AN ALTERNATIVE PROCEDURE FOR THE PREPARATION OF 4-BENZYLISOQUINOLINES FROM ISOQUINOLINE[1]

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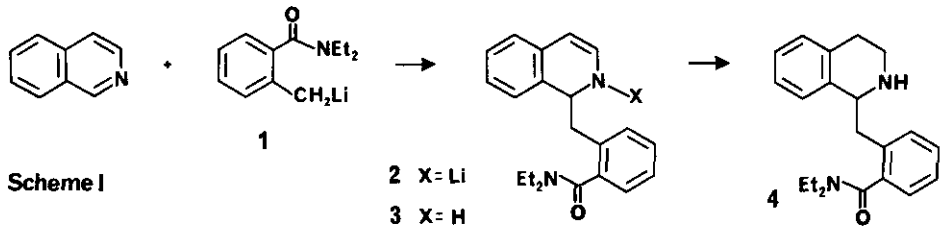
Abstract - Addition of lithiated *N,N*-diethyl-*o*-toluamide to isoquinoline gave an adduct which was treated with benzyl chlorides to afford 4-benzylisoquinolines in yields of 60-78%.

Isoquinoline has been converted to 4-benzylisoquinoline by heating with benzyl alcohol and potassium hydroxide.[2,3] While investigating the addition of lithiated *N,N*-diethyl-*o*-toluamide (1) to isoquinoline, we found an alternative procedure for the introduction of benzyl and substituted benzyl groups into the 4-position of isoquinoline which proceeds under considerably milder conditions than the original procedure.

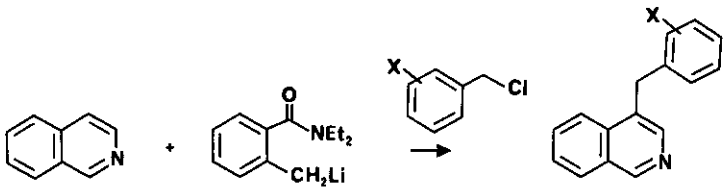
We have previously demonstrated that addition of lithio species 1 to 3,4-dihydroisoquinolines directly afforded fused tetracyclic products with the berbane skeleton.[4] However, addition of 1 to isoquinoline proceeded *smoothly at -70°C to afford an adduct (2) which did not ring close upon* warming to room temperature. Workup afforded the unstable 1,2-dihydroisoquinoline 3[5] which was reduced with sodium borohydride in ethanol to give 4[6,7] in 84% overall yield (Scheme I).



Scheme I

Treatment of the presumed lithio species **2** with benzyl chloride at -70°C followed by warming to room temperature gave 4-benzylisoquinoline (**5a**) as the major basic product in 78% yield. *N,N*-diethyl-*o*-toluamide was recovered in greater than 75% yield as the major neutral product. Application to other substituted benzyl chlorides gave products **5b-e** in yields of 60-73% (Table).

Table: 4-Benzylisoquinolines from Isoquinoline



1 **5a-e**

X	Product[6]	Yield (%)[a]	mp (°C)	mp, HCl Salt (°C)[b]
H	5a	78	116-117[c]	210-212
3-OCH_3	5b	60	oil	185-186
4-OCH_3	5c	68	76-77	207-208
2-CH_3	5d	65	oil	235-236
4-*t*-Butyl	5e	73	135-136	238-240

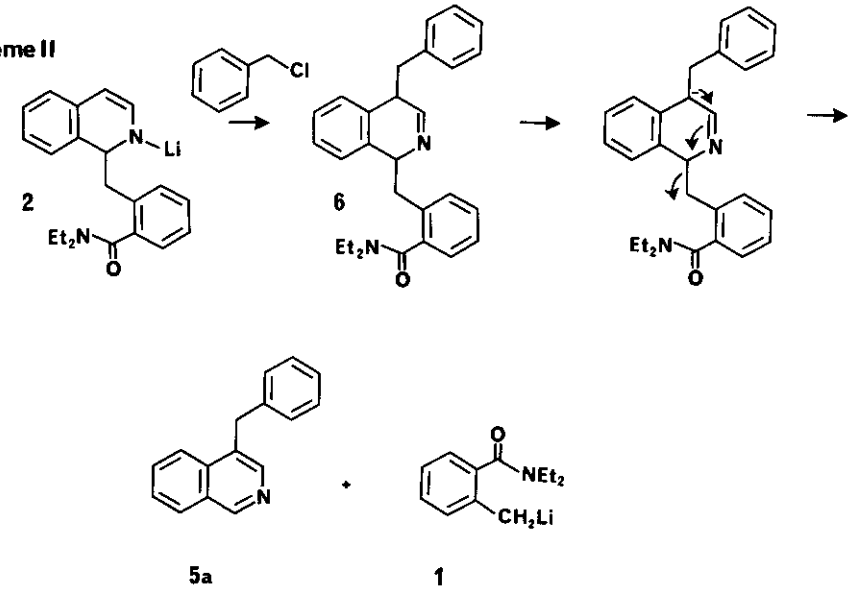
a) Compounds **5a** and **5e** were purified by medium pressure chromatography (silica gel, ethyl acetate/hexane). Compounds **5b-d** were purified by silica gel chromatography (4% methanol/ dichloromethane).

b) Crystallized from ethanol/ether.

c) Lit. mp 119-120°C (reference 2).

The formation of the observed products can be rationalized by benzylation of lithio species 2 in the 4-position to give an adduct 6 which eliminates anion 1 under the basic reaction conditions (Scheme II). The anion 1 so regenerated can serve to (catalytically) deprotonate 6 to continue the cycle.

Scheme II



The relative instability of presumed adduct 6, as opposed to the stable adduct 2, cannot presently be explained. Other electrophiles (e.g. methyl iodide, n-butyl iodide) appear to add to 2 in the 4-position but give product mixtures which do not contain 4-substituted isoquinolines (^{1}H nmr analyses). Further investigation will be required to clarify these points. However, it is clear that this procedure represents a preparatively useful synthesis of 4-benzylisoquinolines which proceeds under milder conditions than the classical benzyl alcohol-potassium hydroxide method.[2]

A typical experimental procedure is as follows. **4-Benzylisoquinoline (5a).** *n*-BuLi (6.25 ml of 1.6 M in hexane, 10 mmol) was added to a -70°C solution of diisopropylamine (1.7 ml, 12 mmol) in 35 ml of THF. A solution of *N,N*-diethyl-*o*-toluamide (1.91 g, 10 mmol) in 3 ml of THF was added to give a deep purple solution of anion 1. A solution of isoquinoline (1.4 g, 11 mmol) in 3 ml of THF was added dropwise to give a faint pink solution which was then treated with benzyl chloride (1.26 g, 10 mmol) and allowed to warm to room

temperature. The mixture was poured into 5% aqueous HCl and washed with ether. Evaporation of the dried (Na_2SO_4) ether extract gave 1.7 g of an oil which by tlc (50% ethyl acetate-hexane) and ^1H nmr analyses was mostly recovered *N,N*-diethyl-*o*-toluamide. The aqueous acidic layer was basified with NH_4OH and extracted with ethyl acetate to afford a crystalline residue which by tlc analysis (50% ethyl acetate-hexane) was mostly 5a with a small amount of isoquinoline. Medium pressure silica gel chromatography (30% ethyl acetate-hexane) afforded 1.7 g (78%) of 4-benzylisoquinoline, mp 117-118°C (lit.[2] 119-120°C). ^1H nmr ($CDCl_3$) 9.08 (*s*, 1 H, H-1), 8.32 (*s*, 1 H, H-3), 7.86 (dd, 1 H, J = 7.5, 1 Hz, H-8), 7.82 (dd, 1 H, J = 7.8, 1 Hz, H-5), 7.54 (*m*, 1 H, H-6), 7.46 (*m*, 1 H, H-7), 7.10 (*m*, 5 H), 4.30 (*s*, 2 H). Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.97; N, 6.39. Found: C, 87.57; H, 5.87; N, 6.26.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Contribution no. 747 from the Institute of Organic Chemistry.
2. M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, 1956, 78, 4090.
3. For other syntheses of 4-benzylisoquinolines see the following references: from ß-benzylphenylethylamine, J. von Braun, O. Bayer, and L. Cassel, *Ber.*, 1927, 60, 2602; from 1,2,3,4-tetrahydroisoquinoline and benzaldehyde, W.D. Burrows and E.P. Burrows, *J. Org. Chem.*, 1963, 28, 1180; from 1,2-dihydroisoquinolines and benzaldehyde, J.M. Bobbitt, D.P. Winter, and J.M. Kiely, *J. Org. Chem.*, 1965, 30, 2459.
4. R.D. Clark, *Heterocycles*, 1985, 23, 825.
5. The ^1H nmr spectrum was in accord with this structure. The compound rapidly decomposed upon standing at room temperature.
6. Satisfactory elemental analyses and ^1H nmr spectra consistent with the assigned structures were obtained for all new compounds.
7. Compound 4: oil; HCl salt, mp 206-207°C (EtOH-Et_2O).

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