

Howard Sard

Organix, Inc., 65 Cummings Park,
Woburn, MA 01801

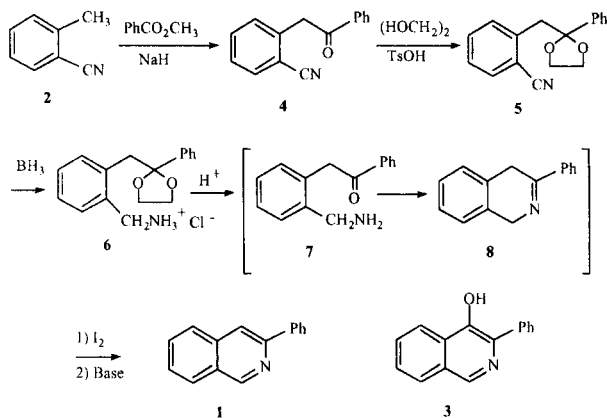
Received January 14, 1994

During repetition of the Bradsher procedure for the preparation of 3-phenylisoquinoline (**1**), an unexpected by-product was isolated, 4-hydroxy-3-phenylisoquinoline (**3**). This product is likely formed *via* allylic oxidation of a 1,4-dihydroisoquinoline intermediate. By minor modification of the reaction conditions, **3** can be obtained in up to 50% yield. This represents a much improved method for the preparation of **3**, as compared with previously reported syntheses.

J. Heterocyclic Chem., **31**, 1085 (1994).

We recently required the preparation of 3-phenylisoquinoline (**1**) as a synthetic intermediate. An efficient route to **1** has been reported by Bradsher and Willis [1], starting from *o*-methyltoluonitrile (**2**) (Scheme 1). Upon repetition and minor modification of this sequence, we have found that 4-hydroxy-3-phenylisoquinoline (**3**) can instead be isolated as the major product.

Scheme 1



Preparation of the ketal **6** was carried out essentially as described [1]. The reaction of **2** and methyl benzoate, with sodium hydride in glyme gave, after overnight reflux, nearly pure ketonitrile **4**, mp 104-110°. One recrystallization from ethanol gave pure **4**, homogeneous on tlc, mp 112-114° (lit [1] mp 110.5-111.5°), in 50% yield [2].

Ketalization of **4** was carried out with ethylene glycol and *p*-toluenesulfonic acid in benzene at reflux overnight. A nearly quantitative yield of crude **5** was obtained, however it was inevitably contaminated with about 10-15% (by nmr) of starting **4**. Substitution of toluene for benzene did not change the amount of **4** present. In our hands **4** could not be removed from crude **5** *via* crystallization from ethanol, in contrast to the published report [1]. However, purification was readily effected by flash chromatography on silica gel (elution with ethyl acetate/hexanes) to afford pure **5**, homogeneous on tlc, mp 103-105° (lit [1] mp 103°), in 55% yield [3].

The reduction of **5** was carried out in 1 *M* borane/tetrahydrofuran at 25° for 2 days, following the published procedure [1]. Addition of ethereal hydrogen chloride to the crude free base of **6** proved to be optimal for isolation of the hydrochloride salt (62% yield). The ^1H nmr and analytical data for samples of **6** obtained in this manner correlated closely with the published data [1]. However, the melting point for **6** ranged from 140° to 189° for different preparations (lit [1] mp 189-190.5°). This variation in melting behavior may be due to a difference in crystallization solvent, as the published procedure used ethanolic hydrogen chloride for preparation of **6** from the free base [1].

Deketalization and cyclization of **6** was then examined, under the published conditions [1]. Brief heating of a mixture of **6**, methanol, and dilute hydrochloric acid at reflux gave a crude product which was expected to be a mixture of the 1,4-dihydro compound **8**, and its 1,2-dihydro derivative, as described by Bradsher and Willis [1]. Concentration to remove methanol, followed by addition of a dilute sodium hydroxide solution then gave precipitation of a yellow solid. The chloroform extract from this mixture was treated with iodine, to effect dehydrogenation to **1**. Analysis (^1H nmr) of the crude reaction product showed the expected singlet for H_1 of **1** at *ca.* 9.3 ppm [1], in addition, however, another singlet at *ca.* 8.9 ppm was present which was not from **1**. Analysis by tlc also suggested the presence of two major components.

Purification by flash chromatography of this mixture afforded first the expected 3-phenylisoquinoline (**1**) as white crystals, mp 101-102° in 52% yield from **6** (lit [1] mp 102.5-103.5°, 70% yield reported). The slower-eluting component was isolated in 21% yield as a crystalline yellow solid, mp 158-159.5°; ^1H nmr (deuteriochloroform): δ 8.86 (s, 1H), 8.22 (dd, 1H, $J = 2, 8$), 7.39-7.91 (m, 8H), 6.40 (br s, 1H). Elemental analysis of this material provided an empirical formula of $\text{C}_{15}\text{H}_{11}\text{NO}$ which corresponds to addition to **1** of one oxygen atom. An examination of mp and nmr spectral data reported for 3-phenylisoquinoline 2-oxide [4] and 1-hydroxy-3-phenylisoquinoline [5] conclu-

sively ruled out these possible structures. However, a comparison of published data for 4-hydroxy-3-phenylisoquinoline (**3**) [6] proved confirmatory. We suspected that allylic oxidation of the 1,4-dihydro derivative **8** was likely responsible for the formation of **3** [7]. Compound **8** has been postulated as an intermediate in the formation of **3** during the flash vacuum pyrolysis of 1-methyl-4,5-diphenyl-1,2,3-triazole [6].

In an attempt to improve the yield of **3** relative to **1**, the effect of a simple modification of the reaction conditions was examined. When iodine treatment was eliminated during preparation of **1**, and the crude product after addition of base was directly purified by flash chromatography, a 50% yield of **3** was obtained, along with 28% of **1**. As the basification step was carried out without the exclusion of oxygen, it seemed likely that the intermediate **8**, in the absence of iodine to promote dehydrogenation to **1**, was being oxidized by oxygen to the 4-keto compound, a tautomer of **3**. To test this hypothesis, another run of the crude reaction mixture, after reflux, was degassed and then treated with a degassed solution of base. Under these conditions, only a 24% yield of **3** was obtained, along with 44% of **1**. Thus, removal of oxygen during the basification plays much the same role as subsequent iodine treatment, to favor formation of **1** over **3**. While both **1** and **3** are already present (by tlc) [8] to some extent immediately upon basification of the reaction mixture, the dihydro intermediate **8** which remains can be converted predominantly to **1** or **3**, depending on the reaction conditions employed.

The new route which has been developed to 4-hydroxy-3-phenylisoquinoline (**3**) is of synthetic, as well as mechanistic interest. Workup without addition of iodine, as described above, affords gram quantities of **3** in 50% yield in a single step from **6**. This represents a significant improvement over the best previously reported preparative route to **3** [6] which requires three steps from **1**, has been reported only on milligram scale, and proceeds in just 16% yield (overall 11% from **6** [9]). Other known routes to **3** are of even less preparative value [10,11].

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus, and are uncorrected. The ^1H nmr spectra were recorded at 100 MHz on a Bruker WP 100SY. Coupling constants are measured in Hertz. Elemental analyses were performed by Atlantic Micro-lab. Thin-layer chromatography was carried out on Baker Si 250F plates. Visualization was accomplished with uv exposure or treatment with phosphomolybdic acid. Flash chromatography was carried out on Baker silica gel (40 m M).

2-(2-Cyanophenyl)-1-phenylethanone (**4**).

A dry round bottom flask equipped with condenser, stirrer, and addition funnel was charged with sodium hydride (103 g, 60% oil dispersion, 2.57 moles) in dry dimethoxyethane (500 ml),

and heated to reflux. *o*-Toluonitrile (**2**) (76.1 g, 650 mmoles) dissolved in 100 ml of dimethoxyethane was added, followed by methyl benzoate (87.5 g, 642 mmoles), also dissolved in 100 ml of dimethoxyethane. The resulting orange suspension was heated at reflux for 20 hours. The next day the reaction mixture was cooled and water (600 ml) added cautiously over 1-2 hours (much foaming). The aqueous phase was extracted several times with ether (250 ml). The combined ether layers were dried (sodium sulfate), filtered, and concentrated to afford 100.1 g of crude **4** as orange crystals (70%), mp 104-110° (lit [1] mp 110.5-111.5°). A portion of this material (81.9 g) was recrystallized from ethanol to give 58.3 g (71%, 50% overall) of pure **4**, homogeneous on tlc, mp 112-114°.

2-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]benzonitrile (**5**).

Ketonitrile **4** (62.6 g, 283 mmoles) was combined with ca. 78 g of ethylene glycol (ca. 1.2 moles) and 0.6 g of *p*-toluenesulfonic acid in 450 ml of benzene in a flask fitted with a Dean-Stark trap, and heated at reflux for 24 hours. Analysis by tlc then showed mostly ketal **5** with a small amount of **4** remaining. The reaction mixture was poured into 800 ml of half saturated sodium bicarbonate and the layers were separated. The organic phase was dried (sodium sulfate), filtered, and concentrated to afford 72.5 g of crude **5** as tan solid (97%). This material was recrystallized from ethanol to afford 61.99 g (83%) of **5**, mp 94-101° (lit [1] mp 103°), still containing about 13% of **4** by nmr. An 11.68 g sample of this material was purified by flash chromatography on 200 g of silica gel eluting with 10% ethyl acetate/hexanes (some crystallization occurred on the column). A total of 7.79 g (67%, 55% overall) of pure **5** was obtained, mp 103-105°, homogeneous on tlc.

2-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]benzylamine Hydrochloride (**6**).

To cyanoketal **5** (7.77 g, 29.5 mmoles) was added 30 ml of 1 *M* diborane in tetrahydrofuran (30 mmoles) and the resulting solution stirred at 25° for 1 day. Another 15 ml of diborane solution was added, and stirring was continued for another 1 day at 25°. The reaction mixture was chilled, and 50 ml of absolute ethanol was added dropwise. Stirring was continued for 1 hour under nitrogen, and then 170 ml of 1 *N* ethereal hydrogen chloride was added. The solution was stored at -30° overnight, and allowed to warm to 25°. The solid that had precipitated was filtered, washing with dry ether. There was obtained 5.58 g (62%) of amine hydrochloride **6**, mp shrinks at 179°, melts at 185-189° (lit [1] mp 189-190.5°); ^1H nmr (dimethyl sulfoxide- d_6): δ 8.1-8.6 (m, 3H), 7.0-7.6 (m, 9H), 3.9-4.2 (m, 2H), 3.6 (s, 4H), 3.25 (s, 2H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{ClNO}_2$: C, 66.77; H, 6.59; Cl, 11.59; N, 4.58. Found: C, 66.53; H, 6.64; Cl, 11.54; N, 4.51.

3-Phenylisoquinoline (**1**) and 4-Hydroxy-3-phenylisoquinoline (**3**).

Amine hydrochloride **6** (5.57 g, 18.3 mmoles) was dissolved in 55 ml of methanol under nitrogen. Concentrated hydrochloric acid (2.8 ml) dissolved in 110 ml of water was then added and the mixture heated at reflux for 10 minutes and then concentrated on a rotary at 40° to remove methanol. The residue was chilled, and 50 ml of 1.5 *N* sodium hydroxide solution was added. The yellow solid that formed was extracted into 150 ml of chloroform. The organic layer was washed with water (2 x 50 ml), and concentrated. The residue was purified by flash chromatography on 21 g of silica gel eluting with 15% ethyl acetate/hexanes, to give first **1**, 1.06 g (28%), mp 99-102.5°. One recrystallization from ethanol

gave mp 102.0-103.7° (lit [1] mp 102.5-103.5°); ¹H nmr (deuteriochloroform): δ 9.35 (s, 1H), 7.3-8.2 (m, 10H).

Later fractions gave 2.03 g (50%) of **3** as a yellow solid, mp 157-159°. The analytical sample was obtained upon recrystallization from benzene, mp 158.0-159.5° (lit [6] mp 159-161°); ¹H nmr (deuteriochloroform): δ 8.86 (s, 1H), 8.22 (dd, 1H, J = 2, 8), 7.39-7.91 (m, 8H), 6.40 (br s, 1H).

Anal. Calcd. for C₁₅H₁₁NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.37; H, 5.01; N, 6.28.

REFERENCES AND NOTES

- [1] C. K. Bradsher and T. G. Willis, *J. Org. Chem.*, **43**, 3817 (1978).
- [2] This crystallization was necessary, for under Dean-Stark conditions crude **4** (mp 104-110°) gave none of the cyanoketal, **5**.
- [3] This purification was also essential, for **5** which contained 10-15% of **4** (mp 94-101°) could not be reduced at all to **6** with borane/tetrahydrofuran.
- [4] 3-Phenylisoquinoline-2-oxide, mp 142-144°; ¹H nmr (deuteriochloroform): δ 8.92 (s, 1H), 7.3-8.0 (m, 10H); T. Sakamoto, Y. Kondo, N. Miura, K. Hayashi and H. Yamanaka, *Heterocycles*, **24**, 2311 (1986).
- [5] 1-Hydroxy-3-phenylisoquinoline (3-phenylisocarbostyryl), mp 198-200°; ¹H nmr (deuteriochloroform): δ 10.7 (br s, 1H), 8.3-8.6 (m, 1H), 7.3-7.9 (m, 8H), 6.75 (s, 1H); T. Sakamoto, M. An-Naka, Y. Kondo and H. Yamanaka, *Chem. Pharm. Bull.*, **34**, 2754 (1986).
- [6] 4-Hydroxy-3-phenylisoquinoline, mp 159-161°; ¹H nmr (deuteriochloroform): δ 8.78 (s, 1H), 7.2-8.3 (m, 9H), 5.75 (br s, 1H); T. L. Gilchrist, G. E. Gymer and C. W. Rees, *J. Chem. Soc., Perkin Trans. I*, 1 (1975).
- [7] To rule out the possibility that **3** was being formed from **1** in iodine, pure **1** was treated with a solution of iodine in chloroform. Under these conditions **1** is completely stable.
- [8] Analysis (tlc) (30% ethyl acetate/hexanes: 2 elutions) at this stage shows, in addition to spots corresponding to **1** (R_f = 0.61) and **3** (R_f = 0.40), a spot just above **1** (R_f = 0.65) which stains intensely with phosphomolybdic acid even without heating. This spot is most likely **8** and/or its 1,2-dihydro analog and disappears when crude samples stand for a few hours, or upon chromatography.
- [9] The published yield for the conversion of **6** to **1** is 70% [1].
- [10] T. L. Gilchrist, G. E. Gymer and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 835 (1973).
- [11] S. E. Whitney and B. Rickborn, *J. Org. Chem.*, **53**, 5595 (1988).