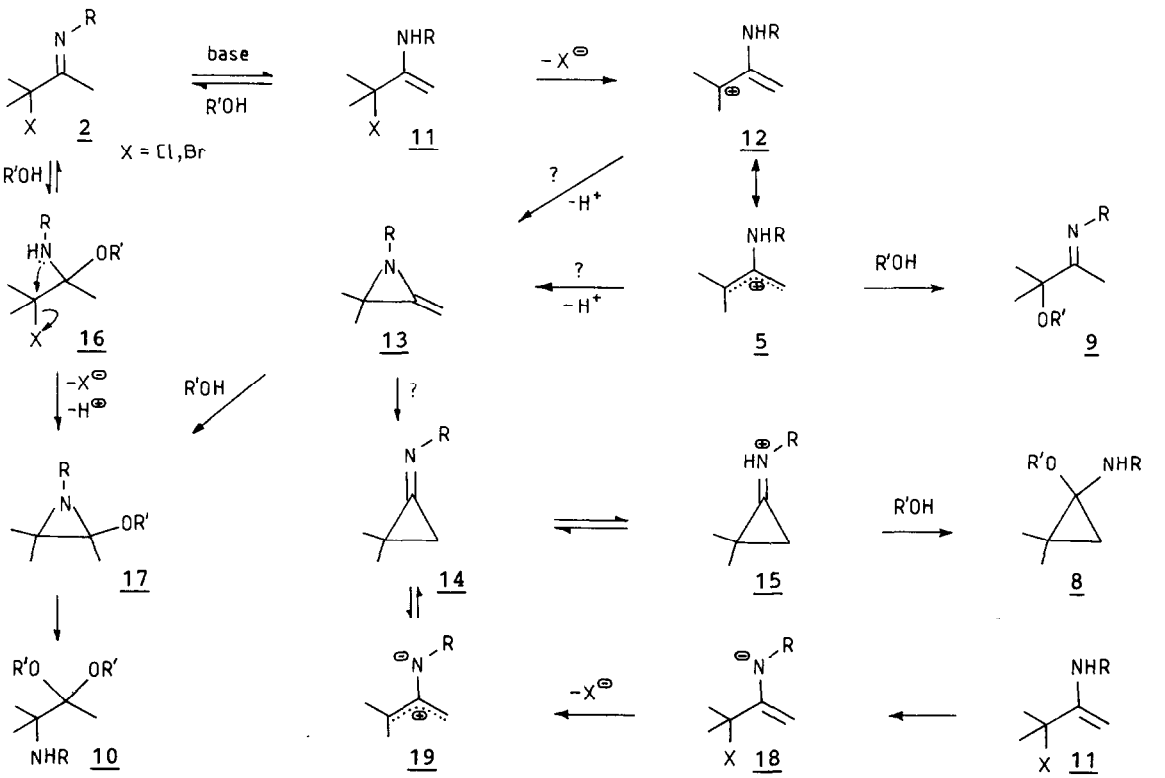
Table I : Reactions[a] of α-Haloketimines 2 with Tertiary Nitrogen Bases in Alcoholic Medium (R_1, R_2=CH_3).

Entry	R	X	N-base[b]	R'OH	Reflux time (hrs)	8	9	10
1	i-Pr	Cl	Et_3N	MeOH	20	13	59	28
2	i-Pr	Br	Et_3N	MeOH	4	48	23	32
3	i-Pr	Cl	DABCO	MeOH	20	6	58	36
4	i-Pr	Br	DABCO	MeOH	4	26	50	24
5	allyl	Cl	DABCO	MeOH	18	16	56	28
6	Et	Cl	DABCO	MeOH	6	18	36	46
7	i-Pr	Br	Proton sponge	MeOH	18	0	38	62
8	i-Pr	Cl	DBN	MeOH	16	79	0	21
9	i-Pr	Br	DBN	MeOH	18	48	0	52
10	i-Pr	Cl	DBN[c]	i-PrOH	28	80[d]	0	0
11	i-Pr	Cl	DBU	i-PrOH	20	78[d]	0	0

a) Analyses were performed by glc and NMR spectrometry (percentages are given in the last three columns); b) Two molar equivents except otherwise mentioned; c) Four molar equivalents; d) In addition to some starting material and/or unidentified products.

Various non-nucleophilic bases were evaluated towards tertiary α-haloketimines to yield variable amounts of compounds 8, 9 and 10 (Table 1). The best cyclopropanation results were obtained with α-chloroketimine 2 (R=i-Pr) and DBN or DBU, preferably in isopropanol, because this seems to limit the amount of α-(N-alkyl)aminoacetal formation (sterical hindrance).

The competitive formation of functionalized cyclopropanes 8, α-alkoxyketimines 9 and α-(N-alkyl)aminoacetals 10 is explained in terms of the sequences outlined in the accompanying scheme. The α-haloketimine 2 is in equilibrium with enamine 11 (via α'-deprotonation) and alcohol adduct 16.[11] It is most probable that loss of a halide anion from 2-aminoallylic halide 11 provides delocalized allylcarbenium ion 5 which can give rise to various products. This reaction step parallels the silver-induced ionization of 2-aminoallylic halides to produce the corresponding carbenium ions 5.[5a,b] Alcoholysis furnishes α-alkoxyketimines 9 while ring closure yields cyclopropaniminium derivatives 15, which will rapidly undergo addition of the alcohol to give stable adduct (8). On the other hand, α-haloketimine adduct 16 is able to give intramolecular nucleophilic substitution with formation of α-alkoxyaziridines 17 which are known to be alcoholyzed into α-(N-alkyl)-aminoacetals 10.[12,13] According to a very recent report,[9] the forma-



tion of α-(N-alkyl)aminoacetals 10 might also originate from 2-(N-alkyl)aminoallylcarbenium ions 5 via ring closure (and following deprotonation) to methyleneaziridines 13 and subsequent addition of the alcohol to afford α-alkoxyaziridine 17. If this proposal would be applicable, then the possible valence-isomerization to cyclopropylideneamines 14 should also be considered and this would present an alternative route to cyclopropane derivatives 8. This valence isomerism of cyclopropylideneamines and methyleneaziridines is an established fact.[9,14] Whether enamine anion 18 can lose a halide anion to generate a zwitter ionic species 19, which would collapse to cyclopropylideneamines 14, is still an open question.

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