Facile Synthesis of 1-Aryl-1,2-ethanediols *via* the Reduction of *N*-Substituted Isatins

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1-Aryl-1,2-ethanediol derivatives are important synthetic intermediates in organic synthesis, in particular for the preparation of biologically active compounds.[1] Synthesis of these compounds, especially in their optically active form, has been studied extensively.[2] Dihydroxylation of olefins,[2a] ozonolysis of alkenyl stannanes followed by reduction,[2b] hydrosilylation of arylacetylenes followed by oxidation,[2c] reduction of α-hydroxy ketones,[2d] and many other methods have been used.[2]

Recently, we examined the reaction of *N*-substituted isatin derivatives with various nucleophiles such as alcohols or amines in the presence of sodium borohydride.[3] In the reaction, we could obtain mandelic esters or mandelic amides as the major products with 1.3 equivalents of $NaBH_4$ at room temperature.[3] As a continuous work, we thought that reduction of *N*-substituted isatins with electron-withdrawing group at the nitrogen atom in alcoholic solvent using excess amounts of $NaBH_4$ might give synthetically useful 1-aryl-1,2-ethanediols in a one-pot reaction by adopting appropriate reaction conditions.

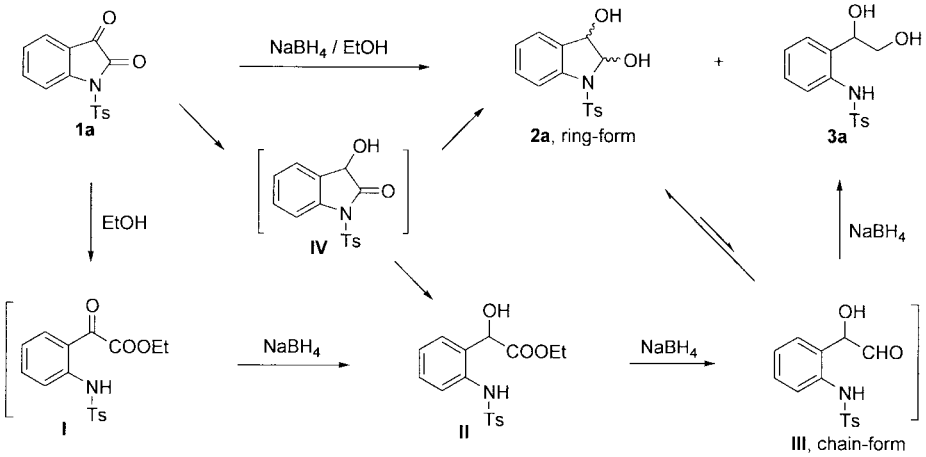
We examined the synthesis of 1-(2-tosylamidophenyl)-1,2-ethanediol (**3a**) from *N*-tosylisatin (**1a**) with 4.0 equivalents of $NaBH_4$. However, we could obtain the desired product **3a** in 27% yield (entry 1 in Table 1). In addition, we could isolate the cyclic diol compound **2a** in 65% yield. This type of compound was known in the literature.[4] According to Merour *et al*., depending on the conditions, **2a** could exist as its chain-form **III** (*vide infra*). We thought the reaction mechanism for the formation of **2a** and **3a** as shown in Scheme 1. (1) Ring opening reaction of **1a** with ethanol gave **I**.[3] (2) Fast reduction of ketone functional group afforded **II**.[3] (3) Somewhat slow reduction of ester to aldehyde formed **III**. (4) The intermediate **III** could exist as its ring-form **2a** or reduced further to diol **3a**. The intermediate **II** and ring-form product **2a** could also be generated *via* the *N*-tosyl-3,3-dihydrodioxindole derivative **IV**.

In order to increase the yield of **3a** we added catalytic amount of acetic acid to the reaction mixture and used excess amounts of sodium borohydride. As expected the amount of **3a** was increased. However, cyclic diol **2a** was

Table 1. Borohydride reduction of *N*-tosylisatin (**1a**)

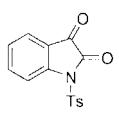
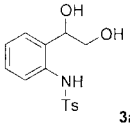
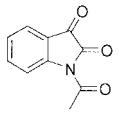
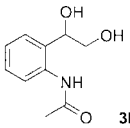
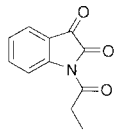
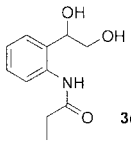
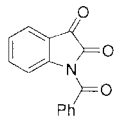
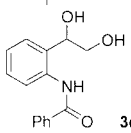
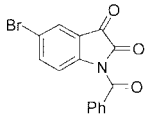
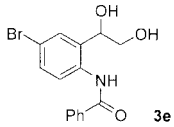
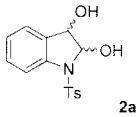
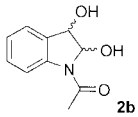
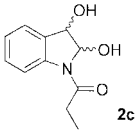
Entry	Conditions	Products (% yield)	
		2a	**3a**
1	$NaBH_4$ (4.0 equiv) EtOH, rt, 4 h	65 (20% de)[a]	27
2	$NaBH_4$ (8.0 equiv) EtOH, rt, 6 days AcOH (cat)	13	68
3	$NaBH_4$ (4.0 equiv) EtOH, 40-50 °C, 3 h	0	99
4	*n*-Bu_4NBH_4 (1.0 equiv) EtOH, -10 °C, 2 h	54	trace
5	*n*-Bu_4NBH_4 (4.0 equiv) EtOH, rt, 1 h	0	81
6	$NaBH_4$ (4.0 equiv) THF, rt, 1 h	49 (20% de)[a]	trace

[a]*Trans* diol is the major[4] and the ratio of *cis*/*trans* can be changed depending on time *via* the chain-form **III**.



Scheme 1

Table 2. Synthesis of diol derivatives **3a-e** and **2a-c**

Entry	Substrate	Conditions	Products (% Yield)
1	 **1a**	$NaBH_4$ (4.0 equiv) EtOH, 40-50 °C, 3 h	 **3a** (99%)
2	 **1b**	$NaBH_4$ (4.0 equiv) EtOH, 40-50 °C, 16 h	 **3b** (68%)
3	 **1c**	$NaBH_4$ (4.0 equiv) EtOH, 40-50 °C, 60 h	 **3c** (78%)
4	 **1d**	$NaBH_4$ (4.0 equiv) EtOH, rt, 1 h	 **3d** (80%)
5	 **1e**	$NaBH_4$ (4.0 equiv) EtOH, rt, 1 h	 **3e** (83%)
6	**1a**	$NaBH_4$ (4.0 equiv) THF, rt, 1 h	 **2a** (49%)[a]
7	**1b**	$NaBH_4$ (4.0 equiv) THF, rt, 1 h	 **2b** (33%)[b]
8	**1c**	$NaBH_4$ (4.0 equiv) THF, rt, 1 h	 **2c** (36%)[c]

[a]20% de (*trans* diol is the major). [b]60% de (*trans* diol is the major). [c]33% de (*cis* diol is the major).

formed together (entry 2). After some trials, we found the best conditions for the formation of **3a**: treatment of **1a** with $NaBH_4$ at elevated temperature (entry 3, 40-50 °C). The use of more reactive *tetra*-butylammonium borohydride could reduce the reaction time (entry 5). With the optimized conditions in hand for the synthesis of 1,2-diol derivative **3a**, we synthesized some diols **3b-e** as shown in Table 2.

For *N*-benzoylisatin (**1d**) and 5-bromo-*N*-benzoylisatin (**1e**), desired diol derivatives **3d** and **3e** were obtained in short time at room temperature. For the preparation of cyclic diol derivatives **2a-c**, the use of THF as solvent is recommended (entry 6 in Table 1 and entries 6-8 in Table 2). The use of ethanol in these cases produced mixtures of products (see entry 1 in Table 1). Although the yields were low, we could obtain the cyclic diols as the major products in THF. The corresponding *N*-benzoyl derivative **2d** could not be obtained even in THF.

We are currently studying the equilibrium between the chain-form and the ring-form. Controlled reduction of *N*-substituted isatins to 3-hydroxyisatins[5] is also under study.

Experimental Section

All materials and solvents were of reagent grade as received from commercial sources. Isatin derivatives **1a-e** were prepared as previously reported.[3]

Typical procedure for the synthesis of 3a: A stirred solution of *N*-tosylisatin (**1a**, 602 mg, 2.0 mmol), sodium borohydride (305 mg, 8.0 mmol) in ethanol (5 mL) was heated to 40-50 °C for 3 h. The reaction mixture was filtered through Celite pad and washed with ether. After removal of solvent and column chromatographic purification (hexane/ethyl acetate, 1 : 2) analytically pure product **3a** was obtained as a white solid, 615 mg (99%): mp 140-142 °C; IR (KBr) 3491, 3340, 3095, 1322, 1153 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.38 (s, 3H), 3.46-3.55 (m, 2H), 3.75 (br s, 1H), 4.72-4.77 (m, 1H), 4.85 (br s, 1H), 7.00-7.72 (m, 8H), 9.26 (br s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 21.52, 66.25, 74.38, 121.40, 124.37, 127.13, 128.06, 128.39, 129.58, 130.60, 136.17, 137.02, 143.58.

The following compounds were synthesized analogously.

3b: white solid, mp 70-72 °C; IR (KBr) 3294, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 3.40 (br s, 1H), 3.58-3.75 (m, 2H), 4.30 (br s, 1H), 4.73-4.78 (m, 1H), 7.04-7.27 (m, 3H), 7.82 (d, J = 7.9 Hz, 1H), 9.11 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.36, 64.90, 73.22, 122.79, 123.98, 126.81, 127.61, 129.44, 135.25, 168.50; Mass (70 eV) *m/z* (rel. intensity) 43 (23), 94 (16), 122 (100), 146 (16), 165 (10), 195 (M^+, 11).

3c: oil; ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.8 Hz, 3H), 2.27 (q, J = 7.8 Hz, 2H), 3.54-3.58 (m, 1H), 3.62-3.69 (m, 2H), 4.58 (br s, 1H), 4.69 (br d, J = 5.4 Hz, 1H), 7.02-7.27 (m, 3H), 7.83 (d, J = 8.1 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.76, 30.96, 65.75, 75.02, 123.32, 124.54, 127.93, 128.83, 129.17, 136.81, 172.73.

3d: white solid, mp 128-130 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.64-3.72 (m, 1H), 3.79-3.87 (m, 1H), 4.52-4.57 (m, 1H), 4.87-4.92 (m, 1H), 5.74 (d, J = 3.3 Hz, 1H), 7.08-8.30 (m, 9H), 10.62 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 64.81, 74.53, 121.86, 123.46, 126.10, 127.03, 127.71, 127.73, 128.11, 130.88, 133.45, 136.06, 164.66.

3e: white solid, mp 158-160 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.66-3.76 (m, 2H), 3.84-3.90 (m, 1H), 4.84-4.90 (m, 1H), 5.18 (d, J = 3.2 Hz, 1H), 7.29-7.96 (m, 7H), 8.31 (d, J = 8.7 Hz, 1H), 10.45 (br s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 65.99, 74.99, 116.59, 124.00, 127.23, 128.74, 130.71, 131.20, 131.83, 134.67, 136.78, 165.15, one carbon is overlapped.

2a: oil; ^1H NMR ($CDCl_3$ + D_2O) δ 2.31 (s, 1.8H, *trans*), 2.35 (s, 1.2H, *cis*), 4.88 (s, 0.6H, *trans*), 4.98 (d, J = 6.3 Hz, 0.4H, *cis*), 5.63 (s, 0.6H, *trans*), 5.71 (d, J = 6.3 Hz, 0.4H, *cis*), 7.00-7.79 (m, 8H, *trans* + *cis*); ^{13}C NMR ($CDCl_3$) δ 21.54, 21.55, 70.95, 76.94, 84.72, 93.28, 114.08, 114.51, 124.27, 124.40, 125.60, 126.17, 127.22, 127.26, 129.87, 129.90, 129.95, 130.04, 130.62, 131.01, 134.83, 135.68, 139.08, 140.54, 144.50, 144.65; Mass (70 eV) *m/z* (rel. intensity) 91 (61), 119 (34), 146 (25), 209 (35), 274 (100), 305 (M^+, 15).

2b: oil; IR (KBr) 3432, 1655 cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O) δ 2.24 (s, 2.4H, *trans*), 2.25 (s, 0.6H, *cis*), 4.68 (s, 0.8H, *trans*), 5.10 (d, J = 6.1 Hz, 0.2H, *cis*), 5.41 (s, 0.8H, *trans*), 5.59 (d, J = 6.1 Hz, 0.2H, *cis*), 7.07-7.94 (m, 4H, *trans* + *cis*); ^{13}C NMR (DMSO-d_6 + D_2O, *trans* isomer) δ 24.12, 77.51, 91.42, 118.01, 125.92, 127.65, 131.24, 132.71, 143.07, 172.56; Mass (70 eV) *m/z* (rel. intensity) 43 (25), 92 (22), 120 (63), 146 (19), 162 (100), 193 (M^+, 7).

2c: mp 126-128 °C; IR (KBr) 3490, 3448, 3380, 1638 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6 + D_2O) δ 1.12-1.28 (m, 3H), 2.46-2.84 (m, 2H), 4.85 (s, 0.35H, *cis*), 5.19 (d, J = 6.5 Hz, 0.65H, *trans*), 5.49 (s, 0.35H, *cis*), 5.60 (d, J = 6.5 Hz, 0.65H, *trans*), 7.08-8.16 (m, 4H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 8.90 (2C), 27.95, 28.33, 70.83, 77.57, 82.92, 90.64, 116.60, 117.04, 123.69, 123.83, 124.87, 125.96, 129.33, 129.71, 131.33 (2C), 140.95, 142.75, 173.84, 173.88; Mass (70 eV) *m/z* (rel. intensity) 57 (15), 92 (18), 120 (79), 176 (100), 207 (M^+, 8).

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