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REDUCTION OF QUINOLINE AND ISOQUINOLINE WITH SODIUM HYDRIDE

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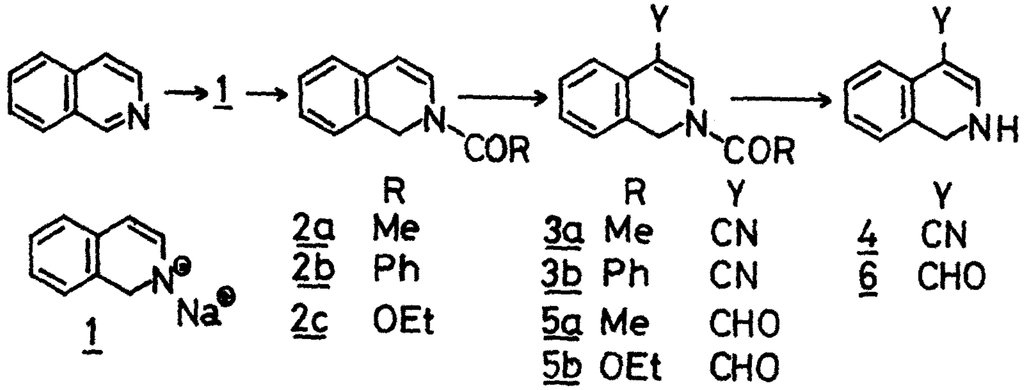
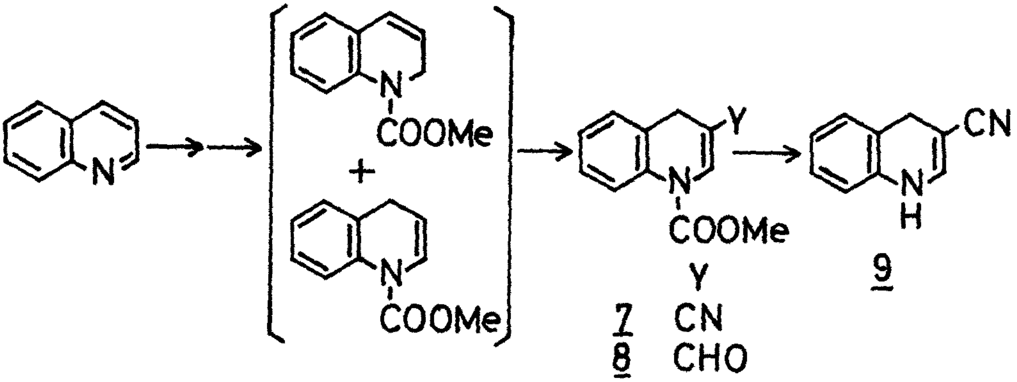
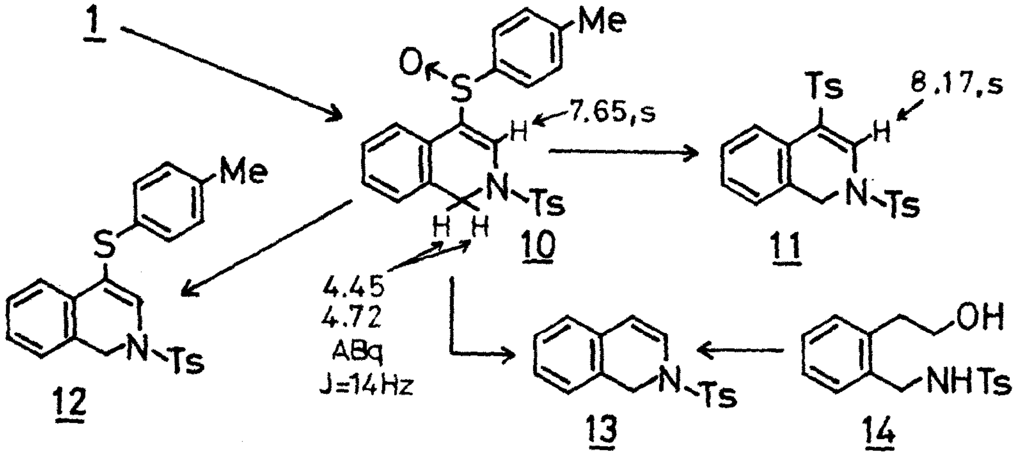
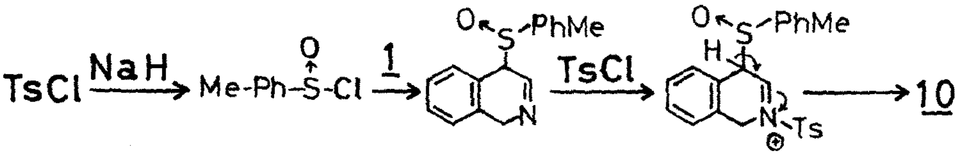
Sodium hydride is highly appreciated as one of very good bases, and reduction with this reagent seldom occurs except in special compounds having a structure of benzyl halides,[1)] non-enolizable carbonyls,[2)] gem-dihalocyclopropanes,[3)] and disulfide[4)] moieties. We wish to report here another instance of this reduction, i.e., NaH reduces aromatic N-heterocycles such as quinoline and isoquinoline in nearly quantitative yield in the medium of a dipolar aprotic solvent, especially in hexamethylphosphoric triamide (HMPT) to afford their NaH adduct. Quenching the adduct in the form of N-acyl derivatives of dihydro-quinoline or -isoquinoline constitutes a facile way to synthesize unstable dihydro-heteroaromatics otherwise hardly accessible.[5)]

Heating of a mixture of isoquinoline and NaH (3-5 molar equivalents) in HMPT at 30-60° for a few hours in nitrogen atmosphere resulted in the formation of a black-green viscous oil. To this was added a benzene solution of acetic anhydride or benzoyl chloride under ice-cooling and 2-acyl-1,2-dihydroisoquinoline, 2a[5)] or 2b,[6)] was isolated as a fairly stable syrup in 77 or 84% yield. Successive treatment of 2a or 2b with chlorosulfonyl isocyanate, followed by dimethylformamide as described in the literature,[7)] gave rise to the expected cyano derivatives, 3a, mp 156.5-157.5°, and 3b, mp 111-111.5°, in respective yields of 50 and 32%. Acyl groups of these compounds could be readily cleaved by warming them with potassium carbonate in aqueous methanol for a short period to obtain the known 4-cyano-1,2-dihydroisoquinoline[8)] in a high yield, and thus, this fact not only verified the structure of 2a and 2b but made it possible to assume the nature of NaH adduct of isoquinoline as a 1,2-dihydro sodium salt such as 1.


1
COR
Y
NH
Na⊕
R
2a Me
2b Ph
2c OEt
R Y
3a Me CN
3b Ph CN
5a Me CHO
5b OEt CHO
Y
4 CN
6 CHO


N
COOMe
+
Y
CN
H
Y
7 CN
8 CHO
9


1
Me
O
S
H
7.65,s
N-Ts
H H
10
4.45
4.72
ABq
J=14Hz
Ts
8.17,s
11
12
13
OH
NHTs
14


TsCl
NaH
Me-Ph-S-Cl
O
1
O←S-PhMe
TsCl
H
N
Ts
⊕
10

The corresponding N-ethoxycarbonyl derivative, 2c, obtained from 1 with ethyl chlorocarbonate, was so unstable that it was treated with the Vilsmeier-Haack reagent to isolate it as 5b, mp 117-119°, in 40.5% yield from isoquinoline. 5b was converted by the above hydrolysis to 6, mp 171.5-172°, which was also synthesized from 2a by the same procedure via 5a (36% yield), and was confirmed to be 4-formyl derivative by transformation to the known isoquinoline-4-carboxylic acid.9)

Quinoline behaved in the same manner against NaH in HMPT and the addition took place both at 2 and 4 positions, since the NMR spectrum of a mixture of N-methoxycarbonyl derivatives obtained in 81.5% yield from quinoline by way of the NaH adduct showed two sets of proton signals ascribable to 1,2- and 1,4-dihydroquinolines in the ratio of 2:3. In order to introduce the cyano or aldehyde function into the dihydroquinoline system, the same reactions as in the case of isoquinoline were applied to the mixture of the N-methoxycarbonyl compounds and 1,4-dihydroquinoline derivatives, 7, mp 94.5-95° (NMR δ ppm in $CDCl_3$: 3.55, br.s, C-4 H; 7.74, t, J=1.0 Hz, C-2 H) and 8, syrup (δ: 3.55, br.s, C-4 H; 7.85, t, J=1.0 Hz, C-2 H), were only obtained in 20 and 22% yields, respectively, calculated from quinoline. The reaction site was confirmed to be the 3 position, because 7 and 8 afforded 3-cyano-1,4-dihydroquinoline,8) 9, (84.5% yield) and quinoline-3-carboxylic acid10) by the afore-mentioned reactions.

The compound having the structure, 10, mp 142.5-143.5°, was the sole isolable substance in 14% yield from isoquinoline when 1 was reacted with tosyl chloride in the presence of an excess of NaH. The sulfoxide character of 10 was proved by its easy transformation either to a ditosyl derivative, 11, mp 167-168°, with m-chloroperbenzoic acid within a few minutes (50% yield) or a sulfide, 12, mp 129-130°, by a partial reduction using an aged Raney nickel (W-2) in hot ethanol (43% yield). A little more active catalyst reduced off the sulfoxide group from 10 to result in the formation of 2-tosyl-1,2-dihydroisoquinoline, 13, mp 121-122° (75% yield), whose structure was rigorously established by its identity with the oxidation product of the reported substance, 14,11) with dicyclohexylcarbodiimide-dimethyl sulfoxide12) or chromium trioxide-pyridine complex. The above fact, together with the NMR spectral data of 10 and 11, clearly demonstrated that the sulfoxide group had been substituted in 13 from the sulfur atom at 3 or 4 position and the structure, 10, was assumed to be the only choice by the mechanistic consideration as illustrated in the Chart.

It can be emphasized here that the present finding not only enlarges the collection of examples with respect to the NaH reduction, but also provides a useful and simple synthetic method for the preparation of the compounds possessing an interesting functionality, i.e., 5 and 8, and these can now converted into various kinds of substances by elongation of their side chains from the aldehyde group. Studies on this line are in progress and will be published in the near future.

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