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New and Convenient Synthesis of 2-Substituted 2,3-Dihydro-1*H*-benz[*de*]isoquinolin-1-ones

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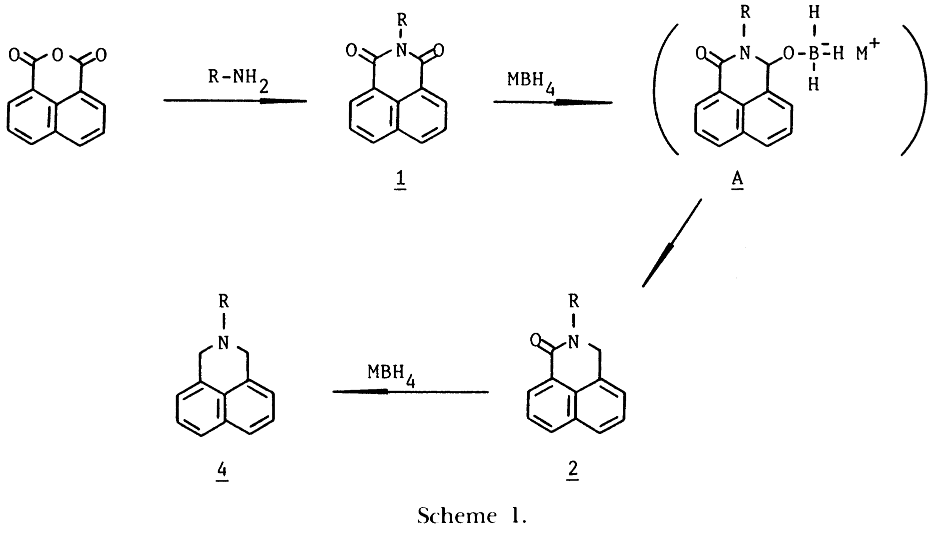
Synopsis. Various 2-substituted 2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-ones were obtained in high yields by chemoselective reduction of 2-substituted 1*H*-benz[*de*]isoquinoline-1,3(2*H*)-diones with sodium or zinc borohydride at room temperature.

Although there have been many reports on the synthesis of isoindoles such as 2,3-dihydro-1*H*-isoindol-1-one,[1] the synthesis of 2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-ones (**2**) have little been studied. Thus, only two papers have been reported on the troublesome synthesis of isoquinoline **2** by electrolytic[2] and catalytic[3] reduction of 2-substituted 1*H*-benz[*de*]isoquinoline-1,3(2*H*)-diones (**1**). In the course of our investigations on the chemistry of isoindoles,[4] we have been looking for new and convenient method for synthesis of isoquinolines **2**, which were novel heterocycles and considered to be versatile for synthesis of biologically active isoquinoline derivatives in connection with alkaloids.[5] It is well-known that carbonyl group of acid anhydride can be reduced to methylene group by sodium borohydride[6] but that of dicarboximides can not be reduced.[1] We could not find actually any example of such reduction in literatures. Therefore, our attempts to synthesize **2** were initially directed to the reactions of 1,8-naphthalenedicarbaldehydes with amines based on the previous results.[7] We could not, however, obtain 2-substituted isoquinolines **2** except for parent isoquinoline **2a**. Meanwhile, a successful example of the demethoxylation of 2,3-dihydro-3-methoxy-1*H*-benz[*de*]isoquinolin-1-one to **2a** with sodium borohydride by Warashawsky[8] was reported to stimulated us to examine selective reduction of 2-substituted 1*H*-benz[*de*]isoquinoline-1,3(2*H*)-diones (**1**), which were readily prepared by treating 1*H*,3*H*-naphtho[1,8-*cd*]pyran-1,3-dione with various amines,[9] to **2** using sodium or zinc borohydride.[10] In this paper, we wish to report a new and convenient chemoselective synthesis of **2** (Scheme 1).

As shown in Table 1, nine isoquinolines **2a—f** and **2o—q** having alkyl substituents were readily formed via intermediate **A** (Scheme 1) in high yields on treatment with sodium borohydride. When desired **2** could not be obtained from **1** with sodium borohydride, zinc borohydride was employed as a reductant to give **2** in moderate yields (Runs 7—11, 13, and 16) together with by-products, 2,3-dihydro-2-alkyl-1*H*-benz[*de*]isoquinoline (**4h—k**). It is noteworthy that the present reduction was compatible with hydroxyl, chloro, and carboxyl groups (Runs 13, 16, and 20—22). Interestingly, three new heterocycles **3l—n** were obtained by treating **1l—n** with sodium borohydride in moderate yields together with desired **2l—n**, as shown in Table 1. Moreover, an addition of magnesium perchlorate to the reaction system using sodium borohydride increased exceedingly the yields of cyclized products **3l—n** (Runs 14, 17, and 19). Although the role of magnesium ion is not necessarily obvious, **3l—n** seem to be formed by intramolecular migration of alkoxyl group of intermediate **B**, in which boron coordinated[11] with two oxygen atom of two hydroxyl groups, in basic conditions as shown in Scheme 2.

3n was obtained as a mixture of two diastereomers. The results of Table 1 show that a bulky substituent **1n** prevented the cyclization and **1o** having five methylene chains did not give the corresponding cyclic compounds (Runs 18 and 20). In the reactions of **1l** and **1m**, the use of zinc borohydride afforded desired **2l** and **2m** preferentially (Runs 13 and 16). Although various solvents such as methanol or tetrahydrofuran were

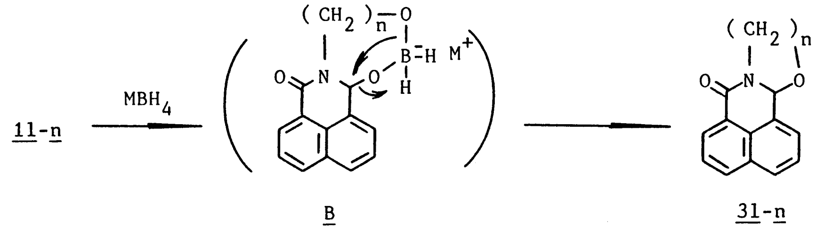


Scheme 1.

Table 1. The Chemoselective Reduction of Benzisoquinoline-1,3-diones **1**

Run[a]	Substrate R	**1**	React. time/h	Boro- hydride	Yield of product/%[b]		
					2	**3**	**4**
1	H-	**1a**	24	$NaBH_4$	97 **2a**[8]	—	—
2	CH_3-	**1b**	24	$NaBH_4$	94 **2b**	—	—
3	$CH_3CH_2CH_2$-	**1c**	24	$NaBH_4$	98 **2c**	—	—
4	$(CH_3)_2CH$-	**1d**	8	$NaBH_4$	79 **2d**	—	—
5	CH_2=CH-CH_2-	**1e**	14	$NaBH_4$	79 **2e**	—	—
6	$CH_3CH_2CH_2CH_2$-	**1f**	5	$NaBH_4$	82 **2f**	—	—
7	C_6H_{11}-	**1g**	24	$Zn(BH_4)_2$	53 **2g**	—	—
8	C_6H_5-	**1h**	25	$Zn(BH_4)_2$	49 **2h**	—	13 **4h**[12]
9	C_6H_5-CH_2-	**1i**	25	$Zn(BH_4)_2$	50 **2i**	—	20 **4i**[13]
10	4-CH_3-C_6H_4-	**1j**	29	$Zn(BH_4)_2$	41 **2j**	—	24 **4j**[12]
11	4-Cl-C_6H_4-	**1k**	23	$Zn(BH_4)_2$	40 **2k**	—	43 **4k**[12]
12	HO-$(CH_2)_2$-	**1l**	4	$NaBH_4$	55 **2l**	22 **3l**	—
13	HO-$(CH_2)_2$-	**1l**	27	$Zn(BH_4)_2$	32 **2l**	—	—
14[c]	HO-$(CH_2)_2$-	**1l**	10	$NaBH_4$	—	81 **3l**	—
15	HO-$(CH_2)_3$-	**1m**	4	$NaBH_4$	34 **2m**	55 **3m**	—
16	HO-$(CH_2)_3$-	**1m**	28	$Zn(BH_4)_2$	36 **2m**	—	—
17[c]	HO-$(CH_2)_3$-	**1m**	10	$NaBH_4$	—	78 **3m**	—
18	HO-CH$(CH_3)CH_2$-	**1n**	4	$NaBH_4$	81 2n	9 **3n**[d]	—
19[c]	HO-CH$(CH_3)CH_2$-	**1n**	12	$NaBH_4$	36 2n	55 **3n**[d]	—
20	HO-$(CH_2)_5$-	**1o**	4	$NaBH_4$	68 **2o**	—	—
21	Cl-CH_2CH_2-	**1p**	4	$NaBH_4$	73 **2p**	—	—
22	HOCO-$(CH_2)_2$-	**1q**	4	$NaBH_4$	83 **2q**	—	—

a) Reaction conditions: **1**, 0.5 mmol, $NaBH_4$, 5 mmol, $Zn(BH_4)_2$, 10 mmol, r.t. b) Isolated yields based on the substrate. c) $Mg(ClO_4)_2$(5 mmol) was added to the reaction system. d) A mixture of two diastereomer was obtained.



Scheme 2.

examined in all cases, only ethanol-water gave preferable results.

Experimental

Measurements. All the melting points were uncorrected. IR spectra were obtained on a Hitachi 295 spectrophotometer and ^1H NMR spectra were obtained on a Hitachi R-22 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-6M mass spectrometer. Elemental analyses were performed with a Yanagimoto MT-3. All the reactions were carried out under a nitrogen atmosphere and monitered by TLC (Merck Kieselgel 60-GF).

Materials. All the reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co. Ltd., or Aldrich Chemical Co. The reagents used were further purified by usual methods such as recrystallization or distillation. Wako gel C-200 was used as a silica gel for column chromatography.

General Procedure. To a solution of sodium borohydride (5 mmol) in $EtOH/H_2O$ (20 ml, v/v : 10/1) was added **1** (0.5 mmol) and then the mixture was stirred for 4 h at 25 °C. After quenching with aq. HCl, the reaction mixture was extracted with CH_2Cl_2 (20 ml×3). The combined organic layer was dried over $MgSO_4$ and evaporation of the solvent followed by chromatography on silica gel gave colorless crystals, 2-substituted 2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-one (**2**). Elemental analyses for **2d**, **2e**, and **2f** were not available because of the lability and the difficulty of further purifications of these compounds.

2a,[8] **4h**,[12] **4i**,[13] **4j**,[12] and **4k**[12] was identified by comparison of the spectral and physical data with those of authentic sample.

2b: Mp 76 °C (from hexane-AcOEt); IR (KBr) 1610 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=3.23$ (s, 3H, CH_3), 4.93 (s, 2H, CH_2), and 7.20—8.36 (m, 6H, arom); MS (20 eV) *m/z* 195 (M^+). Found: C, 79.17; H, 5.67; N, 7.02%. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10%.

2c: Mp 84 °C (from AcOEt); IR (KBr) 1620 and 1645 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.00$ (t, 3H, $J=7$ Hz, CH_3), 1.76 (sex, 2H, $J=7$ Hz, CH_2), 3.64 (t, 2H, $J=7$ Hz, CH_2), 4.94 (s, 2H, CH_2), and 7.15—8.42 (m, 6H, arom); MS (20 eV) *m/z* 225 (M^+). Found: C, 79.64; H, 6.78; N, 6.21%. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%.

2d: Oil; IR (neat) 1620 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.34$ (d, 6H, $J=8$ Hz, CH_3), 4.86 (s, 2H, CH_2), 5.24 (sept, 1H, $J=8$ Hz, CH), and 7.27—8.44 (m, 6H, arom); MS (20 eV) *m/z* 225 (M^+).

2e: Oil; IR (neat) 1610 and 1635 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=4.23$—4.38 (m, 2H, CH_2), 4.88 (s, 2H, CH_2), 5.15—5.43 (m, 2H, =CH_2), 5.68—6.23 (m, 1H, -CH=), and 7.17—8.40 (m, 6H, arom); MS (20 eV) *m/z* 223 (M$^+$).

2f: Oil; IR (neat) 1610 and 1635 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.00 (t, 3H, *J*=7 Hz, CH$_3$), 1.24—1.93 (m, 4H, CH$_2$), 3.71 (t, 2H, *J*=7 Hz, CH$_2$), 4.97 (s, 2H, CH$_2$), and 7.27—8.46 (m, 6H, arom); MS (20 eV) *m/z* 239 (M$^+$).

2g: Mp 127 °C (from AcOEt); IR (KBr) 1610 and 1630 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=0.90—2.30 (m, 1H, cyclohexyl), 4.80 (s, 2H, CH$_2$), and 7.10—8.27 (m, 6H, arom); MS (70 eV) *m/z* 265 (M$^+$). Found: C, 81.67; H, 7.27; N, 5.35%. Calcd for C$_{18}$H$_{19}$NO: C, 81.48; H, 7.22; N, 5.28%.

2h: Mp 164 °C (from AcOEt); IR (KBr) 1615 and 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=5.33 (s, 2H, CH$_2$) and 7.24—8.54 (m, 11H, arom); MS (70 eV) *m/z* 259 (M$^+$). Found: C, 83.36; H, 4.96; N, 5.31%. Calcd for C$_{18}$H$_{13}$NO: C, 83.38; H, 5.05; N, 5.40%.

2i: Mp 102 °C (from AcOEt); IR (KBr) 1615 and 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=4.87 (s, 2H, CH$_2$), 4.93 (s, 2H, CH$_2$), and 7.15—8.55 (m, 11H, arom); MS (70 eV) *m/z* 273 (M$^+$). Found: C, 83.25; H, 5.47; N, 5.09%. Calcd for C$_{19}$H$_{15}$NO: C, 83.49; H, 5.53; N, 5.13%.

2j: Mp 153 °C (from AcOEt); IR (KBr) 1615 and 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=2.40 (s, 3H, CH$_3$), 5.30 (s, 2H, CH$_2$), and 7.11—8.50 (m, 10H, arom); MS (70 eV) *m/z* 273 (M$^+$). Found: C, 83.64; H, 5.47; N, 5.05%. Calcd for C$_{19}$H$_{15}$NO: C, 83.49;H, 5.53; N, 5.13%.

2k: Mp 232 °C (from AcOEt); IR (KBr) 1620 and 1645 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=5.26 (s, 2H, CH$_2$) and 7.18—8.42 (m, 10H, arom); MS (70 eV) *m/z* 293 (M$^+$). Found: C, 73.53; H, 4.06; N, 4.88%. Calcd for C$_{18}$H$_{12}$NOCl: C, 73.60; H, 4.12; N, 4.77%.

2l: Mp 125 °C (from AcOEt); IR (KBr) 1610, 1635, and 3380 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.64—4.14 (m, 5H, CH$_2$×2 and OH), 4.96 (s, 2H, CH$_2$), and 7.09—8.25 (m, 6H, arom); MS (70 eV) *m/z* 227 (M$^+$). Found: C, 73.73; H, 5.77; N, 5.98%. Calcd for C$_{14}$H$_{13}$NO$_2$: C, 73.99; H, 5.77; N, 6.16%.

2m: Mp 86 °C (from AcOEt); IR (KBr) 1640 and 3375 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.89 (quint, 2H, *J*=7 Hz, CH$_2$), 3.55 (q, 2H, *J*=7 Hz, CH$_2$), 3.78 (t, 2H, *J*=7 Hz, CH$_2$), 4.01 (t, 1H, *J*=7 Hz, OH), 4.90 (s, 2H, CH$_2$), and 7.13—8.27 (m, 6H, arom); MS (70 eV) *m/z* 241 (M$^+$). Found: 74.50; H, 6.31; N, 5.73%. Calcd for C$_{15}$H$_{15}$NO$_2$: C, 74.67; H, 6.27; N, 5.80%.

2n: Mp 102 °C (from AcOEt); IR (KBr) 1610, 1635, and 3300 cm^{-1} ; ^{1}H NMR (CDCl$_3$) δ=1.22 (d, 3H, *J*=7 Hz, CH$_3$), 3.51 (d, 2H, *J*=7 Hz, CH$_2$), 3.91 (bs, 1H, OH), 4.14 (sext,1H, *J*=7 Hz, CH), 4.90 (s, 2H, CH$_2$), and 6.96—8.12 (m, 6H, arom); MS (70 eV) *m/z* 241 (M$^+$). Found: C, 74.27; H, 6.34; N, 5.67%. Calcd for C$_{15}$H$_{15}$NO$_2$: C, 74.67; H, 6.27; N, 5.80%.

2o: Mp 103 °C (from AcOEt); IR (KBr) 1615, 1640, and 3390 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=0.95—1.97 (m, 6H, CH$_3$), 2.24 (s, 1H, OH), 3.53—3.83 (m, 4H, CH$_2$), 4.95 (s, 2H, CH$_2$), and 7.23—8.42 (m, 6H, arom); MS (70 eV) *m/z* 269 (M$^+$). Found: C, 75.48; H, 7.05; N, 4.92%. Calcd for C$_{17}$H$_{19}$NO$_2$: C, 75.81; H, 7.11; N, 5.20%.

2p: Mp 64 °C (from AcOEt); IR (KBr) 1610 and 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=2.20 (quint, 2H, *J*=7 Hz, CH$_2$), 3.62 (t, 2H, *J*=7 Hz, CH$_2$), 3.75 (t, 2H, *J*=7 Hz, CH$_2$), 4.94 (s, 2H, CH$_2$), and 7.16—8.38 (m, 6H, arom); MS (20 eV) *m/z* 259 (M$^+$). Found: C, 69.10; H, 5.47; N, 5.53%. Calcd for C$_{15}$H$_{14}$NOCl: C, 69.37; H, 5.43; N, 5.39%.

2q: Mp 149 °C (from AcOEt); IR (KBr) 1605, 1630, 1720, and 3000 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$) δ=2.76 (t, 2H, *J*=7 Hz, CH$_2$), 3.87 (t, 2H, *J*=7 Hz, CH$_2$), 5.17 (s, 2H, CH$_2$), and 7.47—8.52 (m, 7H, arom and COOH); MS (70 eV) *m/z* 182 (M$^+$—CH$_2$CH$_2$COOH). Found: C, 70.00; H, 5.12; N, 5.43%. Calcd for C$_{15}$H$_{13}$NO$_3$: C, 70.58; H, 5.13; N, 5.49%.

3l: Mp 142 °C (from AcOEt); IR (KBr) 1620 and 1640 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$) δ=3.48—4.35 (m, 4H, CH$_2$), 6.14 (s, 1H, CH), and 7.60—8.35 (m, 6H, arom); MS (70 eV) *m/z* 225 (M$^+$). Found: C, 74.59; H, 4.85; N, 6.15%. Calcd for C$_{15}$H$_{13}$NO$_2$: C, 74.65; H, 4.92; N, 6.22%.

3m: Mp 126 °C (from AcOEt); IR (KBr) 1660 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.52—2.41 (m, 2H, CH$_2$), 2.90—3.26 (m, 1H, CH), 3.93—4.42 (m, 2H, CH$_2$), 4.97—5.26 (m, 1H, CH), 6.04 (s, 1H, CH), and 7.44—8.52 (m, 6H, arom); MS (70 eV) *m/z* 239 (M$^+$). Found: C, 75.64; H, 5.52; N, 5.94%. Calcd for C$_{15}$H$_{13}$NO$_2$: C, 75.30; H, 5.48; N, 5.85%.

3n: Mp 111 °C (from AcOEt); IR (KBr) 1670 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.43 (d, 3H, *J*=7 Hz, CH$_3$), 3.37 (d, 2H, *J*=7 Hz, CH$_2$), 3.01—3.25 (m, 0.09H, CH), 4.18—4.75 (m, 0.91H, CH), 6.05 (s, 0.82H, CH), 6.15 (s, 0.18H, CH), and 7.43—8.30 (m, 6H, arom); MS (70 eV) *m/z* 239 (M$^+$). Found: C, 75.47; H, 5.48; N, 5.86%. Calcd for C$_{15}$H$_{13}$NO$_2$: C, 75.30; H, 5.48; N, 5.85%.

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