Registry No. Triethyloxonium hexafluoxophosphate, 17950-40-2; *tert*-butyldimethylsulfonium trifluoromethanesulfonate, 82510-92-7; *tert*-butyldimethylsulfonium iodide, 918-03-6; silver trifluoromethanesulfonate, 2923-28-6.

Convenient Preparation of 3-Substituted 1(2*H*)-Isoquinolinones

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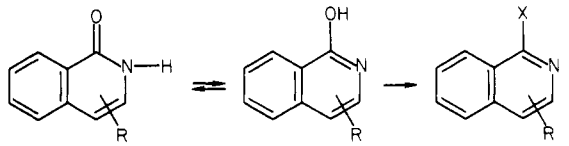
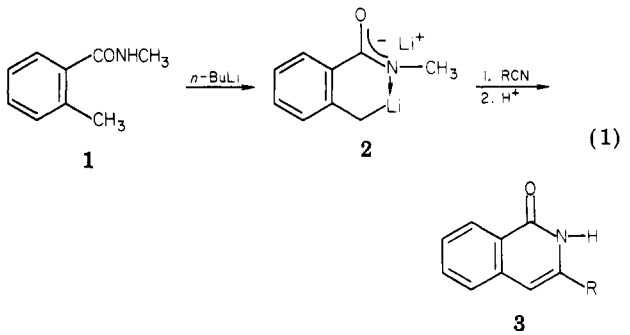
Isoquinolinones or the tautomeric hydroxyisoquinolines



X = H, halo, alkoxy, amino, etc.

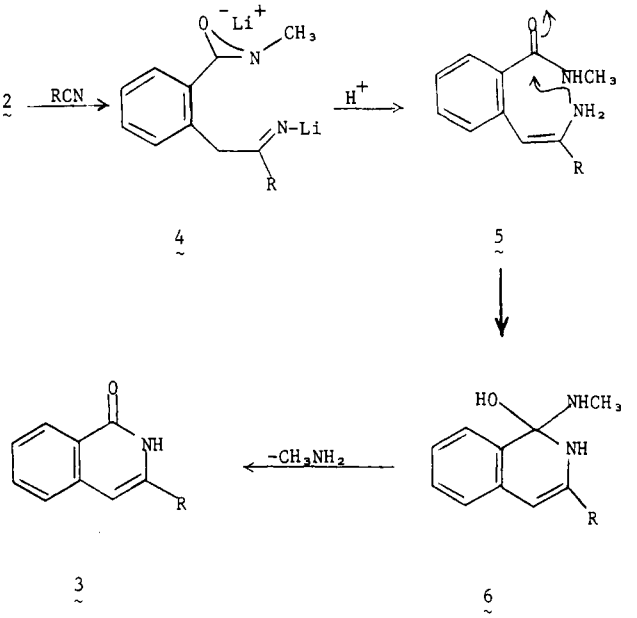
are important synthetic precursors to many biologically active isoquinoline structures. Except for a recent report describing photochemical $S_{RN}1$ reactions between 2-halobenzamides and enolates,[1] efficient methods for their preparation are limited. These include acylation–hydration–cyclization sequences of *o*-toluonitriles,[2] butyl nitrite ring expansions of substituted 1-indanones,[3] and other less general methods.[4] We report an efficient and convenient one-pot procedure for the preparation of 3-substituted 1(2*H*)-isoquinolinones **3** by the reaction of organic nitriles with dilithio anion **2** derived from *N*,2-dimethylbenzamide (**1**, eq 1).



(1)

Hauser has shown that amide **1** can be readily dimetalated by employing 2 equiv of *n*-butyllithium and subsequently reacted with either aldehydes or ketones to furnish various δ-hydroxy amides.[5] Similarly, we have observed that reaction of dilithio anion **2** with organic nitriles yields isoquinolinones **3**. Thus treatment of a tetrahydrofuran solution of amide **1** with 2.1 equiv of *n*-butyllithium at 0 °C resulted in the formation of dianion **2** as evidenced by its orange-red color. Dimetalation was judged complete after 45 min as determined by ^{1}H NMR analysis of a D_2O-quenched aliquot. After the solution cooled to −50 °C and was treated with 1.25 equiv of benzonitrile, the dark solution was warmed to room temperature and quenched with a saturated ammonium chloride solution. Workup afforded an excellent yield of 3-phenyl-1(2*H*)-isoquinolinone (**3c**).[6] The results and yields of this and similar reactions using additional nitriles are summarized in Table I.

Scheme I



Addition of either acetonitrile or propionitrile to dianion **2** failed to give any of the desired isoquinolinones **3** (R = CH_3 and C_2H_5) even with the use of tetramethylethylenediamine as a complexing agent. Presumably the acidity of the α-protons of these nitriles renders them susceptible to trans metalation with **2** and subsequent self-condensation.[8] In contrast, use of less acidic, secondary or tertiary, aliphatic nitriles (entries 1 and 2, Table I) resulted in the formation of the desired isoquinolinones **3a** and **3b** in moderate yields of 42% and 48%, respectively. Higher efficiencies were realized by use of aryl and heteroaryl nitriles (entries 3–6) which furnished the respective isoquinolinones **3c–f** in yields ranging from 58% to 87%. However, reaction with either 2- or 3-pyridinenitrile afforded complex mixtures of products presumably via addition to the pyridine ring.

As suggested by the mechanism shown in Scheme I, addition of the nitrile to dianion **2** would yield adduct **4**, which on quenching with ammonium chloride and tautomerization would give enamino amide **5**.[9] Although this intermediate was never isolated, cyclization to **6** would be expected to occur readily followed by loss of methylamine to furnish the observed products **3**. Cyclization of such enamines is not limited to *o*-amides. After metalation of

(1) Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729.
(2) Boyce, W. T.; Levine, R. *J. Org. Chem.* **1966**, *31*, 3807.
(3) (a) Mariconi, E. J.; Creegan, F. J. *J. Org. Chem.* **1966**, *31*, 2090. (b) Schnur, R. C.; Howard, H. R. *Tetrahedron Lett.* **1981**, *22*, 2843.
(4) (a) Belgaonkar, V. H.; Usgaonkar, R. N. *Indian J. Chem.* **1975**, *13*, 336. (b) Van Der Goot, H.; Oostendorp, J. G.; Nauta, W. T. *Eur. J. Med. Chem.—Chim. Ther.* **1975**, *10*, 603. (c) Wilson, J. W.; Anderson, E. L.; Ullyot, G. E. *J. Org. Chem.* **1951**, *16*, 800. (d) Cologne, J.; Weinstein, G. *Bull. Soc. Chim. Fr.* **1952**, 462. (e) Modi, A. R.; Usgaonkar, R. N. *Cur. Sci.* **1976**, *45*, 832. (f) Kasahara, A. Japanese Kokai, 76 143 672, 1976; *Chem. Abstr.* **1977**, *87*, 39289. (g) Mikol, G. I.; Boyer, J. H. *J. Org. Chem.* **1972**, *37*, 724. (h) Eloy, F.; Deryckere, A. *Helv. Chem. Acta* **1969**, *52*, 1755.
(5) (a) Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 83. (b) Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514.
(6) Dimetalation of 2-methylbenzoic acid according to the method of Creger[7] followed by reaction with benzonitrile also furnished isoquinolinone **3c**, albeit in much lower yield.
(7) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.
(8) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, England, 1974; pp 116–121.
(9) A referee has suggested enamine **5** to probably exist as the tautomeric imine on the basis of earlier results of Ahlbrecht (Ahlbrecht, H.; Rauchschwalbe, G. *Tetrahedron Lett.* **1971**, 4897).

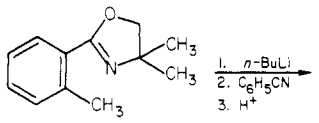
0022-3263/82/1947-3787$01.25/0

Table I. Structures, Yields, and Physical Data for Isoquinolinones 3[a]

entry	R	compd	% yield	mp, °C	solvent	lit. mp (°C) or formula
1	$(CH_3)_2CH$	3a	42	188-190	C_2H_5OH	186-188[b]
2	$(CH_3)_3C$	3b	48	187-188	CH_3OH/H_2O	187.5-189.0[c]
3	Ph	3c	87	198-199	C_2H_5OH	199.5-200.0[d]
4		3d	66	179-180	C_2H_5OH/H_2O	180-181.5[e]
5		3e[f]	60	212-213	$(CH_3)_2CHOH$	$C_{16}H_{10}F_3NO$
6		3f[f]	58	213-214	$(CH_3)_2CHOH/(CH_3)_2NCHO$	$C_{13}H_9NOS$

[a] All reactions were carried out as described in the Experimental Section. [b] Reference 3a. [c] Reference 4b. [d] Gabriel, S. *Chem. Ber.* **1885**, *18*, 3470. [e] Dave, V.; Warhoff, E. *Synth Commun.* **1974**, *4*, 17. [f] Satisfactory analytical values for C, H, and N were obtained.

7[10] with *n*-butyllithium and reaction with benzonitrile, only isoquinoline **9** was obtained.[11] No intermediate enamino



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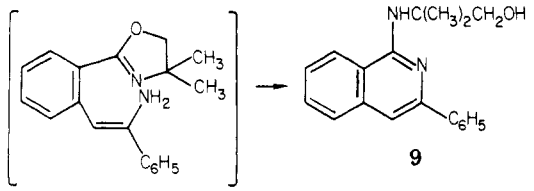


8 9

oxazoline **8** was detected. Thus ring closure of these general types of intermediates to isoquinoline structures is highly favorable.[12]

Experimental Section

General Methods. IR spectra were recorded on a Nicolet MX-1 FT spectrophotometer. ^1H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R32 spectrometer. Data are reported in the following manner: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, spt = septet, br = broadened, and m = unresolved multiplet), integration, coupling constant. ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer at 22.5 MHz by using an internal deuterium lock. Data are reported as follows: $\{^1H\}$ ^{13}C chemical shifts and multiplicity as obtained from the coupled spectra (s = singlet, d = doublet, t = triplet, q = quartet). Melting points were determined by using a Thomas-Hoover capillary apparatus and are both uncorrected and uncalibrated. Starting amide **1** was either purchased from Aldrich Chemical Co., Milwaukee, WI, or prepared according to literature procedures.[5] The tetrahydrofuran (THF) solvent used in all the metalation reactions was distilled under nitrogen from sodium benzophenone ketyl immediately prior to use.

General Preparative Procedure for Isoquinolinones 3. Under nitrogen and with cooling (ice–salt bath) was slowly added 96 mL (0.23 mol) of *n*-butyllithium (2.4 M in *n*-hexane) via syringe to a stirred solution of 14.9 g (0.100 mol) of amide **1** in 200 mL of THF. The addition rate was maintained so that the reaction temperature never exceeded 20 °C. After the addition was complete (ca. 30 min), the orange-red solution was stirred at 0 °C for 1 h and then cooled to −50 °C (dry-ice/2-propanol). A solution of 0.125 mol of the appropriate organic nitrile in 50 mL of THF was quickly added, the cooling bath removed, and the resulting mixture allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (50 mL) was then carefully added via pipet. Occasionally during this operation rapid gas evolution occurred. The resulting phases were separated, and the organic portion was washed with water (50 mL) and saturated sodium chloride solution (50 mL) and then dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo to afford the crude isoquinolinones as pale yellow to dark solids which were subsequently recrystallized. Yields, melting points, and recrystallization solvents for the above experiments are listed in Table I. See the paragraph at the end of the paper about supplementary material. 3-(2-Methylethyl)-1(2*H*)-isoquinolinone (**3a**) for an example was isolated as a colorless solid: IR (KBr) 1648, 1608, 1555, 1478, 1384, 1349, 1257, 822, 754 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.25 (d, 6, J = 6.9 Hz), 2.81 (spt, 1, J = 6.9 Hz), 6.34 (s, 1), 7.55 (m, 3), 8.17 (d, 1, J = 7.5 Hz), 11.16 (br s, 1) ppm; ^{13}C NMR (Me_2SO-d_6), 162.6 (s), 148.2 (s), 138.3 (s), 132.1 (d), 126.5 (d), 125.9 (d), 125.4 (d), 124.5 (s), 99.4 (d), 31.1 (d), 21.2 (q) ppm.

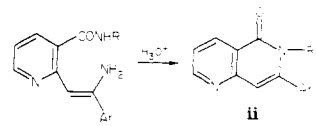
Acknowledgment. We express appreciation to Messrs. C. M. Combs and J. G. Schmidt or their assistance in obtaining spectral data and to Mr. C. I. Kennedy for microanalyses.

Supplementary Material Available: Full spectral data (IR and ^1H and ^{13}C NMR) for compounds **3b–f** (1 page). Ordering information is given on any current masthead page.

(10) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008.

(11) 2,2-Dimethyl-2-[(3-phenyl-1-isoquinolinyl)amino]ethanol (**9**) was isolated as a colorless solid: mp 158–160 °C (CH_3OH); IR (KBr) 3350, 1577, 1567, 1544, 1454, 1427, 1073, 1065, 769, 697 cm^{-1}; ^1H NMR (Me_2SO-d_6) 8.21 (m, 3), 7.50 (m, 7), 6.46 (br s, 1), 5.41 (t, 1, J = 5.8 Hz), 3.82 (d, 2, J = 5.8 Hz), 1.65 (s, 6) ppm; ^{13}C NMR (Me_2SO-d_6) 154.7 (s), 147.8 (s), 140.0 (s), 137.6 (s), 129.8 (d), 128.6 (d), 128.0 (d), 127.3 (d), 126.3 (d), 125.5 (d), 123.2 (d), 117.9 (s), 105.7 (d), 68.9 (t), 55.4 (s), 23.8 (q) ppm.

(12) A recent report by Swiss chemists claims analogous enamino nicotinamides i are isolable compounds and require acid hydrolysis to complete cyclization to the corresponding 6,7-disubstituted naphthyridin-5(6*H*)-ones ii (Damon, R. E.; Nadelson, J., United Kingdom Patent Application GB 2 054 593, 1981).



i ii

Concerning the Formation, Reduction, and Conformations of β-(Trimethylsilyl)- and β-(Trimethylstannyl)cyclohexanones

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There has been considerable interest in the addition of (trimethylsilyl)- and (trimethylstannyl)alkalis to α,β-unsaturated ketones; with cyclohexenones, (kinetic) 1,4-addition and exclusive axial approach are regarded as

