2-Substituted 1,2,3,4-Tetrahydroquinolines from Quinoline

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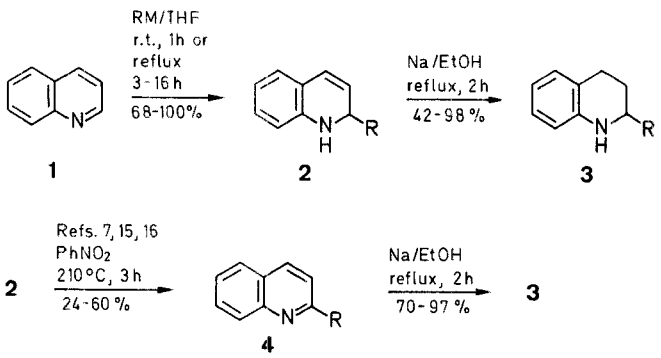
The addition of various organometallic reagents to quinoline occurred solely at the 2-position of the heteroaromatic ring. The resultant 2-substituted 1,2-dihydroquinolines were then easily reduced with sodium in ethanol to the 1,2,3,4-tetrahydro species. The overall transformation of quinoline to 2-substituted 1,2,3,4-tetrahydroquinolines was found to be favorable to the previous literature conditions, which required an intermediate oxidative step. The yields for the last step ranged from 42–98% but were generally greater than 80%.

We desired an efficient entry into the 2-substituted 1,2,3,4-tetrahydroquinoline[1,2] system which would allow for a wide variety of substituents at the 2-position. Several examples of these compounds exist in the literature,[3–16] and while the synthetic routes used to prepare them have their individual merits, they were, in general either too lengthy or too narrow in scope for our purposes. Because of both the ready availability and the ease of chemical manipulation, we judged quinoline to be the starting material of choice for our synthetic efforts. In support of this, the addition of organometallic reagents to quinoline (**1**) in a 1,2-fashion is well precedented[1,2,7] (Scheme), and the resulting 1,2-dihydroquinolines **2** are quite easy to manipulate. An oxidative work-up, or an additional oxidative step gives the corresponding 2-substituted quinolines **4**. The formation of 2-substituted 1,2,3,4-tetrahydroquinolines **3** may be effected by the reduction of the aromatic species or its *N*-alkyl salt with metals,[1,2,7] H_2,[1,2,8–10] or hydride.[1,2,9,11] Additionally, the intermediate 1,2-dihydroquinolines may disproportionate to a mixture of the fully aromatic system and the tetrahydro compound.[12] The only instances of direct reduction of the dihydro to the tetrahydro species involve cases of 2,2-disubstituted substrates.[13,14]



2–4	R	2–4	R
a	*n*-Bu	**e**	Ph
b	*s*-Bu	**f**	2-MeC_6H_4
c	*t*-Bu	**g**	4-MeC_6H_4
d	*c*-C_6H_{11}	**h**	$PhCH_2$

We prepared 2-phenyl-1,2-dihydroquinoline (**2e**) via Oldham and Johns' procedure[7] and oxidized this to the aromatic species with nitrobenzene[7,15,16] to give a 54% yield of 2-phenylquinoline. Although sodium bis(2-methoxyethoxy)aluminum hydride/BH_3[11] failed to give any of the desired tetrahydro compound, sodium in refluxing ethanol successfully afforded the expected[7] 2-phenyl-1,2,3,4-tetrahydroquinoline (**3e**) in 97% yield.

Table. Addition of Organometallic Reagents to Quinoline and Subsequent Sodium Reduction to **3**

Entry	RM	Temp./ Time (h)	Yield **2**[a] (%)	Yield **3**[b] (%)	bp (°C) Torr	Lit. bp (°C)/Torr or Molecular Formula	**3**·HCl mp (°C)[c]	^{1}H-NMR ($CDCl_3$) H-2 δ, J(Hz)
3a	*n*-BuLi	r.t./1	97	96		145–146/11[7]	198–200	3.23 (ddt, J = 3.0, 6.4, 16)
3b	*s*-BuLi	r.t./1	quant.	98		$C_{13}H_{19}N$ (189.3)	150–153	3.23 (ddd, J = 2.8, 5.6, 10)
3c	*t*-BuLi	r.t./1	quant.	89	110/2.5	$C_{13}H_{19}N$ (189.3)	194–196	3.05 (dd, J = 2.6, 11)
3d	*c*-$C_6H_{11}Li$	reflux/3	75	42[d]		314–315[8]	226–229	3.06 (ddd, J = 3.0, 6.3, 9.6)
3e	PhLi	r.t./1	68	86	176/2	196/8[7]	219–222	4.45 (dd, J = 3.4, 9.2)
	PhMgBr	reflux/16	quant.	55				
3f	2-MeC_6H_4MgBr	reflux/12	92	82		200–202/6[7]	221–223	4.71 (dd, J = 3.0, 9.0)
3g	4-MeC_6H_4MgBr	reflux/12	94	82[e]	140/0.8	210/14[7]	225 (dec)	4.50 (dd, J = 3.3, 9.2)
3h	$PhCH_2MgCl$	r.t./1	quant.	43	180/1.5	$C_{16}H_{17}N$ (223.3)	187–190	3.52 (m)

[a] Yield of isolated but unpurified **2**.
[b] Yield of isolated **3** found to be >95% pure as judged by ^{1}H-NMR.
[c] Satisfactory microanalyses obtained: C ±0.21, H ±0.11, N ±0.33.
[d] Purification via chromatography on silica gel with EtOAc/hexanes (1:9).
[e] HRMS for $C_{16}H_{17}N$, calc.: 223.1361, found: 223.1344.

Although the overall yield for this sequence was an acceptable 52%, we were bothered by the need for a two-electron oxidation followed by a four-electron reduction. Ideally the reduction should be done at the dihydroquinoline stage, thus eliminating the low yield and aesthetically unpleasing extra step. To this end, recrystallized 2-phenyl-1,2-dihydroquinoline was subjected to a reduction with sodium in ethanol (see General Procedure) to afford the tetrahydro species in 86% yield.

The overall yield in this sequence (59%) compared favorably to the oxidation–reduction scenario while eliminating a step. From a mechanistic viewpoint, the four-electron reduction of the quinoline may well proceed through the dihydro species, although we have not confirmed this. Indeed, when the two-step reaction sequence was applied using benzyl magnesium chloride, the overall yield of 2-benzyl-1,2,3,4-tetrahydroquinoline was 43%, in contrast with 16% for the three-step procedure.

As can be seen in the Table, the reaction appears to be general for alkyl- and aryllithium and Grignard reagents. The more hindered and less nucleophilic reagents tend to give overall lower yields of the desired 2-substituted tetrahydroquinolines.

In summary, 2-substituted 1,2-dihydroquinolines were easily reduced with sodium in ethanol to the 1,2,3,4-tetrahydro species. The yield of tetrahydro compound was usually higher via this direct reduction than from an oxidation-reduction[7] scenario.

^{1}H-NMR spectra were recorded on a Bruker WM-250 instrument with $CDCl_3$ utilized as internal standard and deuterium lock. Chemical shifts are reported in ppm. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. Low resolution and high resolution mass spectra were obtained on Finnigan 4510 and AEI MS-30 instruments, respectively. Melting points are uncorrected and determined in open capillaries. Combustion analyses were performed by the Analytical Department of Pfizer, Inc. Solvents and reagents were used as obtained from commercial sources except THF, which was distilled from sodium benzophenone ketyl.

1,2,3,4-Tetrahydroquinolines 3; General Procedure:

To a solution (0°C) of the commercial organometallic reagent (47 mmol, 1–3 M in Et_2O or hydrocarbon solvent, 19–47 mL) is added dropwise a solution of quinoline (6.0 g, 47 mmol) in THF (20 mL). After allowing the reaction to proceed for the time indicated (Table), it is quenched by pouring into H_2O (200 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers are dried (K_2CO_3), filtered, and concentrated to give the 2-substituted 1,2-dihydroquinoline **2**, which is used directly in the next step.

A 0.25 M solution of **2** in abs. EtOH (200 mL) is heated to reflux and, over the period of 1 h, Na (18 equiv) is added portionwise. After refluxing for an additional hour, the thick reaction mixture is allowed to cool to r.t. and poured into H_2O (500 mL). The aqueous solution is extracted with Et_2O (3 × 100 mL), and the combined organic layers are dried (K_2CO_3), filtered, and concentrated to afford **3**. Compounds produced in this manner frequently contain no impurities as judged by TLC and high field ^{1}H-NMR; however, additional purification can be accomplished by bulb-to-bulb distillation or silica gel chromatography. Hydrochloride salts are formed by passing HCl gas into solution of the amine **3** in Et_2O (25 mL) and collecting the precipitate by vacuum filtration. These are then recrystallized from *i*-PrOH. Yields, spectral data, and HCl salt melting points are in the Table.

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