Notes

Direct Introduction of Nitriles via Use of Unstable Reissert Intermediates: Convenient Procedures for the Preparation of 2-Cyanoquinolines and 1-Cyanoisoquinolines

Dale L. Boger,*[1a] Christine E. Brotherton,[1b] James S. Panek, and Daniel Yohannes

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045-2500

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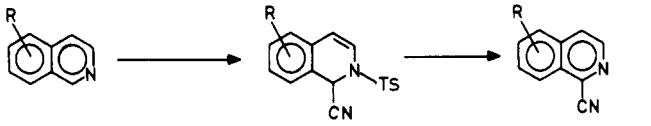
The use of Reissert intermediates in the preparation of substituted quinoline or isoquinoline derivatives is widely recognized, and the synthetic potential of such intermediates, e.g., alkylation and reduction, has been employed in the synthesis of heterocycles.[2] The successful use of Reissert intermediates in the preparation of such derivatives can be attributed to the stability of the *N*-acyl-1-cyano-1,2-dihydroisoquinolines or *N*-acyl-2-cyano-1,2-dihydroquinolines. In contrast, Reissert intermediates derived from arylsulfonyl chlorides lack the necessary stability for similar applications as synthetic intermediates.[3]

Herein we describe convenient procedures which we have utilized[4] for the direct preparation of 1-cyanoisoquinolines and 2-cyanoquinolines based on the advantageous use of this recognized instability of Reissert intermediates generated with the use of *p*-toluenesulfonyl chloride–potassium cyanide, eq 1 and 2. The survey of



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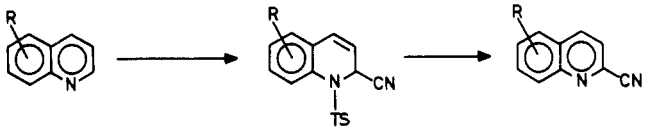

(2)

results detailed in Table I summarizes this investigation.

Simple treatment of isoquinolines with *p*-toluenesulfonyl chloride (1.5 equiv), potassium cyanide (3–6 equiv) in the two-phase system of methylene chloride–water[3,5] (25 °C, 3–48 h) provides the isolable *N*-(*p*-tolylsulfonyl)-1-cyano-1,2-dihydroisoquinolines. Exposure of the crude Reissert intermediates, which are stable to the conditions employed in conventional purification techniques, to mild base [e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N*,*N*-diisopropylethylamine, potassium *tert*-butoxide] affords the 1-cyanoisoquinolines in good overall yield.

In contrast, the Reissert intermediates derived from the reaction of quinolines with *p*-toluenesulfonyl chloride (1.5 equiv) in the presence of potassium cyanide (3.0 equiv, methylene chloride–water, 25 °C)[3,5] are sufficiently unstable to the reaction conditions that the 2-cyanoquinolines may be isolated directly in good yield simply by extending the reaction time (3–5 days). Attempts to reduce this overall reaction time with the addition of tertiary bases (e.g., triethylamine) to the reaction mixture or by isolation of the Reissert intermediate and subsequent mild base treatment resulted in diminished yields of isolated 2-cyanoquinoline. As anticipated, hindered quinolines (e.g., 8-hydroxy- or 8-benzyloxyquinoline) and those bearing strong electron-withdrawing groups (e.g., 6-methoxy-5-nitroquinoline) which are known not to afford Reissert intermediates failed to afford the corresponding 2-cyanoquinolines under the described reaction conditions.[2,5]

Experimental Section

General Procedure for the Preparation of 1-Cyanoisoquinolines: 1-Cyano-5,6,7-trimethoxyisoquinoline (2b). A solution of 5,6,7-trimethoxyisoquinoline[6] (**2a**, 383 mg, 1.75 mmol) and *p*-toluenesulfonyl chloride (1.5 equiv, 502 mg, 2.63 mmol) in 30 mL of methylene chloride was combined with a solution of potassium cyanide (6 equiv, 683 mg, 10.5 mmol) in 10 mL of water, and the reaction mixture was stirred vigorously overnight (12 h) at 25 °C. The solution was poured onto water, extracted with methylene chloride (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude Reissert intermediate was dissolved in 20 mL of dry THF, and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 equiv, 0.32 mL, 2.1 mmol) under nitrogen. After 1 h at 25 °C the reaction mixture was treated with saturated ammonium chloride, poured onto water, extracted with ethyl acetate (3 × 30 mL), and dried ($MgSO_4$). MPLC (15 × 500 mm, 25:75 ethyl acetate:hexane eluant) afforded 310 mg (427 mg theoretical, 73%) of pure **2b** as a white solid: mp 124–125 °C (ethanol, white needles); ^1H NMR ($CDCl_3$) δ 8.50 (1 H, d, J = 6 Hz, C*H*=N), 8.03 (1 H, d, J = 6 Hz, C*H*=CH=N), 7.31 (1 H, s, C=CH=C), 4.08 (6 H, s, two OCH_3), 4.03 (3H, s, OCH_3); IR ($CHCl_3$) ν_{max} 3010, 2950, 2230 (C≡N), 1610, 1575, 1555, 1475, 1420, 1400, 1370, 1300, 1255, 1235, 1180, 1145, 1115, 1030, 1005, 950, 905, 870, 830, 815 cm^{-1}; MS, m/e (relative intensity) 245 (M + 1, 20), 244 (M^+, 100), 229 ($-CH_3$, 49), 201 (20), 186 (34), 158 (15), 115 (40), 88 (13), 75 (14), 63 (26); HRMS, $C_{13}H_{12}N_2O_3$ requires m/e 244.0847, found, 244.0833.

1-Cyanoisoquinoline (1b) (Table I): mp 89–90 °C (ethanol, white needles) (lit.[3] mp 87–89 °C); ^1H NMR ($CDCl_3$) δ 8.6 (1 H, d, J = 7 Hz, C*H*=N), 8.3 (1 H, m), 7.85 (4 H, m); IR ($CHCl_3$) ν_{max} 3090, 3025, 2250 (C≡N), 1625, 1580, 1560, 1500, 1395, 1345, 1320, 1150, 880, 840 cm^{-1}; MS, m/e (relative intensity) 154 (M^+, 100), 128 (10), 127 (43); HRMS, $C_{10}H_6N_2$ requires m/e 154.0531, found, 154.0531.

8-Bromo-1-cyano-5,6,7-trimethoxyisoquinoline (3b) (Table I): mp 116.5–118 °C (ethanol, white needles); ^1H NMR ($CDCl_3$) δ 8.58 (1 H, d, J = 6 Hz, CH=N), 8.15 (1 H, d, J = 6 Hz, C*H*=CH=N), 4.08, 4.06, 4.01 (9 H, three s, three OCH_3); IR ($CHCl_3$) ν_{max} 3060, 2960, 2880, 2250, 1600, 1580, 1460, 1405, 1390, 1375, 1300, 1250, 1200, 1115, 1050, 1010, 965, 910, 866 cm^{-1}; MS, m/e

(1) (a) Searle Scholar recipient, 1981–85; National Institutes of Health career development award recipient, 1983–88 (CA 00898). (b) National Institutes of Health predoctoral trainee, 1981–84 (GM 07775).

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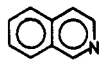
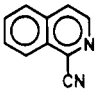
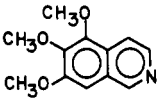
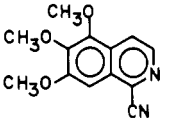
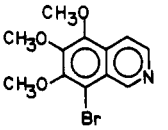
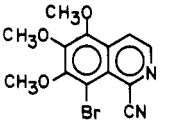
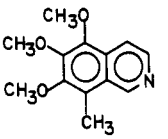
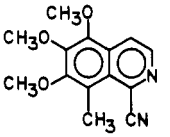
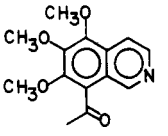
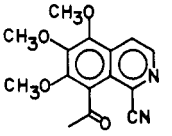
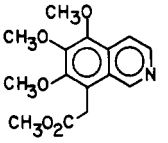
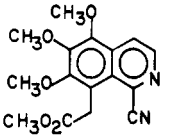
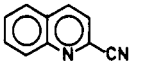
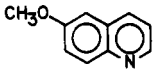
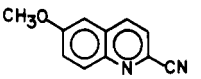
Table I. Preparation of 1-Cyanoisoquinolines and 2-Cyanoquinolines

substrate	conditions: equiv *p*-TsCl, KCN, time h (temp, °C);[a] equiv base, time h (temp, °C)[b]	product[c]	% yield[d]
 1a	1.5, 6.0, 48 (25); 1.1 DBU, 1 (0)	 1b	58
 2a[e]	1.5, 6.0, 12 (25); 1.2 DBU, 1 (25) 3.0 (*i*-Pr)$_2$NEt,[f] 72 (25)	 2b	73 68
 3a[e]	1.5, 6.0, 48 (25); 1.1 DBU, 1 (0) 1.3 *t*-BuOK, 1 (0–25)[g]	 3b	90 64
 4a[e]	1.5, 3.0, 6 (25); 3.0 *t*-BuOK, 1 (25)[g]	 4b	59
 5a[e]	1.5, 3.0, 18 (25); 2.4 DBU, 13 (25)[h]	 5b	75
 6a[e]	1.5, 3.0, 12 (25); 2.0 DBU, 4 (25)[i]	 6b	76
 7a	1.5, 3.0, 72 (25)	 7b	64
 8a	1.6, 3.0, 120 (25) 1.5, 6.0, 22 (25); 1.1 DBU, 0.5 (0)	 8b	81 11

[a] See Experimental Section and ref 3. [b] All reactions were run 0.05–0.1 M in substrate in tetrahydrofuran unless otherwise noted. [c] All products exhibited the expected ^{1}H NMR, IR, and MS characteristics consistent with the assigned structure. Satisfactory C, H, N analysis or HRMS information was obtained for each product. [d] All yields are based on purified product isolated by chromatography (SiO_2) or crystallization. [e] See ref 4a. [f] The reaction was run with chloroform as solvent, 1.5 equiv (*i*-Pr)$_2$NEt (48 h) plus an additional 1.5 equiv (*i*-Pr)$_2$NEt (24 h). [g] The reaction was run with THF/*t*-BuOH (2:1) as solvent. [h] 1.2 equiv of DBU (12 h) plus an additional 1.2 equiv of DBU (1 h). [i] 1.0 equiv of DBU (1 h) plus an additional 1.0 equiv of DBU (3 h).

(relative intensity) 324/322 (M^+, 1/1, 70), 309/307 (1/1, 28), 281/279 (1/1, 38), 266 (35), 264 (24), 213 (23), 195 (41), 193 (43), 185 (56), 170 (51), 157 (58), 142 (87), 127 (44), 114 (33), 87 (91); HRMS, $C_{13}H_{11}N_2BrO_2$ requires *m/e* 321.9952, found 321.9938.

1-Cyano-5,6,7-trimethoxy-8-methylisoquinoline (4b) (Table I): mp 89–90 °C (ethanol–water, white needles); ^{1}H NMR ($CDCl_3$) δ 8.48 (1 H, d, J = 6 Hz, CH=N), 8.07 (1 H, d, J = 6 Hz, C*H*=CH=N), 4.10, 4.05, 3.95 (9 H, three s, three OCH_3), 2.95 (3 H, s, CH_3); IR ($CHCl_3$) ν_{max} 3030, 2960, 2870, 2250 (C≡N), 1600, 1580, 1462, 1395, 1380, 1340, 1255, 1200, 1120, 1080, 1010, 960, 860 cm^{-1}; MS, *m/e* (relative intensity) 259 (M + 1, 21), 258 (M^+, 100), 243 ($-CH_3$, 42), 215 (16), 201 (12), 200 (21), 185 (9), 171 (10), 157 (12), 129 (16), 114 (11), 102 (21), 75 (12), 63 (11); HRMS, $C_{14}H_{14}O_3N_2$ requires *m/e* 258.1004, found 258.1000.

8-Acetyl-1-cyano-5,6,7-trimethoxyisoquinoline (5b) (Table I): ^{1}H NMR ($CDCl_3$) δ 8.55 (1 H, d, J = 6 Hz, C*H*=N), 8.15 (1 H, d, J = 6 Hz, C*H*=CH=N), 4.09, 4.07, 3.98 (9 H, three s, three OCH_3), 2.82 (3H, s, CH_3C=O); IR (film) ν_{max} 2970, 2880, 2250 (C≡N), 1710 (C=O), 1595, 1580, 1550, 1480, 1460, 1420, 1395, 1360, 1260, 1205, 1175, 1110, 1060, 1005, 960, 940, 910, 860 cm^{-1}; MS, *m/e* (relative intensity) 286 (M^+, 29), 272 (16), 271 ($-CH_3$, 100); HRMS, $C_{15}H_{14}N_2O_4$ requires *m/e* 286.0953, found 286.0962.

Methyl 2-(1-cyano-5,6,7-trimethoxy-8-isoquinolyl)acetate (6b) (Table I): mp 109.5–110 °C (ethanol, white needles); ^{1}H NMR ($CDCl_3$) δ 8.53 (1 H, d, J = 6 Hz, CH=N), 8.14 (1 H, d, J = 6 Hz, C*H*=CH=N), 4.58 (2 H, s, $CH_2CO_2CH_3$), 4.06, 4.04 (6 H, two s, two OCH_3), 3.94 (3 H, s, OCH_3), 3.80 (3 H, s, CO_2CH_3); IR ($CHCl_3$) ν_{max} 3020, 2960, 2860, 2250 (C≡N), 1735 (C=O), 1600,

1580, 1460, 1415, 1395, 1380, 1255, 1200, 1175, 1120, 1080, 1030, 1010, 990, 960; MS, *m/e* (relative intensity) 317 (M + 1, 24), 316 (M^+, 70), 258 (20), 257 (100), 242 (11), 227 (10), 215 (21), 199 (11), 156 (9), 128 (14), 101 (10), 75 (12).

Anal. Calcd for $C_{16}H_{16}O_5N_2$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.35; H, 5.29; N, 8.66.

General Procedure for the Preparation of 2-Cyanoquinolines: 2-Cyano-6-methoxyquinoline (8b). A mixture of 6-methoxyquinoline (11.1 g, 70.0 mmol) in CH_2Cl_2 (140 mL) and H_2O (40 mL) containing KCN (13.70 g, 210 mmol, 3.0 equiv) was treated dropwise (30 min) with a solution of *p*-toluenesulfonyl chloride (*p*-TsCl; 22.0 g, 115.0 mmol, 1.6 equiv) in CH_2Cl_2 (150 mL) at 25 °C. After being stirred for 120 h at 25 °C, the mixture was filtered through Celite (washed with CH_2Cl_2, 4 × 30 mL) and the filtrate was concentrated in vacuo. The crude product was dissolved in $CHCl_3$ and passed through a plug of SiO_2 ($CHCl_3$ eluant). The combined $CHCl_3$ fractions were concentrated in vacuo and the product was recrystallized from ethanol–water, affording 10.40 g (12.81 g theoretical, 81%) of pure 8b: mp 175–176 °C (ethanol–water) (lit.[3] mp 177–178 °C); ^1H NMR ($CDCl_3$) δ 8.15 (1 H, d, J = 9 Hz), 8.04 (1 H, d, J = 9 Hz), 7.62 (1 H, d, J = 9. Hz), 7.42 (1 H, dd, J = 9, 2 Hz), 7.09 (1 H, d, J = 2 Hz), 3.96 (3 H, s, $ArOCH_3$); ^{13}C NMR ($CDCl_3$) δ 160.0 (C-6), 144.6 (C-8a), 135.6 (C-4), 131.5 (C-8), 130.8 (C-4a/C-2), 130.3 (C-2/C-4a), 124.6 (C-5), 123.8 (C-3), 117.9 (CN), 104.7 (C-7); IR (KBr) ν_{max} 2949, 2228, 1622, 1499, 1472, 1412, 1387, 1246, 1201, 1167, 1115, 1019, 860, 835 cm^{-1}; MS, *m/e* (relative intensity) 184 (M^+, base), 169 (8), 155 (12), 154 (37), 142 (4), 141 (63), 115 (4), 114 (28), 89 (4), 88 (5), 87 (4), 63 (5), 62 (6), 61 (2).

Anal. Calcd for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.45; H, 4.21; N, 15.00.

2-Cyanoquinoline (7b) (Table I): mp 94–95 °C (ethanol) (lit.[7] mp 91–93 °C); ^1H NMR ($CDCl_3$) δ 8.25 (1 H, d, J = 9 Hz), 8.25–8.05 (1 H, m), 7.82–7.55 (4 H, m); IR (KBr) ν_{max} 3016, 2234, 1501, 1304, 1215 cm^{-1}.

Acknowledgment. The financial support of the National Institutes of Health (CA 33668) and the Chicago Community Trust/Searle Scholars Program is gratefully acknowledged.

Registry No. **1a**, 119-65-3; **1a** Reissert intermediate, 3340-68-9; **1b**, 1198-30-7; **2a**, 36982-71-5; **2a** Reissert intermediate, 91523-13-6; **2b**, 58189-36-9; **3a**, 81925-37-3; **3a** Reissert intermediate, 91523-14-7; **3b**, 91523-06-7; **4a**, 91523-07-8; **4a** Reissert intermediate, 91523-15-8; **4b**, 91523-08-9; **5a**, 91523-09-0; **5a** Reissert intermediate, 91523-16-9; **5b**, 91523-10-3; **6a**, 91523-11-4; **6a** Reissert intermediate, 91523-17-0; **6b**, 91523-12-5; **7a**, 91-22-5; **7a** Reissert intermediate, 91523-18-1; **7b**, 1436-43-7; **8a**, 5263-87-6; **8a** Reissert intermediate, 91523-19-2; **8b**, 5467-79-8; 8-quinolinol, 148-24-3; 8-(benzyloxy)quinoline, 84165-42-4; 6-methoxy-5-nitroquinoline, 6623-91-2.

Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 20.[1] Pdc, a New, Very Selective Heterogeneous Hydrogenation Catalyst

Jean-Jacques Brunet and Paul Caubere*

Laboratoire de Chimie Organique I, ERA CNRS No. 476, Université de Nancy I, 54506 Vandoeuvre-les-Nancy Cêdex, France

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Catalytic semihydrogenation of acetylenes to (*Z*)-olefins constitutes a very important process in organic chemistry.[2] However, although numerous studies have been devoted to this problem,[3] no catalyst of general applicability has been reported so far that exhibits both quantitative bond selectivity (alkene/(alkene + alkane) ratio) and stereoselectivity ($Z/(Z + E)$ ratio).[4] Moreover, as underlined by Friefelder,[3] some catalysts which had been claimed to exhibit high selectivities and stereoselectivities appeared somewhat less successful since chromatographic techniques have been improved. So, numerous works are still aimed at devising highly selective catalysts.[5] Indeed, obtention of highly pure (*Z*)-olefins is often a key step during the synthesis of important substances such as pheromones,[6] biological or natural products,[7] etc.

Among the catalysts reported as efficient in performing selective semihydrogenations of acetylenes, the well-known Lindlar palladium[8] (used in the presence of quinoline) and the more recent P_2 nickel[9] (used in the presence of ethylenediamine) are the most usual.[6]

As part of our study on complex reducing agents,[10] we have recently described a new nickel heterogeneous hydrogenation catalyst (prepared from NaH, *t*-AmOH, and $Ni(OAc)_2$), referred to as Nic.[11] Nic exhibits selectivities and stereoselectivities comparable to those of P_2Ni for the semihydrogenation of acetylenes to (*Z*)-alkenes, even on a preparative scale.[12] The interesting outcomes of this study encouraged us to extend our investigations to catalysts prepared in the same way from other metallic salts.

We present here our first results concerning the atmospheric pressure semihydrogenation of acetylenes over Pdc (prepared from $Pd(OAc)_2$).

Results and Discussion

Preliminary experiments led us to find that the semihydrogenation of monosubstituted acetylenes must be conducted in solvents such as hexane or octane whereas the semihydrogenation of disubstituted ones must be conducted in ethanol, ethanol–hydrocarbon mixtures, or ethanol–THF mixtures.[13] Moreover, in all cases, the presence of quinoline as a catalyst modifier was found to be necessary. In these conditions, Pdc was found to allow highly selective, *self-terminating* semihydrogenations of acetylenes.

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