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STEREOSPECIFIC ADDITIONS TO OLEFINS. SYNTHETIC UTILITY OF NITRILIUM ION INTERMEDIATES[1]

Alfred Hassner, Louis A. Levy and Robert Gault

Department of Chemistry, University of Colorado, Boulder, Colo.

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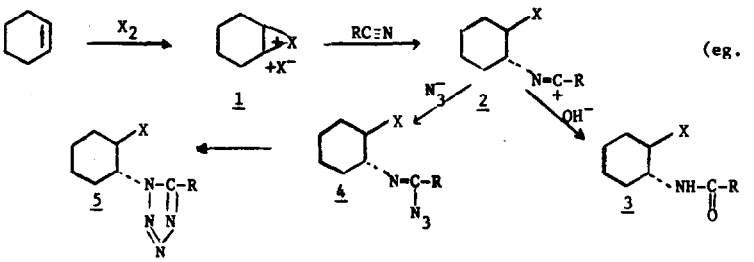
Additions of halogens to olefins are believed to normally proceed via a cyclic three-membered ring halonium ion intermediate which is opened subsequently by a halide nucleophile. Other anions can be used to introduce diverse functional groups. Our efforts towards the stereospecific introduction of nitrogen functions into organic compounds[2] led us to envisage a pathway whereby a neutral molecule, i.e. a nitrile, might act as a nucleophile[3] in the opening of a bromonium ion intermediate such as 1, thus leading to a nitrilium ion 2. The latter should be a useful synthetic intermediate. In fact, Cairns and coworkers[4] have reported that imino chlorides, convertible to amides, are formed as minor products in the reaction of chlorine or bromine with olefins in acetonitrile. However, for a pathway such as shown in equation 1 to proceed in good yield, the halide ion present (X^-) must be made ineffective as a competing nucleophile.



(eq. 1)

This scheme can indeed be realized by the addition of silver ions which remove the halide ions from the solution. For example, when cyclohexene is added at 0° to one equivalent of bromine in the presence of one equivalent of silver perchlorate in acetonitrile as a solvent immediate precipitation of silver bromide occurs. Within a few minutes the resulting solution of the nitrilium ion 2 can be treated with aqueous potassium hydroxide and amide 3 (X:Br,R:CH_3) can be isolated in 60% yield. If, instead, sodium azide is added to the solution, the resulting tetrazole 5 (X:Br,R:CH_3;5.6(H_2 broad), τ 7.38(H_3 singlet) can be obtained pure in 70% yield. The presence of the silver perchlorate is essential since in its absence only 0-5% of the mentioned products are obtainable. The structure of tetrazole 5 (X:Br, R:CH_3) was confirmed by its hydride reduction to 1-cyclohexyl-5-methyltetrazole, m.p. 117-118°, which in turn was prepared independently by a Ritter type reaction from cyclohexene, perchloric acid, acetonitrile and azide ion.

It is interesting to note from the point of view of the mechanism of halogen addition to olefins, that no precipitation occurs on mixing solutions of bromine and of silver perchlorate in acetonitrile prior to the addition of an olefin to this mixture. This suggests that the reaction does not involve the formation of bromine perchlorate but that the olefin acts as a nucleophile on bromine, releasing a bromide ion to the silver cation. Similarly, whereas iodine does not readily give olefin addition products, it does react readily in presence of silver perchlorate to lead ultimately to iodo amides (3,X:I) or iodo tetrazoles (5,X:I).

The stereochemistry of the reaction was shown to be trans, consistent with ring opening of the intermediate halonium ion. Thus, the product of reaction of cyclohexene, iodine, acetonitrile, silver perchlorate and then potassium

TABLE I

Synthesis of Halo Amides and Halo Tetrazoles from Olefins via Nitrilium Ions[a]

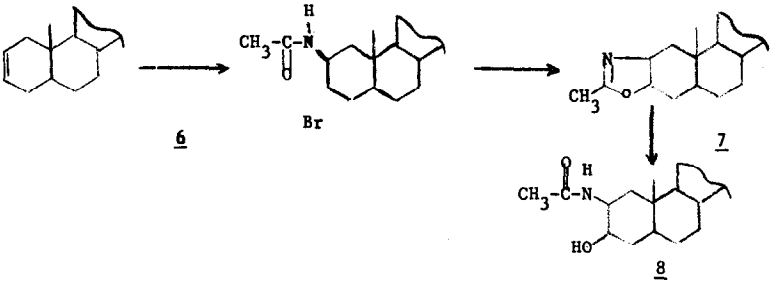
Olefin	Products[b]	m.p.	Yield%
Cyclohexene	N-(trans-2-bromocyclohexyl) acetamide (3,X:Br,R:CH_3)	125-127°	70
Cyclohexene	N-(trans-2-iodocyclohexyl) acetamide (3,X:I;R:CH_3)	122-123°	60
Cyclohexene	1-(trans-2'-bromocyclohexyl)-5-methyltetrazole (5,X:Br;R:CH_3)	122-123°	70
Cyclohexene	1-(trans-2'-iodocyclohexyl)-5-methyltetrazole (5,X:I;R:CH_3)	143°	45
Cyclohexene	1-(trans-2'-bromocyclohexyl)-5-phenyltetrazole (5,X:Br;R:C_6H_5)	147-149°	20
1-Methyl-cyclohexene	1-(1'-methyl-2'-bromocyclohexyl) -5-methyltetrazole	109-111°	65
Isobutene	1-(2'-bromo-1',1'-dimethylethyl) -5-methyltetrazole	63-64°	55
Styrene	1-(1'-phenyl-2'-bromoethyl)-5-methyltetrazole	109-111°	35
2-Cholestene	2β-acetamido-3α-bromo cholestane (6)	213°	75
3β-acetoxy-5-cholestene	6β-acetamido-3β-acetoxy-5-bromocholestane	134-135°	50

a. Amides were obtained upon addition of water or of aqueous potassium hydroxide, whereas the tetrazoles resulted on addition of sodium azide.

b. Satisfactory analyses were obtained for all compounds. The spectral data are consistent with the assigned structures; the amides show infrared absorption near 3250, 1665 (shoulder), 1640 and 1560 cm^{-1}, whereas the tetrazoles[9] exhibit a wealth of peaks below 1525 cm^{-1}.

hydroxide was identified as N-(trans-2-iodocyclohexyl) acetamide, which was independently synthesized from the corresponding trans iodo amine. Furthermore with steroid olefins the reaction takes place in a trans diaxial manner.

In the reaction of 2-cholestene the diaxial 2β-acetamido-3α-bromocholestane (6) underwent cyclization under the reaction conditions to oxazoline 7 (50% yield)[5] which in the presence of an excess of base was converted to the amino alcohol derivative 8[10]. This reaction should therefore be applicable to the synthesis of bifunctional compounds such as cis 2-amino alcohols from olefins.



6 7 8

The reaction of halogens with olefins in acetonitrile can be employed in the synthesis of tetrazoles of type 5 (see Table I) by adding azide ions to the nitrilium ion intermediate stage. That nitrilium ions readily react with azide ions to yield tetrazoles has recently been demonstrated.[6] The logical imino azide intermediates 4 could not be isolated, but such compounds are known to cyclize rapidly to tetrazoles.[7]

Other nitriles can be substituted for acetonitrile in this reaction, and silver perchlorate can be replaced by other reagents that complex halide ions, such as aluminum chloride. The reaction of nitrilium ions with other nucleophiles is being investigated.

Analogies for the concept of ring opening of three-membered ring ionic species by nitriles (1→2) can be found in the recently reported opening of aziridium ions (1, X:NR_2) by acetonitrile leading to heterocyclic compounds[8].

References

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(b) Support of this work by Grant CA-4474 of the National Cancer Institute, National Institute of Health and Grant 2004 A1,4 by the Petroleum Research Fund, American Chemical Society is gratefully acknowledged.

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