(2) For a description of the synthesis and biological activity of the carbocyclic analogues of the series, see I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, **13**, 203 (1970).
(3) M. Carmack and M. A. Spielman, *Org. React.*, **3**, 83 (1946).
(4) F. Alvarez, U.S. Patent 3 808 277 (1974); J. H. Fried and I. T. Harrison, U.S. Patent 3 998 966 (1976).
(5) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958).
(6) The *E* stereochemistry of this acid was assigned on the basis of the inability of its reduction product (hydroxy acid) to undergo lactonization, an assignment consistent with ref 5 above.
(7) M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972); J. L. Herrmann, G. R. Kleczykowski, and R. H. Schlessinger, *ibid.*, 2433 (1973).
(8) The alkylation of the dilithium salts of hydracrylate esters has been reported and our ester **4** represents a vinylog of this system; cf. J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 2429 (1973).

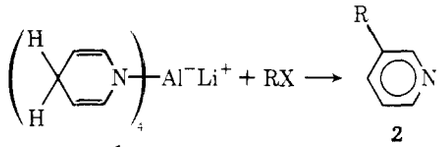
A Direct Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectral Analysis of 4-Substituted Isoquinolines[1]

C. S. Giam* and T. E. Goodwin

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received March 28, 1978

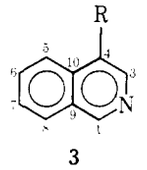
We have shown[2] that the reaction of lithium tetrakis(*N*-dihydropyridyl)aluminate (LDPA, **1**; from pyridine and lithium aluminum hydride ($LiAlH_4$))[3] with electrophilic reagents leads directly to 3-substituted pyridines, **2**, in high



1 **2**

yields. It was demonstrated[4] that the optimum yields of 3-substituted pyridines were obtained when 1 molar equiv of the appropriate alkyl halide was added per mol of LDPA. The addition of larger amounts of electrophilic reagent did not increase the yield of 3-substituted products. These results suggest that only one "dihydropyridyl" moiety per molecule of LDPA is reactive.

We now report the extension of this reaction to the synthesis of 4-substituted isoquinolines **3** from isoquinoline, $LiAlH_4$,



3

and electrophilic reagents. Isoquinoline compounds with substitution in the 4 position have been shown to possess significant antispasmodic and vasodilatory properties,[5] and a tetrahydro derivative exhibited selective β_2-adrenergic agonist activity.[6] A number of synthetic studies have been directed toward these substances.[7]

Initially, the reaction of isoquinoline, $LiAlH_4$, and benzyl chloride was investigated. We first wished to ascertain if the desired reaction would occur at all and then to determine the reaction stoichiometry which is necessary for optimum yields.

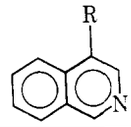
A series of reactions was carried out in tetrahydrofuran (THF) in which the molar ratio of isoquinoline to $LiAlH_4$ was kept constant at 4:1, but the number of molar equivalents of benzyl chloride was varied in increments of 1, from 1 to 4. The results of these experiments are shown in Table I and illustrate that the most efficient conversion of alkyl halide to 4-benzylisoquinoline occurs when 1 molar equiv is present (yield ≃ 90%). In contrast to the pyridine series,[4] the yield of 4-benzylisoquinoline increases as the amount of benzyl chloride increases (column 3, Table I); therefore, more than 1 of the 4 molar equiv of isoquinoline is rendered reactive by treatment with a single molar equiv of $LiAlH_4$. Since the yield increased in an irregular manner, we are as yet unable to speculate on the exact nature of the reactive species.

Table I. Effect of Various Molar Ratios of Reagents on the Yield[a] of 4-Benzylisoquinoline[b]

$PhCH_2Cl$/$LiAlH_4$	% yield based on $PhCH_2Cl$	% yield based on $LiAlH_4$
1:1	91 (88)[c]	91 (88)[c]
2:1	59 (45)	118 (91)
3:1	46 (45)	134 (128)
4:1	39 (35)	158 (142)

[a] The percent yields in this table were obtained by GLC analysis. [b] Isoquinoline (4 molar equiv) was present in THF solvent in each reaction. [c] Values in parentheses were obtained in a duplicate experiment.

Table II. Yields of 4-Substituted Isoquinolines



R	registry no.	% yield (isolated)	% yield (GLC)[a]	% yield (lit)
$PhCH_2$	10166-05-9	43[a] (56)[b]	90	34[c]
$H_2C{=}CHCH_2$	66967-18-8	24 (9)	80	
CH_3CH_2	41219-10-7	2 (13)[d]	35	<4[e]

[a] Molar ratio of isoquinoline/$LiAlH_4$/RX, 4:1:1. [b] Molar ratio of isoquinoline/$LiAlH_4$/RX, 4:1:4. [c] Reference 9. [d] Based on recovered isoquinoline. [e] Reference 10.

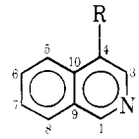
Subsequent reactions have been carried out using both a 4:1:1 molar ratio and a 4:1:4 molar ratio of isoquinoline/$LiAlH_4$/alkyl halide. The yields of 4-benzyl- (**4**), 4-allyl- (**5**), and 4-ethylisoquinolines (**6**) are listed in Table II. In each instance the isolated yield of purified material is less than the GLC yield, owing to nonoptimal isolation procedures. In spite of the modest isolated yields, we feel that this method is a useful one due to its simplicity and the ready availability of the inexpensive starting materials. In addition, the alkylation may be carried out using a simple aliphatic alkyl halide, which has not always been possible using other methodologies.[7,8] Work is in progress in our laboratories to optimize the yields of this process and to extend it to the preparation of more complex substances.

^{13}C NMR Spectral Analysis. As part of a thorough characterization of the 4-substituted isoquinolines prepared in this study, their ^{13}C NMR spectra were recorded. Most of the carbon resonances were readily assigned using standard chemical shift theory[11] and by comparison to a previous rigorous assignment of the spectrum of isoquinoline itself.[12] Using these data, however, it was not possible to unambiguously assign the C-7 and C-8 resonances, which are separated by about 1.5 ppm in the 4-substituted isoquinolines and by only 0.4 ppm in the parent heterocycle.

A straightforward solution to this problem results from recognition that the nonnitrogenous ring of isoquinolines can be viewed as an unsymmetrically ortho-disubstituted benzene

0022-3263/78/1943-3780$01.00/0

Table III. ^{13}C NMR Chemical Shifts of Isoquinolines[a]



carbon no.	R = H[b]	R = $PhCH_2$	R = CH_2=$CHCH_2$	R = CH_3CH_2
1	152.5	151.8	151.9	151.1
3	143.0	143.8	143.0	141.8
4	120.4	129.6	129.2	132.9
5	126.4	123.4	123.3	122.7
6	130.2	130.2	130.1	130.0
7	127.2	126.8	126.8	126.6
8	127.6	128.1	128.3	128.2
9	128.6	127.2	126.1	127.5
10	135.7	134.8	134.7	134.5

[a] The δ values are in ppm downfield from Me_4Si. The spectra were taken in $CDCl_3$ solutions where $\delta(Me_4Si) = \delta(CDCl_3) + 77.1$ ppm. [b] Reference 12; the numbers reported here were obtained in our laboratory.

and is therefore amenable to spectral analysis using the "fingerprint" technique described by Günther and his coworkers.[13,14]

In the ^1H-coupled spectra of the 4-alkylisoquinolines, the resonances of C-6 and C-7 were predictably observed as clean doublets of doublets and that of C-8 appeared as a doublet of multiplets. It was thus possible to easily differentiate the C-7 and C-8 resonances, thereby completing the chemical shift assignments of the 4-substituted isoquinolines, which are catalogued in Table III. Chemical shifts of the exocyclic carbons are shown in Chart I.

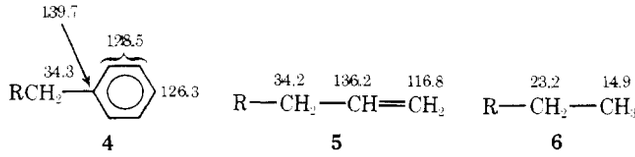
A potentially useful phenomenon was observed for the signal arising from C-5, which in the ^1H-coupled ^{13}C NMR spectrum of each 4-substituted isoquinoline is simplified to a distinct doublet of doublets. This may be ascribed to the absence of a hydrogen at the 4 position and should prove useful in spectral analysis of more complex isoquinolines.

The data in Table III reveal that the major chemical shift perturbations resulting from the introduction of a 4 substituent to an isoquinoline skeleton occur at C-4 and C-5, the former position being deshielded and the latter shielded with respect to analogous centers in isoquinoline itself. This observation is reminiscent of perturbations produced upon the introduction of an alkyl group at the 1 position of naphthalene[15] and may be attributed in part to steric interactions between the alkyl group and the peri hydrogen (at C-5 in the isoquinolines).

Experimental Section.

Boiling points and melting points are uncorrected. Infrared spectra of neat liquids were recorded on a Perkin-Elmer 227B spectrophotometer, and mass spectra were obtained on a Hewlett-Packard 5982A spectrometer. ^1H and ^{13}C NMR spectra were run on $CDCl_3$ solutions with Me_4Si as an internal standard (δ = 0 ppm) on a Varian T-60 spectrometer and a Jeol JNM-PS-100 spectrometer operating at 25.034 Hz in the Fourier transform mode, respectively. GLC analyses were performed on a 6 ft × 0.25 in 3% OV-1 on 100–120 mesh Gas Chrom Q column in a Varian Aerograph Series 1520 chromatograph. 4-Benzylisoquinoline was analyzed at a column temperature programmed from 125–250 °C at 20 °C/min, while other analyses were run isothermally at 168 °C. Peak height comparisons were made to a five point calibration curve obtained by injecting a standard solution of the appropriate pure isoquinoline. Preparative TLC utilized Merck silica gel 60 PF-254 as adsorbent. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$ before each reaction. Solutions of reaction mixtures were dried over anhydrous sodium sulfate. A representative procedure appears below. Similar reactions were carried out using this procedure with modified quantities and types of reagents where appropriate.

Chart I. ^{13}C NMR Chemical Shifts (δ) of Exocyclic Carbons (R = 4-Substituted Isoquinoline)



4 5 6

4-Allylisoquinoline (5). A solution of 7.250 g (0.056 mol) of isoquinoline in 10 mL of dry THF was added over 0.5 h under nitrogen to a stirring mixture of 0.551 g (0.015 mol) of lithium aluminum hydride in 20 mL of THF at room temperature. After 24 h a solution of 1.755 g (0.0145 mol) of allyl bromide in 5 mL of THF was added over 15 min. The mixture was stirred and refluxed for 1 h, quenched cautiously with 10 mL of water, and diluted with 50 mL of acetone. The mixture was filtered over Celite, and most of the acetone and THF was removed in vacuo. The residue was diluted with 100 mL of dichloromethane and dried. Evaporation of the solvent provided 8.482 g of orange liquid which was fractionally distilled twice to provide, after a forerun of isoquinoline, 788 mg of a colorless liquid, bp 133–160 °C (5–6 Torr), which was primarily 4-allylisoquinoline (80% pure by GLC). This could be further purified (with some sacrifice of material) by repeated distillation to give a colorless liquid: bp 86 °C (0.25 Torr); IR 1645, 1630, 1590, 1520 cm^{-1}; ^1H NMR δ 3.69 (d, 2, J = 6 Hz, CH_2), 4.83–5.09 (m, 1, olefinic H), 5.11–5.29 (m, 1, olefinic H), 5.50–6.42 (m, 1, olefinic H), 6.95–8.12 (m, 4, C-5, C-6, C-7, and C-8 H's), 8.38 (s, 1, C-3 H), 9.11 (s, 1, C-1 H); mass spectrum, m/e 169 (M^+), 168 (base), 167, 157, 141, 115; picrate mp 157 °C (from aqueous ethanol).

Anal. Calcd for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.55; N, 14.07. Found: C, 54.48; H, 3.57; N, 14.06.

Acknowledgment. The authors are grateful to the Robert A. Welch Foundation for the financial support of this work and to members of our laboratory for their comments and assistance.[16]

Registry No.—5 picrate, 66967-19-9; isoquinoline, 119-65-3; allyl bromide, 106-95-6; benzyl chloride, 100-44-7.

References and Notes

(1) Presented at the 33rd Southwest Regional American Chemical Society Meeting, Little Rock, Ark., Dec 1977.
(2) C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.*, **93**, 1294 (1971).
(3) P. T. Lansbury and J. D. Peterson, *J. Am. Chem. Soc.*, **85**, 2236 (1963).
(4) S. D. Abbott, Ph. D. Dissertation, Texas A&M University, Tex., 1971.
(5) P. Bouvier et al., *Eur. J. Med. Chem. Chim. Ther.*, **11**, 271 (1976).
(6) P. F. Kador et al., *J. Med. Chem.*, **20**, 891 (1977).
(7) T. Kametani et al., *J. Chem. Soc., Perkin Trans. 1*, 386 (1977), and references contained therein.
(8) Cf. S. F. Dyke et al., *Tetrahedron*, **26**, 2239 (1970).
(9) W. D. Burrows and E. P. Burrows, *J. Org. Chem.*, **28**, 1180 (1963).
(10) G. Jones, *J. Chem. Soc.*, 1918 (1960).
(11) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972; J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(12) D. M. Grant et al., *J. Am. Chem. Soc.*, **91**, 6381 (1969).
(13) H. Günther, H. Schmickler, and G. Jikeli, *J. Magn. Reson.*, **11**, 344 (1973).
(14) See also, C. S. Giam, T. E. Goodwin, and T. Yano, *J. Chem. Soc., Perkin Trans. 2*, in press.
(15) Cf. N. K. Wilson and J. B. Stothers, *J. Magn. Reson.*, **15**, 31 (1974).
(16) The first preparation of 4-benzylisoquinoline in our laboratories was by Dr. S. D. Abbott.

Stereoselective Oxidation by Thionyl Chloride Leading to the Indeno[1,2-*c*]isoquinoline System

Mark Cushman* and Leung Cheng

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received February 28, 1978

Thionyl chloride is commonly used for the conversion of carboxylic acids to acid chlorides and alcohols to alkyl chlorides. Several transformations are also known in which this

0022-3263/78/1943-3781$01.00/0