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Reaction of Benzocyclobutenoxides with Nitriles: Synthesis of Hypecumine and Other 3-Substituted Isoquinolines

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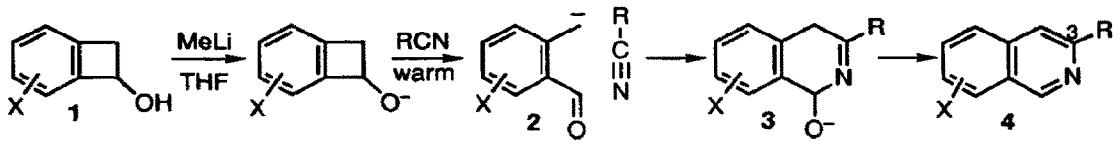
Summary: Treatment of benzocyclobuten-2-ols with MeLi affords *o*-tolualdehyde anions which in the presence of nitriles cyclize to 3-substituted isoquinolines. Examples include the synthesis of the alkaloid hypecumine from the precursors, **14** and **19** (1:1), in 50% yield.

When treated with strong bases, benzocyclobuten-2-ols **1** undergo facile ring-opening to *o*-tolualdehyde anions **2**[1] in a process which can be performed to minimize the presence of *o*-tolualdehyde (no self-aldol problems). Since **1** is now readily available,[2] it is a preferred source of **2** which we have added regiospecifically to benzynes to give unsymmetrical anthracenes[3] and also cyclized with aldehydes to form benzopyranols in high yields.[4] The latter are easily oxidized to 3,4-dihydroisocoumarins including intermediates on the routes to natural products.[4] In this paper, a related reaction of the anions **2** with nitriles to produce 3-substituted isoquinolines **4** is introduced.

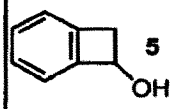
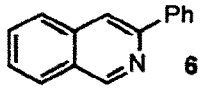
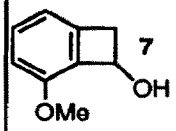
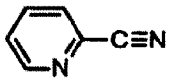
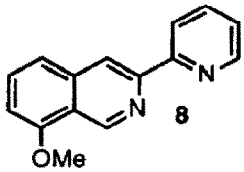
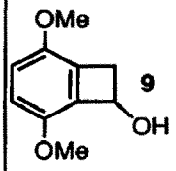
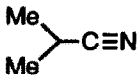
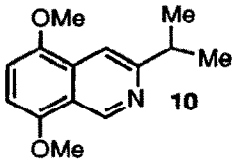
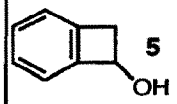
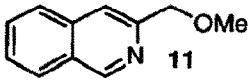
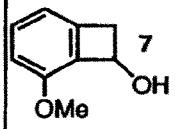
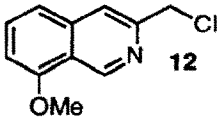
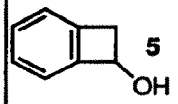
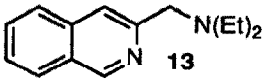
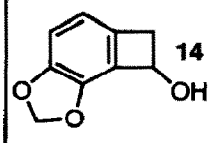
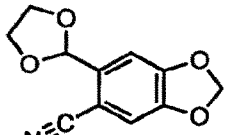
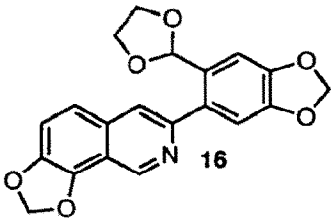
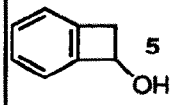
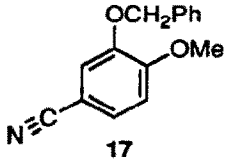
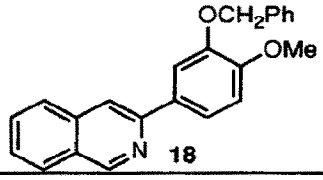


Some 3-arylisoquinolines including alkaloids of this type are pharmaceutically active[5] (*e.g.*; antihypertensives) while others have been utilized as precursors to other important classes of alkaloids[5] (*e.g.*; protoberbines, pavines, isopavines, benzo[c]phenanthridines).

In the first system tested, benzocyclobutenol **5** was deprotonated with MeLi (1.1 equiv.) in THF at –78 °C. Benzonitrile (1.1 equiv.) then was added and the mixture was warmed to rt. After 1 h, the mixture was acidified, extracted into water, basified, and extracted into CH_2Cl_2 to obtain 3-phenylisoquinoline[6] (**6**) in 47% yield after crystallization. In a related experiment, the benzocyclobutenol **7**[3] was converted to the novel pyridylisoquinoline **8**[7] with 2-cyanopyridine (1.5 equiv.) in 55% crystallized yield. These and other cyclizations are summarized in Table 1.

When the alkoxide from **9**[3] reacted with isobutyronitrile, crystalline 3-isopropylisoquinoline **10**[7] was isolated indicating that proton transfer with concomitant nitrile enolate formation is not a

Table 1

Benzocyclobutenol	Nitrile	Product	Yield	mp
 5	Ph–C≡N	 6	47%[a]	104-105 °C[b]
 7		 8	55%[c]	139-140 °C
 9		 10	49%[c]	72-73 °C
 5	$MeOCH_2-C\equiv N$	 11	66%[c,d]	bp 71-73 °C at 0.2 mm[e]
 7	$ClCH_2-C\equiv N$	 12	68%[c]	77-79 °C
 5	$Et_2NCH_2-C\equiv N$	 13	80%[a]	oil; NMR, tlc pure
 14	 15	 16	48%[a]	163-166 °C
 5	 17	 18	90%[f,g]	oil; NMR, tlc pure

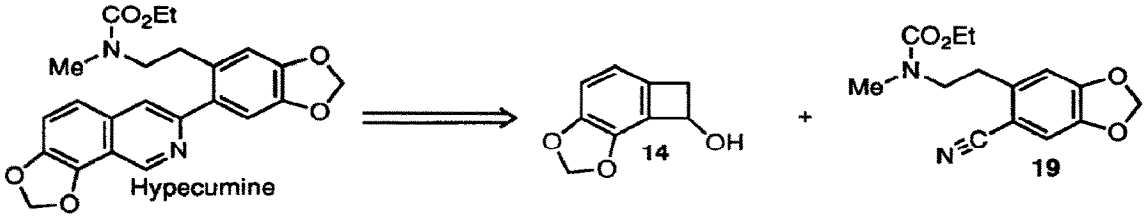
[a]With 1.1 equiv. nitrile. [b]lit[7] mp 104-105 °C [c]With 1.5 equiv. of nitrile. [d]Quantitative yield of crude **12** (pure, ^{1}H NMR); given yield is of **12** distilled on a 0.5 g scale. [e]lit.[8] bp 82 °C at 0.6 mm; [f]Yield is with 5.0 equiv. of **5**. [g]42% yield with 1.5 equiv. of **5**.

significant side reaction. This experiment provided more information when the hydroxyimine species related to **3** was isolated upon initial workup. Dehydration of this hydroxyimine with more acid gave **10** which demonstrates that loss of water from protonated **3** only occurs after acidification.

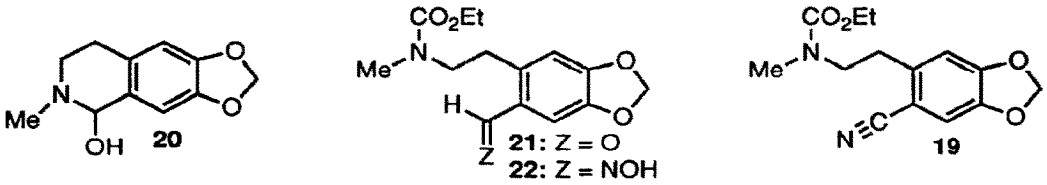
Cyclizations also were performed with the functionalized nitriles, methoxyacetonitrile, chloroacetonitrile, and *N,N*-diethylaminoacetonitrile, to obtain the isoquinolines, **11**,[8] **12**,[7] and **13**,[7] in 60-80% yields. This result is surprising considering the increased C-H acidity of these nitriles *vs.* isobutyronitrile. The improved yields may be a consequence of the greater electrophilicity of nitriles substituted with electron withdrawing groups. The 68% yield of **12** is especially surprising, since the benzylic chloride in the product should be labile in the basic reaction medium. Note that the isoquinolines **11-13** are important because they are primed for further functionalization at the CH_2 position.

In the last entries in Table 1, the more complex nitriles, **15**[9] and **17**[10], were converted into the isoquinolines, **16**[7] and **18**,[7] respectively. In this last model study, the sensitivity of the reaction to excess benzocyclobutenol was examined. With **5**:**17** ratios of 1.5:1, 3:1, and 5:1, the yield of **18** increased from 42% to 59% to 90%.

Attention next focused on the application of this new method to the synthesis of the alkaloid, hypecumine, with its rare urethane moiety. Hypecumine was isolated [from *Hypecoum procumbens* L. (Papaveraceae)] and identified in 1986 by Onur, Abu Zarga, and Gozler.[11]



The required nitrile **19** was prepared by standard oxidation of commercial hydrastine·HCl with HNO_3 to hydrastinine (**20**, 85% yield) which was cleaved to known aldehyde **21**[12] with $ClCO_2Et$ in 97% yield under Schotten-Bauman conditions.[12] Conversion of **21** with NH_2OH·HCl and NaOAc in EtOH to the oxime **22** (Kametani's method[13]) and then treatment of **22** with Et_3N and $(CF_3CO)_2O$ in dioxane at 5-15 °C (Carotti's process[14]) afforded **19** in 72% overall yield from **20**. Finally, deprotonation of **14**[3] (1.0 equiv.) with LiTMP at –78 °C and treatment with **19** (1.0 equiv.) produced hypecumine in 50% yield [IR, ^{1}H NMR (360 MHz), and MS data match published values[11]].



In conclusion, while the cyclization of *o*-tolualdehyde anions with nitriles occurs in lower yield than the similar process with the more electrophilic aldehydes,[4] it still constitutes a convenient and convergent route to 3-substituted isoquinolines.

General Procedure: **8-Methoxy-3-(2-pyridyl)isoquinoline (8).** Methyllithium (2.70 mL, 1.4 M in Et_2O, 3.78 mmol) was dripped into a stirred solution of **7** (0.500 g, 3.33 mmol) in THF (20 mL) at –78 °C. After 5 min, 2-cyanopyridine (0.520 g, 5.00 mmol) was added, the solution was warmed to rt, stirred for 1 h, and then poured into 10% HCl (30 mL) and extracted with CH_2Cl_2 (30 mL). The organic phase was discarded and the aqueous phase was made basic with $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 20 mL). The dried (Na_2SO_4) organic extract was concentrated and crystallized from methanol to isolate **8** as a white solid of mp 139-140 °C; 0.430 g (55% yield); IR (CCl_4) 3065 (m), 2940 (m), 2840 (w), 1625 (s), 1575 (s), 1430 (s), 1355 (s); ^1H NMR ($CDCl_3$) δ 9.65 (s, 1 H), 8.69 (d, J = 5.8 Hz, 1 H), 8.67 (s, 1 H), 8.50 (d, J= 8 Hz, 1 H), 7.79 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 8.2 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 1 H), 7.24 (t, J = 6.1 Hz, 1 H), 6.79 (d, J = 7.6 Hz, 1 H), 3.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.4, 150.2, 149.1, 147.1, 137.6, 136.8, 130.9, 123.1, 121.2, 120.5, 119.4, 117.0, 105.8, 105.4, 55.4; MS (EI) m/z (relative intensity) 236 (M^+, 100), 193 (21); HRMS (EI) calcd. for $C_{15}H_{12}N_2O$ 236.0950, found 236.0932.

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(5) Note that the standard Bischler-Napieralski isoquinoline synthesis often fails in the synthesis of 3-aryl-isoquinolines. For examples, see: Larsen, R. D.; Reamer, R. A., Corley, E. G., Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034; and ref. 2 therein. See ref. 3 therein for papers on pharmaceutical activities and use in the syntheses of other classes of isoquinoline alkaloids.

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(7) The isoquinolines, **8**, **10**, **12**, **13**, **16**, and **18**, and the nitrile **19** all are new compounds which have been characterized by IR, HRMS (EI), ^1H and ^{13}C NMR spectroscopy. ^1H NMR ($CDCl_3$): **10**: δ 9.51 (C_1H), 3.92 and 3.91 (OMe), 3.23 (h, iPr) and 1.39 (d, iPr); **12**: δ 9.56 (C_1H), 3.98 (OMe), 4.81 (CH_2Cl); **13**: δ 9.20 (C_1H), 3.86 (CH_2N), 2.64 (q, Et) and 1.05 (t, Et); **16**: δ 9.35(C_1H), 6.24 and 6.02 (OCH_2O), 5.85 (OCHO), 4.2-3.9 (m, CH_2CH_2); **18**: δ 9.30 (C_1H), 3.92 (OMe), 5.29 (OCH_2Ph); **19**: δ 5.94 (OCH_2O), 2.77 (NMe), 3.37 (t, CH_2CH_2) and 2.84 (t, CH_2CH_2). IR cm^{-1} (CCl_4): **19**: 2220 (m), 1695 (s), 1620 (m).

(8) Farge, D.; Jossin, A.; Ponsinet, G.; Reisdorf, D. US Patent 4,261,992 (Apr. 14, 1981).

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