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A NEW APPROACH TO ISOQUINOLINES.[1]

Alfred Hassner, Robert A. Arnold[1b], Robert Gault and Akira Terada

Department of Chemistry, University of Colorado, Boulder, Colorado

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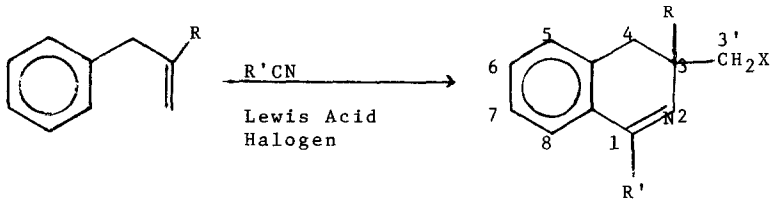
A major source of 3,4-dihydroisoquinolines is the Bischler-Napieralski reaction, which involves the cyclization of aryl-ethyl amides by dehydrating agents[2]. Buu-Hoi and co-workers, in their study of α,α-dimethyl - β-aryl-ethylamines found that the corresponding N-acetyl and N-benzoyl derivatives could not be cyclodehydrated to 3,3-dimethyl-3,4-dihydroisoquinolines[2]. Buu-Hoi attributed this failure to steric hindrance, while Prajsnar[3] explained it as the result of a reverse Ritter reaction. Based on our studies of nitrilium ion intermediates as a method of introducing nitrogen functions into organic molecules[3], we have developed a method of synthesis of 3,4-dihydroisoquinolines from olefins. This has allowed us to synthesize 3,3-disubstituted-3,4-dihydroisoquinolines, which can not be obtained from the Bischler-Napieralski reaction.

An additional advantage of our method is the functionalization of the 3' position with a halogen substitutent, which should be useful in alkaloid synthesis.

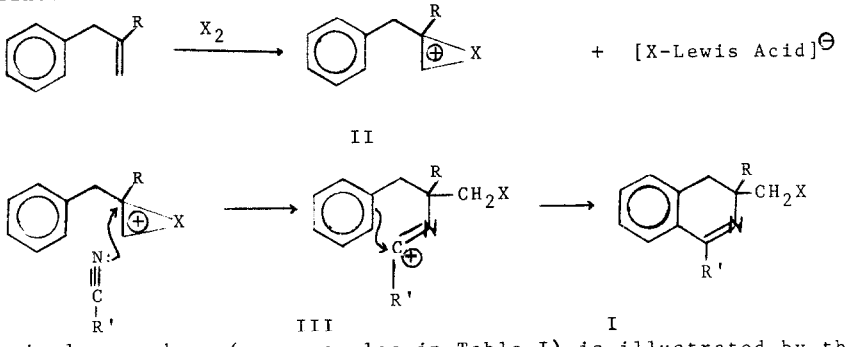
Our method involves the reaction of an olefin with bromine or iodine and a Lewis acid in the presence of a nitrile which also serves as the solvent.



I

A mechanism consistent with our data involves the nucleophilic attack

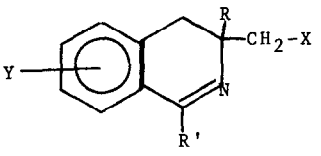
of an olefin on the halogen to give the three-membered ring halonium ion (II). The halide ion is inhibited from further reaction by a Lewis acid complexing agent. This allows the halonium ion to be opened by the nitrile. The resulting nitrilium ion (III) then undergoes ring closure to the 3,4-dihydroisoquinoline.



A typical procedure (see examples in Table I) is illustrated by the preparation of Ia. To 50 ml. of anhydrous acetonitrile previously cooled to -10°C, 3 ml. of stannic chloride (a two fold excess) is added. To the resulting slurry 1.59 g. of (2-methylallyl) benzene (0.012 mole) is added, followed by dropwise addition of 0.6 ml. (0.012 mole) of bromine. Reaction at -10° for 1 hour is followed by standing at room temperature for two days (refluxing for eight hours can sometimes be substituted with little decline in yield). Solvent removal under reduced pressure results in an oil which is dissolved in ether and dilute hydrochloric acid. Neutralization of the acidic solution liberates the 3,4-dihydroisoquinoline Ia which is extracted with ether, washed with water, and dried over magnesium sulfate, yielding 2.18 g. of colorless oil (72%). The infared spectrum (neat) shows absorption at 1631 (C=N), 1575, 1453, 1429, (orthodisubstituted phenyl), and 765, 736, 716, (orthodisubstituted phenyl). The nmr spectrum ($CDCl_3$) shows at τ 2.43-3.04 a H_4 multiplet; an AB system centered at 6.60, J=10 cps., (benzylic H_2); another AB system centered at 7.20, J=16 cps. (H_2); and two methyl singlets at 7.66 and 8.80. The 3,4-dihydroisoquinoline was converted to the picrate (mp 178-180°) for an analytical sample. Correct analytical data for all new compounds have been obtained.

Table I

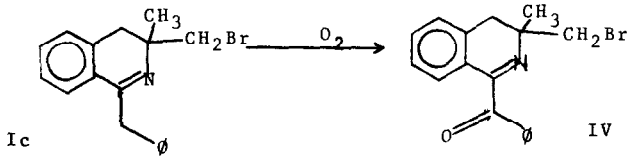
Synthesis of 3-Substituted 3,4-Dihydroisoquinolines



Compound	R	R'	Y	X	% yield
Ia	CH_3	CH_3	H	Br	51[a]
Ia	CH_3	CH_3	H	Br	72[c]
Ib	CH_3	C_6H_5	H	Br	66[b]
Ib	CH_3	C_6H_5	H	Br	37[c]
Ic	CH_3	$C_6H_5CH_2$	H	Br	32[a]
Id	H	CH_3	H	Br	15[b]
Ie	H	CH_3	6,7-OCH_2O-	I[d]	20[c]

a. using one equivalent of aluminum chloride; b. using two equivalents of aluminum chloride; c. using two equivalents of stannic chloride; d. ICl or I_2 can be employed as the halogenation agent.

Unlike in the Bischler-Napieralski reaction, (2-methylallyl) benzene has proved a much more valuable starting olefin than allyl benzene with regard to both yields and purity of basic product. The only other product isolated from the preparation of Ia and Ib is the neutral dibromide, which is easily separated from the basic 3,4-dihydroisoquinoline and from which the olefin can be regenerated. In the preparation of Ic some of the air oxidation product IV is also obtained[6].

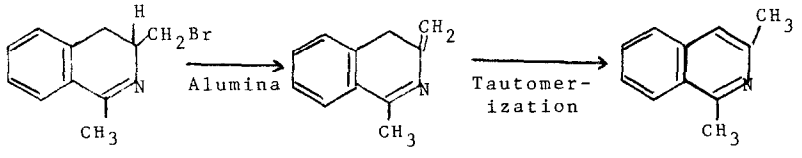


Preparation of Ie from safrole using stannic chloride leads in addition to the 3,4-dihydroisoquinoline Ie (20%), to the iodine monochloride adduct of

safrole and a large amount of a stannic chloride safrole complex. Using aluminum chloride with safrole results in a 16% yield of the 3,4-dihydroisoquinoline Ie, a 65% yield of the ICl adduct, and a smaller amount of aluminum chloride safrole complex.

Stannic chloride has been found to be a superior complexing agent in some cases and is generally much more convient to use than aluminum chloride.

Unambiguous confirmation of the 3,4-dihydroisoquinoline structure has been obtained by converting the 3H,-3,4-dihydroisoquinolines Id and Ie to the aromatic isoquinolines. When an ethereal solution of Id and Ie are passed through a column of alumina, elimination of HX occurs to give the isoquinolines. Under the same conditions, Ia undergoes no reaction, consistent with the folowing mechanism:



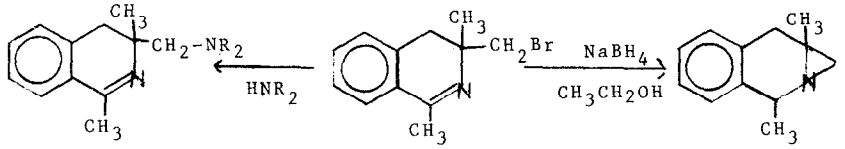
Id
Ie: 6,7-O-CH_2-O-

V

VI
VIII: 6,7-O-CH_2-O-

The melting points of the picrate of VI and free base VIII are indentical with those reported[7,8], and the structures are further substantiated by nmr and i.r. spectra.

Displacement of the halogen function in Ia-c with amines leads to amino substituted dihydroisoquinolines such as IX. The 3' functionality has allowed us to prepare previously unknown systems, such as the fused aziridine X from Ia and sodium borohydride.



IX
NR_2: $N(CH_3)_2$

Ia

X

Expansion of this reaction to other systems, and synthetic investigations of the 3-halomethyl-3,4-dihydroisoquinolines as intermediates to antimalarials and alkaloids are in progress.

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