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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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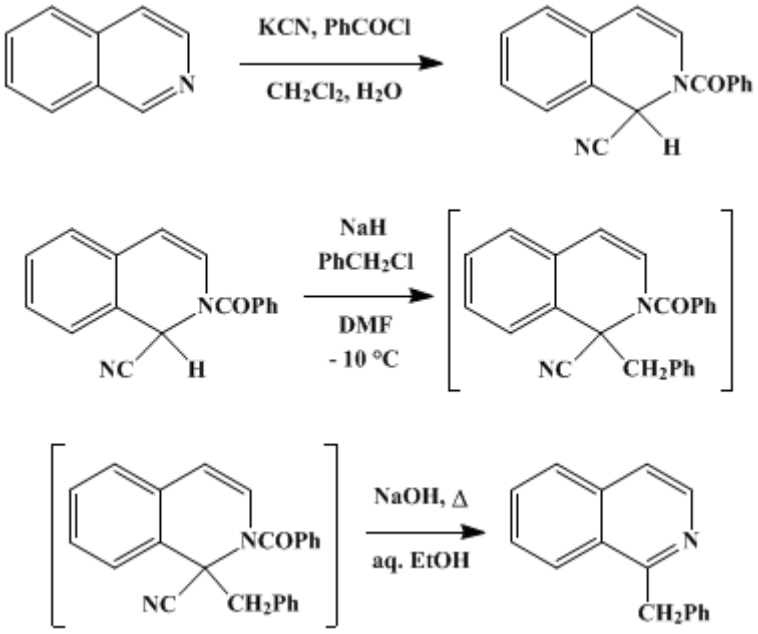
ALKYLATION OF ISOQUINOLINES *via* 2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILES: 1-BENZYLISOQUINOLINE

[Isoquinoline, 1-(phenylmethyl)-]



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1. Procedure

Caution! This reaction involves highly toxic cyanide salts. It may be carried out safely, however, if prudent laboratory procedures are practiced. In particular, cyanide residues should be collected and disposed of separately (Note 1), and the entire sequence should be performed in an efficient hood.

A. *2-Benzoyl-1,2-dihydroisoquinaldonitrile*. A 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a 250-ml., pressure-equalizing dropping funnel is charged with 64.6 g. (0.499 mole) of freshly distilled isoquinoline (Note 2) in 400 ml. of dichloromethane and 97.7 g. (1.50 moles) of potassium cyanide (Note 2) in 200 ml. of water. The mixture is stirred vigorously as 126.5 g. (121 ml., 0.900 mole) of freshly distilled benzoyl chloride is added from the dropping funnel over 1 hour. As the addition proceeds, the temperature rises to 38°, and the dichloromethane comes to reflux. Stirring is continued for an additional 3 hours, and the resulting brown reaction mixture is filtered through 20 g. of Dicalite Speedex. After the insoluble material has been washed with 200 ml. of water and 200 ml. of dichloromethane, the filtrate and washings are transferred to a separatory funnel. The layers are separated (Note 1) and (Note 3), and the dichloromethane layer is washed successively with 300 ml. of water, three 200-ml. portions of 2 *N* hydrochloric acid, 200 ml. of water, three 200-ml. portions of aqueous 2 *N* sodium hydroxide, and 200 ml. of water (Note 1). After drying over anhydrous potassium carbonate, the dichloromethane solution is filtered and evaporated under reduced pressure, giving 108–110 g. of a pale brown solid. This crude product is dissolved in 200 ml. of boiling ethyl acetate, filtered, and set aside to cool. On standing, the Reissert compound crystallizes as cream rhombs, which are collected on a Büchner funnel and dried in a vacuum desiccator, giving 89.9 g. (69%) of 2-benzoyl-1,2-dihydroisoquinaldonitrile, m.p. 125–127° (Note 4) and (Note 5).

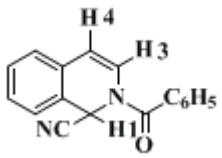
B. 1-*Benzylisoquinoline*. An 11.4-g. portion of 55% sodium hydride–mineral oil dispersion (Note 6) is washed free of oil by slurrying with two 40-ml. portions of dry hexane (Note 7) and decanting the liquid. The sodium hydride is transferred to a dry, 2-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a 500-ml., pressure-equalizing dropping funnel, and a nitrogen-inlet tube (Note 8). A slurry formed by adding 200 ml. of *N,N*-dimethylformamide (Note 9) is cooled to −10° with a methanol-ice bath. Stirring is begun, and a solution of 65.0 g. (0.250 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile and 32 g. (29 ml., 0.25 mole) of benzyl chloride in 400 ml. of dry *N,N*-dimethylformamide is added dropwise over 1 hour. During addition the reaction mixture becomes dark, then fades to light brown. Ice is added as required to hold the bath temperature near −10° (Note 10).

When the addition is complete, the reaction mixture is stirred overnight at room temperature, maintaining a nitrogen atmosphere. Excess sodium hydride is destroyed by slow addition of 10 ml. of water. The *N,N*-dimethylformamide is evaporated at 40° (0.01 mm.), and the residue is diluted with 800 ml. of toluene and 800 ml. of water. After thorough shaking, the mixture is transferred to a separatory funnel. The aqueous layer is discarded, and the toluene layer is washed with two 200-ml. portions of water, dried over anhydrous potassium carbonate, and filtered. Removal of toluene under reduced pressure leaves a yellow oil, which crystallizes on standing (Note 11).

This material is dissolved in 500 ml. of ethanol and transferred to a 2-l., round-bottomed flask. A solution of 200 g. of sodium hydroxide in 200 ml. of water is added, and the mixtured is refluxed for 2 hours. Ethanol is then removed by distillation, and the residue is shaken with 500 ml. of water and 800 ml. of toluene. The toluene layer is separated, washed with two 200-ml. portions of water, and then vigorously shaken with 600 ml. of 2 *N* hydrochloric acid. A portion of the 1-benzylisoquinoline hydrochloride precipitates at this point and is collected on a Büchner funnel and washed with 200-ml. portions of water and toluene. The filtrate is then transferred to a separatory funnel, the acidic layer is separated, and the crystals from the Büchner funnel are suspended in this layer. After basifying the suspension with 50% aqueous sodium hydroxide, the oil that separates is extracted with three 200-ml. portions of dichloromethane. The combined dichloromethane layers are dried over anhydrous potassium carbonate, filtered, and evaporated under reduced pressure, leaving the crude product as a yellow oil. Distillation under reduced pressure yields 49.8 g. (91%) of pure 1-benzylisoquinoline as a pale yellow oil, b.p. 145–150° (0.01 mm.). The product solidifies on standing and may be crystallized from chloroform–hexane, giving colorless prisms, m.p. 54–55° (Note 12).

2. Notes

1. The original aqueous layer and the aqueous washings of the dichloromethane layer contain cyanide residues. These should be destroyed prior to disposal by making the solution strongly basic with sodium hydroxide and then adding, with stirring, a large excess of iron(II) sulfate. The resulting suspension should be boiled for several hours in the hood before disposal. This process converts cyanide to the nontoxic Prussian Blue [iron(III) ferrocyanide], which precipitates.
2. This product is supplied by Fluka AG, Buchs, Switzerland.
3. Any precipitate occurring during the washing procedure was removed by filtration through a small amount of Dicalite Speedex, obtained from Chemische Fabrik Schweizerhalle, Switzerland.
4. A further fraction of less pure material can be obtained by evaporating the filtrate to approximately 50 ml. and refrigerating the solution overnight.
5. The literature[3] gives m.p. 124–126°. IR (KBr)cm.$^{-1}$: 2240 very weak (-C≡N), 1658 strong (C=O), 1632 strong (C=C-N); ^{1}H NMR (8% w/w in $CDCl_3$, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 6.06 (d, $J_{3,4}$ = 7.8, 1H, H_4), 6.57 (broad s, 1H, H_1), 6.60 (d of d, $J_{3,4}$ = 7.8 and $J_{1,3}$ = 1, 1H, H_3), 7.0–7.7 (m, 9H, aromatic C*H*).



6. This product is supplied by Fluka AG, Buchs, Switzerland. The amount of dispersion used should provide 6.25 g. (0.260 mole) of pure sodium hydride. A small molar excess is used to allow for

variation in the sodium hydride: oil ratio of commercial material.
7. The hexane was dried by filtration through alumina.
8. The apparatus was dried in an oven and assembled hot under a stream of dry, oxygen-free nitrogen. A nitrogen atmosphere was maintained throughout the reaction, since oxygen reacts with the Reissert anion, giving 1-cyanoisoquinoline.[4] Commercial nitrogen was dried by bubbling through concentrated sulfuric acid and found to be sufficiently oxygen-free, requiring no special treatment.
9. *N,N*-Dimethylformamide was purchased from Merck, Darmstadt and dried over molecular sieves (Union Carbide, type 4A).
10. It is necessary to hold the reaction temperature below −5° in order to prevent 1,2-rearrangement of the Reissert anion to 1-benzoylisoquinoline.[5]
11. The intermediate 1-benzyl-2-benzoyl-1,2-dihydroisoquinaldonitrile can be crystallized from ethyl acetate–hexane, m.p. 130–131°. The compound has been described as an oil[5,6] and as a crystalline product, m.p. 129°.[7] IR (KBr) cm.$^{-1}$: 2236 weak (C≡N), 1669 strong (C=O), 1641 strong (C=C-N); ^{1}H NMR 8% w/w in $CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.48 and 3.78 (AB qtr, *J* = 13, 2H, $C_6H_5CH_2$), 5.54 (d, *J* = 8, 1H, H_4), 6.37 (d, *J* = 8, 1H, H_3), 6.75–7.8 (m, 14H, aromatic C*H*). Analysis calculated for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.08; H, 5.29; N, 7.89.
12. The literature gives m.p. 56°[8] IR (KBr) cm.$^{-1}$: 1621, 1601, 1585, 1560, 1500, 1493; ^{1}H (8% w/w in $CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 4.66 (s, 2H, CH_2), 7.1–8.25 (m, 10H, aromatic C*H*), 8.5 (d, *J* = 6, 1H, H_3).

3. Discussion

Other methods for the synthesis of 1-benzylisoquinolines include: (a) dehydrogenation of 1-benzyl-3,4-dihydroisoquinolines,[9,10] which in turn are produced in the BischlerNapieralski reaction by heating *N*-phenylacetyl-β-phenylethylamines with a dehydrating agent such as phosphorus pentoxide in xylene,[9,10] (b) the Pictet-Gams modification of (a), in which *N*-phenylacetyl-2-hydroxy-2-phenylethylamines are dehydrated with phorphorus pentoxide,[8,10,11,12] (c) thermal rearrangements of *N*-benzylisoquinolinium chlorides in the presence of copper,[13] and (d) addition of benzylmagnesium chloride to isoquinolines.[14] The first two methods are limited in scope by the accessibility of starting materials and the requirement that the aromatic ring carry an electron-donating substituent *para* to the point of closure for reasonable yields. The last two methods often lead to mixtures and have not been shown to be of general applicability.

The Reissert method[15]—conversion of an isoquinoline to a 2-benzoyl-1,2-dihydroisoquinaldonitrile (Reissert compound), alkylation, and hydrolysis—has enjoyed wide success in the synthesis of benzylisoquinoline and related alkaloids.[16,17] In particular, aporphines are prepared conveniently by converting isoquinolines to 1-(o-nitrobenzyl)-isoquinolines *via* a Reissert sequence, followed by *N*-alkylation, reduction, and Pschorr cyclization.[17]

The present procedure illustrates two recent and highly useful modifications of the Reissert method. First, the Reissert compound is formed by the two-phase method of Popp and Blount.[18] This modification generally gives much higher yields for isoquinolines[19] and quinolines[20] than does the single (aqueous) phase method used previously,[21] succeeding in many cases where the aqueous method fails altogether. The aqueous method is generally less clean and has the disadvantage that both starting material and product are insoluble in water. A nonaqueous benzene–hydrogen cyanide method[22] has also been used for Reissert compound formation, but it has the obvious drawbacks associated with the use of hydrogen cyanide. Second, the Reissert anion is formed with sodium hydride–*N,N*-dimethylformamide. This modification, developed by the submitters[23] and independently by Popp and Wefer,[6,24] has several advantages over the earlier reagent, phenyllithium in ether,[5,21] in that the sodium hydride does not have to be specially prepared, and its strength is known without titration; cessation of hydrogen evolution indicates that carbanion generation is complete; and the use of *N,N*-dimethylformamide overcomes solubility problems often encountered because of the ether used in the earlier method.

It has been observed[25,26] that in lower yielding syntheses of Reissert compounds improvements can be obtained by the inclusion of a phase transfer catalyst such as benzyltrimethylammonium chloride, in

1–3% quantities by weight with respect to the weight of potassium cyanide. For example, methyl 1-cyano-1,2-dihydoisoquinoline-2-carboxylate forms in 69% yield in the presence of benzyltrimethylammonium chloride, but in only 24% in its absence.[25]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

1-benzylisoquinolines

1-benzyl-3,4-dihydroisoquinolines

N-phenylacetyl-β-phenylethylamines

N-phenylacetyl-2-hydroxy-2-phenylethylamines

phorphorus pentoxide

N-benzylisoquinolinium chlorides

isoquinolines

1-(o-nitrobenzyl)-isoquinolines

methyl 1-cyano-1,2-dihydoisoquinoline-2-carboxylate

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

hydrogen cyanide (74-90-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

iron(II) sulfate (13463-43-9)

copper (7440-50-8)

benzoyl chloride (98-88-4)

toluene (108-88-3)

benzyl chloride (100-44-7)

benzylmagnesium chloride (6921-34-2)

xylene (106-42-3)

dichloromethane (75-09-2)

Phenyllithium (591-51-5)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

hexane (110-54-3)

benzyltrimethylammonium chloride (56-93-9)

isoquinoline (119-65-3)

2-Benzoyl-1,2-dihydroisoquinaldonitrile (844-25-7)

1-Benzylisoquinoline,
Isoquinoline, 1-(phenylmethyl)-,
benzylisoquinoline (6907-59-1)

1-cyanoisoquinoline (1198-30-7)

1-benzylisoquinoline hydrochloride

iron(III) ferrocyanide

1-benzoylisoquinoline (16576-23-1)

phosphorus pentoxide (1314-56-3)

1-benzyl-2-benzoyl-1,2-dihydroisoquinaldonitrile