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Mild and Efficient Synthesis of 1,8-Naphthalide and 1,8-Naphthalenedimethanol

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Mild and Efficient Synthesis of 1,8-Naphthalide and 1,8-Naphthalenedimethanol

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ABSTRACT

Mild and efficient procedures have been developed for synthesis of 1,8-naphthalide and 1,8-naphthalenedimethanol. In an ice-water bath, 1,8-naphthalide was prepared from 1,8-naphthlic anhydride using LiAlH₄ as reducing agent. 1,8-Naphthalenedimethanol was obtained with good yield from reduction of 1,8-naphthalic anhydride by LiAlH₄

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and Lewis acids at room temperature. The effects of various factors on the reduction of 1,8-naphthalic anhydride with $LiAlH_4$ were investigated.

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Key Words: Lewis acids; LiAlH₄; 1,8-Naphthalic anhydride; 1,8-Naphthalide; 1,8-Naphthalenedimethanol.

INTRODUCTION

1,8-Naphthalide and 1,8-naphthalenedimethanol are intermediates for synthesis of pharmaceuticals^[1] and theoretical research.^[2] 1,8-Naphthalide can be made by multiple-step reactions,^[3] by oxidation of expensive 1,8-naphthalenedimethanol,^[4] or by reduction of 1,8-naphthalic anhydride with NaBH₄ (44% yield).^[2a] Besides synthesis by multiple steps,^[5] 1,8-naphthalenedimethanol is usually prepared by reduction of naphthlic anhydride with LiAlH₄ under reflux (in THF for a long time in common),^[1b,2c,6] even so long as 6 days (in a mixture solvent of benzene and ether).^[2b] However long-time refluxing in THF (30 hr) led to a lot of by-products benzonorcaradiene.^[7] Besides, due to the high vapor pressure and flammability of THF, long-time reflux in THF is latent danger for experiment room. We report mild and efficient methods for synthesis of 1,8-naphthalide and 1,8-naphthalene-dimethanol from 1,8-naphthalic anhydride (Sch. 1).

When we tried to prepare 1,8-naphthalenedimethanol, we added naphthlic anhydride into a flask with a THF solution of LiAlH₄ in an ice-water bath, and then the mixture was heated to reflux for 2 hr. After workup and purification by recrystallization from *n*-hexane and ethyl acetate, the product discovered was unexpected not 1,8-naphthalenedimethanol but 1,8-naphthalide. In another experiment, 1,8-naphthalic anhydride was reduced by LiAlH₄ in an ice-salt bath to give a crude product composing of 94.1% 1,8-naphthalide



Scheme 1. Synthesis of 1,8-naphthalide and 1,8-naphthalenedimethanol.





Synthesis of 1,8-Naphthalide and 1,8-Naphthalenedimethanol

and 5.9% 1,8-naphthalenedimethanol measured by ¹H NMR, which was recrystallized to give crystalline 1,8-naphthalide with 73.2% isolated yield.

As we know, combination of Lewis acids and metal hydride has produced a number of efficient reducing agent.^[8] In order to find a mild condition for preparing 1,8-naphthalenedimethanol, we resorted to combine LiAlH₄ with Lewis acids. 1,8-Naphthalic anhydride was reduced efficiently by LiAlH₄ and Lewis acids. The results are listed in Table 1.

The mole ratios of reducing agent to substrate apparently affected yields. Yields increased when the mole ratios of LiAlH₄ to 1,8-naphthalic anhydride varied from 1.2/1 to 3/1 (entries 1-3), and then slowed down while the mole ratio up to 4/1 (entries 3 and 4). Therefore, 3/1 was adopted as the choice mole ratio for other test. With the mole ratio of 3/1, good yields were achieved when AlCl₃, ZnCl₂, and BF₃ were used as Lewis acids.

The mole ratios of LiAlH₄ to Lewis acids also had impact on results. Except for $BF_3 \cdot Et_2O$, excess Lewis acids resulted in formation of by-products,

Entries	Reactants and its adding order	Ratios of reactants	Isolated yield (%)
1	LiAlH ₄ /AlCl ₃ /anhydride	1.2/0.4/1	60.2
2	LiAlH ₄ /AlCl ₃ /anhydride	2/0.67/1	70.5
3	LiAlH ₄ /AlCl ₃ /anhydride	3/1/1	78.3
4	LiAlH ₄ /AlCl ₃ /anhydride	4/1/1	79.1
5	LiAlH ₄ /ZnCl ₂ /anhydride	1.2/0.6/1	67.2
6	LiAlH ₄ /anhydride/ZnCl ₂	3/1/1	84.1
7	LiAlH ₄ /anhydride/ZnCl ₂	3/1/3	$(64.1/16.9/19.0)^{a}$
8	LiAlH ₄ /BF ₃ · Et ₂ O/anhydride	2/1/1	63.7
9	LiAlH ₄ /anhydride/BF ₃ · Et ₂ O	3/1/1.5	80.6(92.9/7.1/0) ^a
10	LiAlH ₄ /anhydride/SnCl ₄	3/1/1	40.9
11	LiAlH ₄ /anhydride/SnCl ₄	3/1/3	$(70.6/19.1/10.3)^{a}$
12	LiAlH ₄ /CaCl ₂ /anhydride	3/1/1	$16.4 + 36.1^{b}$
13	LiAlH ₄ /anhydride	3/1	69.5 [°]

Table 1. Synthesis of 1,8-naphthalenedimethanol by reduction of naphthalic anhydride with LiAlH_4 and Lewis acids.

^aData in parentheses are measured by ¹H NMR, and are corresponding to the mole ratios of 1,8-naphthalenedimethanol/1,8-naphthalide/1,8-di(chloromethyl)naphthalene. Anhydride was added in a THF solution of LiAlH₄ in an ice-water bath for 2 hr, and then Lewis acids were added at room temperature for 3 hr.

^bIsolated yields of 1,8-naphthalenedimethanol (16.4%) and 1,8-naphthalide (36.1%), respectively.

^cRefluxing for 15 hr.

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mainly 1,8-di(chloromethyl)naphthalene (entries 7 and 11). Because BF_3 is covalent compound, and others are ionic compounds (entry 9).

For Lewis acids, AlCl₃, ZnCl₂, and BF₃ · Et₂O, their yields were comparable as a whole under similar conditions (entries 3, 6, and 9). The reason probably is the same active reducing agent AlH₃ was produced in situ when LiAlH₄ and Lewis acids were mixed.^[8a] The results demonstrate that the reducing behavior of AlH₃ to 1,8-naphthalic anhydride are distinctly different from B_2H_6 , the former gives 1,8-naphthalenedimethanol and the latter affords 2,1,3-peri-naphthopyran.^[9]

When $SnCl_4$ was used in the reduction, the yield of 1,8-naphthalenedimethanol was lower than those with Lewis acids above (entry 10). The consumption of partial LiAlH₄ by reducible Sn^{4+} leaded to the lower yield.

1,8-Naphthalic anhydride was reduced into a mixture of 16.4% 1,8-naphthalenedimethanol and 36.1% 1,8-naphthalide when anhydrous $CaCl_2$ was added into the reduction system (entry 12). The result is alike to that of only $LiAlH_4$ used (27% and 39%, respectively).^[10] The ionicity of Li^+ and Ca^{2+} are analogous, so no AlH_3 was produced when $CaCl_2$ met with $LiAlH_4$.

1,8-Naphthalenedimethanol was achieved with 69.5% yield by refluxing in THF for 15 hr (entry 13), whose yield was lower than that obtained by reduction with $LiAlH_4$ and Lewis acids.

CONCLUSION

In an ice-water bath, 1,8-naphthalic anhydride was reduced with LiAlH₄ to give 1,8-naphthalide with good isolated yield. With AlH₃ formed in situ by LiAlH₄ and Lewis acids, 1,8-naphthalic anhydride was reduced under room temperature to give 1,8-naphthalenedimethanol with high yield. The effects of various Lewis acids, the mole ratios of LiAlH₄ to 1,8-naphthalic anhydride and of LiAlH₄ to Lewis acids on the reduction of 1,8-naphthalic anhydride with LiAlH₄ were investigated.

EXPERIMENTAL

Melting points (uncorrected) were measured on an Electro-thermal digital melting point apparatus. Electrospray ionization mass spectra (ESI-MS, positive and negative mode) were recorded using a Finnigan LCQ^{DECA} mass spectrometer. ¹H NMR spectra were recorded in CDCl₃ or CD₃COCD₃ on a Bruker Avance 600 MHz spectrometer. Infrared spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer (KBr discs). 1,8-Naphthalic





Synthesis of 1,8-Naphthalide and 1,8-Naphthalenedimethanol

anhydride, lithium aluminum hydride, anhydrous ferrous chloride, anhydrous tin tetrachloride, and boron trifluoride ethyl ether were purchased from Acros Chemical Co. and were used without further purification. Anhydrous zinc chloride (analytic purity) was melted to remove water for 15 min over electric oven. THF was distilled from sodium benzophenone ketyl.

Typical Procedure for Reduction of 1,8-Naphthalic Anhydride to 1,8-Naphthalide by LiAlH₄

LiAlH₄ (15 mmol), and dry THF (20 mL) were placed in a 100 mL flask fitted with a CaCl₂ guard tube. The flask was cooled to about 0°C with an ice bath and mounted over a magnetic stirrer. 1,8-Naphthalic anhydride (0.99 g, 5 mmol) was added into the flask slowly. After 3 hr, the excess LiAlH₄ was destroyed by addition of 5 mL water, and the mixture was adjusted with 1 N HCl to weak acidity. The resultant two-phase solution was extracted with three portions of ethyl acetate, followed by washing with brine. After the solvent was evaporated, the crude product was recrystallized from ethanol to give yellow sheet crystals 0.624 g (73.2% yield). M.p.: 157–159°C (lit.^[3] 156–157°C) ESI-MS (positive mode, *m*/*z*): 185 (M + H)⁺; (negative mode, *m*/*z*): 169 (M – H – H₂O)⁻, 183 (M – H)⁻; IR (cm⁻¹): 1719, 1626,1585, 1516, 1456, 1350, 1244, 1085, 1052, 777; ¹H NMR (600 MHz, CDCl₃), δ 5.85 (s, 2H), 7.40 (d, 1H, *J* = 7.2 Hz), 7.57 (t, 1H, *J* = 7.8 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 8.13 (d, 1H, *J* = 8.4 Hz), 8.42 (d, 1H, *J* = 7.2 Hz)

Typical Procedure for Preparation of 1,8-Naphthalenedimethanol with LiAlH₄ and Lewis Acids

Dry THF (20 mL), LiAlH₄ (6 mmol) and anhydrous ZnCl₂ (3 mmol) were added in a 100 mL round-bottom flask fitted with a CaCl₂ guard tube and mounted over a magnetic stirrer. 1,8-Naphthalic anhydride (0.99 g, 5 mmol) was added into the flask slowly at room temperature. After 6 hr, the excess LiAlH₄ was destroyed by addition of 5 mL water, and the mixture was adjusted with 1 N HCl to weak acidity. The resultant two-phase solution was extracted with ethyl acetate (3 × 15 mL), washed with brine and then dried over anhydrous MgSO₄. After the solvent was evaporated, the crude product was recrystallized with benzene and methanol (1/1) to give white crystals 0.790 g (84.1% yield). M.p.: 161–163°C (lit.^[2c] 157–158°C); ESI-MS (*m*/*z*): 171 (M + H – H₂O)⁺, 189 (M)⁺; IR (cm⁻¹): 3345, 3241, 1601, 1510,1425, 1366, 1320, 1058, 1035, 1013, 998, 826, 774.724; ¹H NMR (600 MHz,



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CD₃COCD₃), δ 4.54 (s, 2H), 5.27 (s, 4H), 7.44 (t, 2H, J = 7.5 Hz), 7.64 (d, 2H, J = 7.2 Hz), 7.87 (d, 2H, J = 7.8 Hz).

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