Synthesis of *ortho*-Acetamidomandelic Acid Derivatives from Isatins

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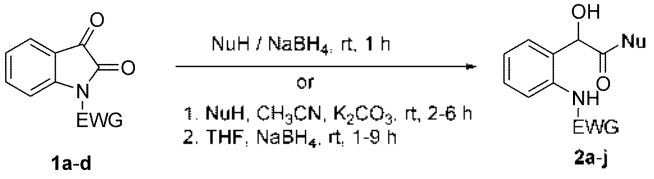
Mandelic acid derivatives are important synthetic intermediates in organic synthesis for many biologically active compounds.[1] Recently, asymmetric version of the Friedel-Crafts type reaction with ethyl glyoxylate for the synthesis of chiral mandelic esters has been reported.[2a] Although various synthetic methods are available for the synthesis of these compounds,[2] development of another facile preparation method would be beneficial until now.

During the Baylis-Hillman reaction of isatin and its derivatives[3] we found that isatin derivatives with electron withdrawing substituent at the nitrogen atom, such as *N*-acetylisatin (**1a**), *N*-propionylisatin (**1b**), *N*-benzoylisatin (**1c**) and *N*-tosylisatin (**1d**), are very labile toward some nucleophiles. The labile properties of *N*-acetyl- or *N*-tosylisatin toward nucleophiles such as ammonia, amines, alcohols and hydroxylamine have been reported.[4] Ring opening reaction by the nucleophile at the N_1-C_2 bond of these compounds can occur easily.[4] Thus, we presumed that we could prepare the mandelic acid derivatives directly in a one-pot reaction by combining the ring-opening reaction and reduction process.

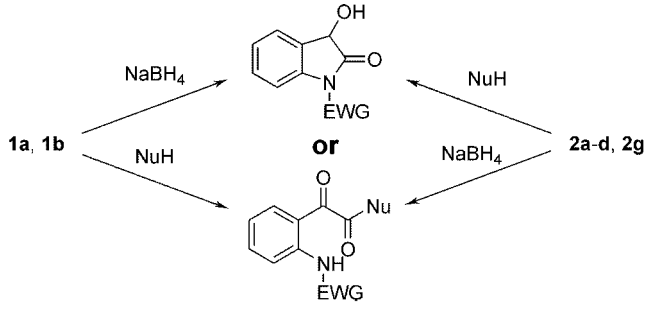
Isatin derivatives **1a-d** could be prepared by the general procedure without difficulty.[5] As shown in Scheme 1 and in Table 1, *N*-acetylisatin (**1a**) in various alcoholic solvents in the presence of $NaBH_4$ (1.3 equiv) gave the corresponding mandelic acid derivatives **2a-d** in good yields. We did not aware which step proceeds first, whether the ring opening reaction or the reduction process (Scheme 2). Menthol derivative **2e** was prepared *via* a two-step procedure. Ring opening reaction of **1a** with (1R, 2S, 5R)-(-)-menthol, a solid alcohol, in acetonitrile in the presence of K_2CO_3 gave the ring-opened intermediate in 52% yield. This compound was reduced as before to give the desired product **2e** in 82% yield. In the reduction stage, low diastereoselectity (*ca.* 20% de) was observed. For the preparation of **2f**, ring opening ($TsNH_2$, K_2CO_3, CH_3CN, rt, 2 h, 54%) was performed before reduction. The reduction of *N*-propionylisatin (**1b**) was carried out under the similar reaction conditions. For the reduction of **1c** and **1d**, however, the yields of **2h** and **2i** were low when the reaction was performed in ethanol solvent. The corresponding 1,2-diol derivatives were formed as side products *via* further reduction of the ester group. Thus, we prepared **2h** and **2i** *via* successive two-step procedure as for the synthesis of **2e** and **2f**. Mandelic amide derivative **2j** was also synthesized by a two-step procedure using pyrrolidine as solvent before reduction.



EWG = COMe, COEt, COPh, SO_2Tol-*p*

NuH = EtOH, MeOH, *i*PrOH, allyl alcohol, menthol, $TsNH_2$, pyrrolidine

Scheme 1



Scheme 2

The reaction procedure is simple as exemplified by the synthesis of ethyl 2-acetamidomandelate (**2a**): To a stirred solution of **1a** (378 mg, 2.0 mmol) in ethanol (5 mL) was added sodium borohydride (100 mg, 2.6 mmol) and stirred at room temperature during 1 h. After usual workup and column chromatographic purification (hexane/ethyl acetate, 2 : 1) analytically pure **2a** was obtained as an oil, 413 mg (87%).[6]

In conclusion, we disclosed a facile synthetic method for the preparation of mandelic acid derivatives from the easily available isatin derivatives.

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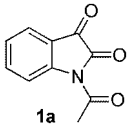
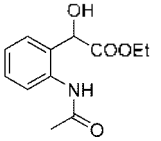
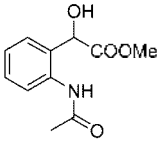
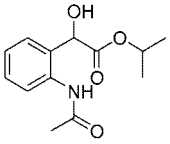
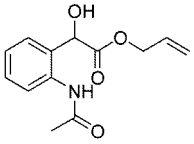
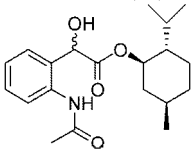
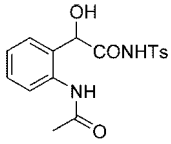
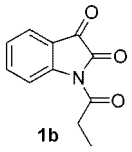
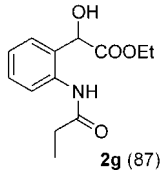
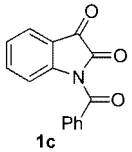
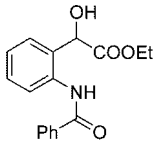
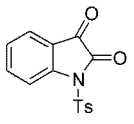
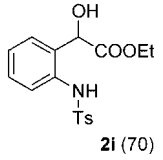
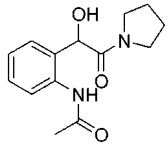
References and Notes

1. (a) Khalaj, A.; Shadnia, H.; Sharifzadeh, M. *Pharm. Pharmacol. Commun.* **1998**, *4*, 373. (b) Miersch, O.; Kramell, R.; Parthier, B.; Wasternack, C. *Phytochemistry* **1999**, *50*, 353. (c) El-Nimr, A. E.; Salama, H. A.; Khalil, R. M.; Kassem, M. A. *Pharmazie* **1983**, *38*, 728. (d) Nishihata, T.; Takahagi, H.; Yamamoto, M.; Tomida, H.; Rytting, J. H.; Higuchi, T. *J. Pharm. Sci.* **1984**, *73*, 109. (e) Yoshioka, M.; Yoshida, A.; Ichihashi, Y.; Saito, H. *Chem. Pharm. Bull.* **1985**, *33*, 2145. (f) Hoover, J. R. E.; Dunn, G. L.; Jakas, D. R.; Lam, L. L.; Taggart, J. J.; Guarini, J. R.; Phillips, L. *J. Med. Chem.* **1974**, *17*, 34.

Table 1. Synthesis of mandelic acid derivatives **2**

Substrates	Conditions	Products (%)
 **1a**	EtOH $NaBH_4$ (1.3 equiv) rt, 1 h	 **2a** (87)
1a	MeOH $NaBH_4$ (1.3 equiv) rt, 1 h	 **2b** (80)
1a	*i*PrOH $NaBH_4$ (1.3 equiv) rt, 1 h	 **2c** (86)
1a	allyl alcohol $NaBH_4$ (1.3 equiv) rt, 1 h	 **2d** (85)
1a	1. menthol (1.0 equiv) K_2CO_3 (1.2 equiv) CH_3CN, rt, 6 h 52% 2. $NaBH_4$ (1.3 equiv) THF, rt, 9 h 82%	 **2e**[a] (43)
1a	1. $TsNH_2$ (3.0 equiv) K_2CO_3 (1.2 equiv) CH_3CN, rt, 2 h 54% 2. $NaBH_4$ (1.3 equiv) THF, rt, 4 h 82%	 **2f** (44)
 **1b**	EtOH $NaBH_4$ (1.3 equiv) rt, 1 h	 **2g** (87)
 **1c**	1. EtOH rt, 9 h 91% 2. $NaBH_4$ (2.0 equiv) THF, rt 10 h, 83%	 **2h** (76)
 **1d**	1. EtOH rt, 40 h 77% 2. $NaBH_4$ (1.3 equiv) EtOH, rt 1 h, 91%	 **2i** (70)
1a	1. pyrrolidine rt, 1 h 91% 2. $NaBH_4$ (1.3 equiv) THF, rt, 1 h 89%	 **2j** (81)

[a]Diastereomeric mixture (20% de based on ^{1}H NMR).

2. (a) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (b) Byun, I. S.; Kim, Y. H. *Synth. Commun.* **1995**, *25*, 1963. (c) Xiang, Y. B.; Snow, K.; Belley, M. *J. Org. Chem.* **1993**, *58*, 993. (d) Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290. (e) Soai, K.; Hasegawa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 769. (f) Soai, K.; Ishizaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1016. (g) Soai, K.; Komiya, K.; Shigematsu, Y.; Hasegawa, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1282. (h) Kiegiel, J.; Papis, A.; Jurczak, J. *Tetrahedron: Asymmetry* **1999**, *10*, 535. (i) Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009. (j) Solodin, I.; Goldberg, Y.; Zelcans, G.; Lukevics, E. *J. Chem. Soc., Chem. Commun.* **1990**, 1321. (k) Soai, K.; Isoda, T.; Hasegawa, H.; Ishizaki, M. *Chem. Lett.* **1986**, 1897. (l) Russell, A. E.; Miller, S. P.; Morken, J. P. *J. Org. Chem.* **2000**, *65*, 8381. (m) Dayan, S.; Bareket, Y.; Rozen, S. *Tetrahedron* **1999**, *55*, *3657*.
3. Baylis-Hillman Reaction of Isatin Derivatives: Isatins as a New Entry for the Baylis-Hillman Reaction, manuscript in preparation.
4. (a) Angell, E. C.; Black, D. St C.; Kumar, N. *Magn. Reson. Chem.* **1992**, *30*, 1. (b) Meyer, F. J. *Chem. Ber.* **1966**, *99*, 3060. (c) Popp, F. D.; Piccirilli, R. M. *J. Heterocyclic Chem.* **1971**, *8*, 473. (d) de Mayo, P.; Ryan, J. J. *Can. J. Chem.* **1967**, *45*, 2117. (e) Bergman, J.; Carlsson, R.; Lindstrom, J.-O. *Tetrahedron Lett.* **1976**, 3611. (f) Franke, A. *Liebigs Ann. Chem.* **1982**, 794.
5. Isatin derivatives **1a-d** were prepared from isatin as follows: *N*-acetylisatin (**1a**) with acetic anhydride (80-90 °C, 3 h, 79%); *N*-propionylisatin (**1b**) with propionyl chloride (CH_2Cl_2, pyridine, rt, 2 h, 94%); *N*-benzoylisatin (**1c**) with benzoic anhydride (CH_2Cl_2, Et_3N, rt, 3 h, 80%); *N*-tosylisatin (**1d**) with *p*-toluenesulfonyl chloride (CH_2Cl_2, Et_3N, rt, 3 h, 50%).
6. Selected spectroscopic data. **2a**: oil; IR (KBr) 3455, 1735, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3H), 2.08 (s, 3H), 4.07-4.20 (m, 2H), 4.97 (br s, OH, 1H), 5.18 (s, 1H), 7.07-7.32 (m, 3H), 7.86 (d, J = 8.1 Hz, 1H), 8.74 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 13.90, 24.18, 62.09, 72.68, 123.77, 124.72, 128.33, 129.09, 129.21, 136.17, 169.26, 172.66; Mass (70 eV) *m z* (rel. intensity) 43 (20), 93 (18), 122 (100), 149 (14), 163 (15), 237 (M$^+$, 14). **2b**: white solid, mp 144-146 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.58 (d, J = 2.9 Hz, 1H), 3.75 (s, 3H), 5.23 (d, J = 2.9 Hz, 1H), 7.12-7.40 (m, 3H), 7.93 (d, J = 8.1 Hz, 1H), 8.31 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.39, 53.29, 72.80, 124.17, 124.90, 127.66, 129.33, 129.68, 136.29, 168.84, 173.47. **2c**: oil; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H), 2.12 (s, 3H), 4.36 (d, J = 2.5 Hz, 1H), 5.03 (heptet, J = 6.2 Hz, 1H), 5.17 (d, J = 2.5 Hz, 1H), 7.08-7.35 (m, 3H), 7.91 (d, J = 7.5 Hz, 1H), 8.56 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.30, 21.51, 24.27, 70.32, 72.68, 123.70, 124.55, 128.08, 128.92, 129.19, 136.15, 168.82, 172.35. **2d**: oil; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 4.57-4.61 (m, 2H), 4.65 (br s, 1H), 5.12-5.19 (m, 2H), 5.23 (s, 1H), 5.70-5.85 (m, 1H), 7.08-7.35 (m, 3H), 7.90 (d, J = 8.1 Hz, 1H), 8.63 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.22, 66.30, 72.74, 118.96, 123.66, 124.65, 127.91, 129.12, 129.30, 130.92, 136.19, 169.14, 172.24. **2h**: oil; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3H), 3.73 (br s, 1H), 4.14-4.24 (m, 2H), 5.31 (s, 1H), 7.12-7.98 (m, 8H), 8.25 (d, J = 8.1 Hz, 1H), 9.36 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.98, 62.70, 73.09, 123.48, 124.62, 127.17, 127.38, 128.77, 129.12, 129.62, 131.90, 134.50, 136.67, 165.46, 172.86.