Versatile and Efficient Synthesis of Aryl-1,2,3,4-tetrahydroisoquinolines: Nickel(II) Phosphine Ligand Catalyzed Coupling of Arylmagnesium Halides to Haloisoquinolines

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Dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (dppp) was used as catalyst to prepare some previously unreported arylisoquinolines **3**, which were in turn hydrogenated to aryl-1,2,3,4-tetrahydroisoquinolines **2**. This procedure is the most direct and efficient method currently available for the preparation of many compounds of the type **2** and **3**.

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Recently, Ellefson (1) reported a synthesis of 8-phenyl-1,2,3,4-tetrahydroisoquinoline which is structurally similar to the apomorphine ring system, missing only the C-7 methylene bridge. We were also interested in synthesizing similar aryl-1,2,3,4-tetrahydroisoquinolines for pharmacological studies but felt Ellefson's route to be too lengthy. We, therefore, sought a more direct method of preparation of this potentially important class of tetrahydroisoquinolines.

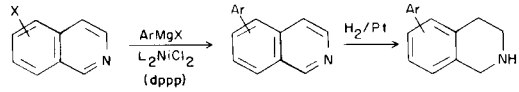
Syntheses of tetrahydroisoquinolines substituted with nonactivating substituents, such as halogen or phenyl, are effected with difficulty if at all using conventional methods, *i.e.*, the Pictet-Spengler, Bischler-Napieralski, or the Pomeranz-Fritsch reaction (2-5). Because this laboratory has recently reported success in the preparation of halogenated 1,2,3,4-tetrahydroisoquinolines using aluminum chloride (6), we therefore investigated the use of this catalyst for the cyclization of *N*-(*o*-arylbenzyl)-*N*-(2-chloroethyl)amines **1** to aryl-1,2,3,4-tetrahydroisoquinolines **2**. However, our cyclization attempts using

1 2

1 (Ar = phenyl) yielded, by gc/ms an isomeric mixture of phenyl-1,2,3,4-tetrahydroisoquinolines (7). Clearly, a simple unambiguous route to these isoquinolines is still necessary.

An alternative method of preparing tetrahydroisoquinolines is to catalytically hydrogenate the parent isoquinoline. After a careful search of the literature, we did not find an applicable synthesis of arylisoquinolines. However, Dyall and Pullin (8) have most recently prepared all seven phenylisoquinolines using a modification of Hey's (9) phenylation procedure with yields ranging from 10 to 48%. In addition to being lengthy, this procedure is further restricted in that the isoquinoline substitution is limited to phenyl.

Using dichloro[1,3-bis(diphenylphosphino)propane]-nickel(II) (dppp) (10) as catalyst we have successfully coupled aryl Grignard reagents to haloisoquinolines **3** obtaining several previously unreported arylisoquinolines **4** in good to excellent yield (averaging 72%). Arylisoquinolines **4** were then routinely hydrogenated to 1,2,3,4-tetrahydroisoquinolines **2**. We had previously reported our success



3 4 2

X = Br, Cl

employing this coupling reaction on halopyridines by Grignard reagents (11). Since that publication, several reports have appeared utilizing this catalyst in the synthesis of a variety of heterocycles, *i.e.*, quinolines (12), indoles (12), benzazepines (12), pyridazines (13), 2,6-pyridinophanes (14), pyrimidines (15), and thiophenes (16). In none of these reports have scrambling products been observed (17-19).

Although we did not investigate quantitatively the rate of reaction, we nevertheless found the positional order of reactivity for the halo isomers in the coupling step to be similar to that reported by Dyall (8). The 1- and 5-haloisoquinoline reacted much faster than its 6-, 7-, and 8-analogs. But even so, the slowest reaction was complete after stirring overnight in THF at ambient temperature. Higher temperature was avoided to prevent potential side reactions initiated by Grignard addition to the azomethine bond.

This approach to aryl-1,2,3,4-tetrahydroisoquinolines provides a versatile isoquinoline synthesis which is not limited to aryl Grignards since aliphatic Grignards may be used if the proper catalyst is employed (17). The coupling reaction does not proceed if the nickel(II) catalyst is absent. As a result of performing the coupling reaction under neutral conditions, acid or base sensitive substituents are unaffected. However, if employing this route

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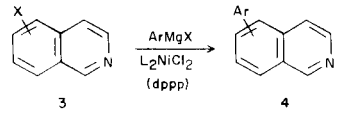
Table I

Dichloro[1,3-bis(diphenylphosphino)propane]Nickel(II) (dppp) Catalyzed Coupling of Aryl Grignards to Haloisoquinolines **3**



3 4

Isoquinoline **3**	Isoquinoline **4**	M.p., °C	Elemental Analysis Calcd. (Found)	Yield (%)
8-Chloroisoquinoline	8-Phenylisoquinoline	201-202 (picrate) lit. 205-206 (9)	C 58.07 (57.97); H 3.24 (3.60); N 12.9 (12.85)	83 (a)
7-Chloroisoquinoline	7-Phenylisoquinoline	209-211 (HCl)	C 74.53 (74.90); H 5.00 (5.05); N 5.79 (5.73)	69
1-Chloroisoquinoline	1-Benzylisoquinoline	187-189 ($HCl \cdot 1/4H_2O$)	C 70.33 (70.16); H 3.69 (3.88); N 5.13 (5.12)	48
8-Chloroisoquinoline	8-(4-Methoxyphenyl)isoquinoline	92-93	C 81.68 (81.81); H 5.56 (5.52); N 5.95 (6.10)	68
6-Bromoisoquinoline	6-Phenylisoquinoline	252-254 (HBr)	C 62.96 (62.81); H 4.23 (4.23); N 4.89 (4.80)	90
5-Bromoisoquinoline	5-Phenylisoquinoline	215 ($HBr \cdot H_2O$)	C 59.23 (59.15); H 4.63 (4.18); N 4.60 (4.88)	85
1-Chloroisoquinoline	1-(4-Trifluoromethylphenyl)isoquinoline	126-128	C 70.33 (70.16); H 3.69 (3.88); N 5.13 (5.12)	58 (a)

(a) Average of several runs.

there are limitations that should be considered: (1) the sensitivity of some substituents to Grignards; (2) the limited availability of many haloisoquinolines, although methods of preparing monohalogenated isoquinolines are well established (3b,20); and (3) susceptibility of the substituent to reduction. However, the facility with which the arylisoquinolines and subsequent aryl-1,2,3,4-tetrahydroisoquinolines are prepared using this procedure makes this route promising for general applications.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H nmr spectra were obtained using either a Perkin-Elmer R-600 or R-24 using TMS as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 283 spectrometer. Gc/ms data were obtained on a Finnigan-3300.

General Procedure for Preparation of Arylisoquinolines **4**.

A 100 ml. 3-neck flask containing a stirring bar was fitted with a nitrogen inlet and outlet tube. The flask was then flame-dried and nitrogen swept. After cooling, 40 mg. of nickel(II) catalyst (dppp) and ~ 1 g. of the haloisoquinoline **3** were added along with 60 ml. of ketyl dried THF. The flask was fitted with a neoprene septum and the appropriate Grignard (1.1 equivalent) was added under a nitrogen atmosphere using a syringe. The reaction mixture was stirred at ambient temperature under positive nitrogen pressure for 16 hours then poured into cold dilute hydrochloric acid. The acidic layer was washed with ether then basified with potassium carbonate and extracted with ether several times. The combined and dried ether extracts were concentrated to yield the arylated(alkylated)isoquinoline.

General Procedure for Catalytic Hydrogenation of Arylisoquinolines **4** to Aryl-1,2,3,4-tetrahydroisoquinolines **2**.

The arylisoquinolines **4** (~ 12 mmoles) was dissolved in 50 ml. of ethanol contained in a Parr hydrogenation bottle. Platinum oxide (50 mg.) was then added to the bottle bulkwise. The suspension was made distinctly acidic with concentrated hydrochloric acid then kept under 50 psi of hydrogen pressure 1-3 hours. The catalyst was then removed by filtration and the filtrate concentrated to dryness to yield an oil which was basified with potassium carbonate and extracted with ether. The dried ether layer was concentrated to yield the aryl-1,2,3,4-tetrahydroisoquinolines **2**.

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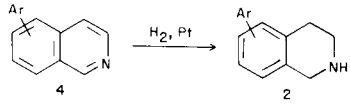
Table II

Catalytic Hydrogenation of Arylisoquinolines **4** to Aryl 1,2,3,4-Tetrahydroisoquinolines **2**



4 2

Isoquinolines **4**	Isoquinolines **2**	M.p. (HCl), °C	Elemental Analysis Calcd. (Found)
8-Phenylisoquinoline	8-Phenyl-1,2,3,4-tetrahydroisoquinoline	267-269 lit. (268-270) (1)	C 73.31 (73.13); H 6.56 (6.73); N 5.70 (5.61)
7-Phenylisoquinoline	7-Phenyl-1,2,3,4-tetrahydroisoquinoline	248-250 lit. (249-251) (2)	C 73.31 (73.41); H 6.56 (6.67); N 5.70 (5.60)
8-(4-Methoxyphenyl)isoquinoline	8-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline	161-163	C 69.67 (69.28); H 6.58 (6.78); N 5.08 (5.04)
6-Phenylisoquinoline	6-Phenyl-1,2,3,4-tetrahydroisoquinoline	200-202 (HBr)	C 62.08 (62.01); H 5.56 (6.23); N 4.83 (4.83)
5-Phenylisoquinoline	5-Phenyl-1,2,3,4-tetrahydroisoquinoline	280-282 (ethanol-ether) (a)	C 73.13 (73.06); H 6.56 (6.48); N 5.61 (5.58)
8-(3,4-Dimethoxyphenyl)isoquinoline	8-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline	156-157	C 66.77 (66.72); H 6.59 (6.72); N 4.58 (4.48)

(a) Recrystallizing solvent system.

REFERENCES AND NOTES

(1) C. R. Ellefson, *J. Org. Chem.*, **44**, 1533 (1979).

(2) J. Sam, R. M. Shafik and K. Aparajitham, *J. Pharm. Sci.*, **59**, 59 (1970).

(3a) K. Freter, E. Dubois, and A. Thomas, *J. Heterocyclic Chem.*, **7**, 159 (1970); (b) E. V. Brown, *J. Org. Chem.*, **42**, 3208 (1977).

(4a) W. M. Whaley and T. R. Govindachari, in "Organic Reactions", in Vol. 6, R. Adams, Ed., John Wiley and Sons, Inc., New York, NY, 1951, pp. 74-150 and pp. 151-190; (b) W. Gensler, in "Organic Reactions", Vol, 6, R. Adams, Ed., John Wiley and Sons, Inc., New York, NY, 1951, p. 191.

(5a) J. M. Bobbitt, J. M. Kiely, K. L. Khanna and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965); (b) F. W. Bergstrom, *Chem. Rev.*, **35**, 217 (1944); (c) R. H. F. Manske, *ibid.*, **30**, 145 (1942); (d) W. Gensler in "Heterocyclic Compounds", Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, NY, 1952, p. 344; (e) P. A. Claret, in "Comprehensive Organic Chemistry", Vol. 4, "Heterocyclic Compounds", P. G. Sames, Ed., Pergamon Press, London, Eng., 1979, p. 205.

(6) W. Mendelson, C. B. Spainhour, S. Jones, B. Lam, and K. Wert, *Tetrahedron Letters*, 1393 (1980); and references therein.

(7) The conditions for this cyclization and mechanism of the rearrangement have been further investigated and will be reported at a later date.

(8) L. K. Dyall and C. J. Pullin, *Aust. J. Chem.*, **32**, 345 (1979).

(9) Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 3882 (1961).

(10) G. R. Van Hecke and W. Dew. Horrocks, *J. Inorg. Chem.*, **5**, 1968 (1966); also available from Strem Chemicals of Newburyport, Mass.

(11) L. N. Pridgen, *J. Heterocyclic Chem.*, **12**, 443 (1975).

(12) M. Mori, S. Kudo and Y. Ban, *J. Chem. Soc., Perkin Trans. I*, 771 (1979) and references therein.

(13) A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Pharm. Bull.*, **26**, 2550 (1978).

(14) K. Tamoa, S. Kodama, T. Nakatsuka, Y. Kiso and M. Kumada, *J. Am. Chem. Soc.*, **97**, 4405 (1975).

(15) H. Yamanaka, K. Edo, F. Shoji, S. Konno, T. Sakamoto and M. Mizugaki, *Chem. Pharm. Bull.*, **26**, 2160 (1978).

(16) M. Zembayashi, K. Tamao, J. Yoshida and M. Kumada, *Tetrahedron Letters*, 4089 (1977).

(17) For leading reviews of Nickel-Phosphine complexes as catalysts in Grignard cross-coupling reactions see: (a) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato and M. Kumada, *Bull. Chem. Soc. Japan*, **49**, 1958 (1976); (b) H. Felkin and G. Swierczewski, *Tetrahedron*, **31**, 2735 (1975); (c) A. Kozikowski and H. Wetter, *Synthesis*, 561 (1976).

(18) Nickel(II) acetylacetonate has been reported to catalyze the coupling of bromonaphthalenes and various arylmagnesium halides [K. Komatsu, N. Abe, K. Takahashi and K. Okamoto, *J. Org. Chem.*, **44**, 2712 (1979)] and references therein.

(19) The palladium analog of NiL_2Cl_2 has been successfully used as a coupling catalyst on many of the heterocycles mentioned above with excellent regiospecificity. For recent reports see: (a) S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita and K. Kondo, *J. Org. Chem.*, **44**, 2408 (1979); (b) H. Yamanaka, M. Shiraiwa, K. Edo and T. Sakamoto, *Chem. Pharm. Bull.*, **27**, 270 (1979); (c) K. Edo, *ibid.*, **27**, 193 (1979); (d) J. E. Plevyak, J. E. Dickerson and R. F. Heck, *J. Org. Chem.*, **44**, 4078 (1979); (e) Y. Tamaru, Y. Yamada and Z. Yoshida, *Tetrahedron Letters*, 919 (1978); (f) C. F. Bigge, P. Kalaritis and M. Mertes, *ibid.*, 1653 (1979); (g) Y. Abe, A. Ohsawa, H. Arai and H. Igeta, *Heterocycles*, **9**, 1397 (1978).

(20a) H. Weiler-Feilshenfeld, Y. L. Mao, and E. D. Bergmann, *Israel J. Chem.*, **9**, 111 (1971); (b) J. L. Butler, F. L. Bayer and M. Gordon, *Trans. K. Acad. Scie.*, **38**, 15 (1977); and references therein.