A Facile and Selective Synthetic Method for the Preparation of Aromatic Dialdehydes from Diesters via the Amine-Modified SMEAH Reduction System

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Abstract: A new reduction system employing N-methylpiperazine-modified sodium bis(2-methoxyethoxy)aluminum hydride (NMP-SMEAH) for the conversion of aromatic diesters to dialdehydes is described. The method is plain and efficient, and can be carried out under mild and operationally simple conditions applicable for large scale productions.

Key words: aldehydes, amines, esters, hydrides, reductions

Preparation of aldehydes from corresponding esters through reduction has a potential difficulty because produced aldehydes tend to be further reduced to give alcohols. To circumvent this classical problem, two strategies have been employed. One approach is the derivation of esters to more activated forms such as acid halides or acid anhydrides, the other is the stabilization of the reduced form giving aldehydes. Typical methods in the ester activation strategy are Pd(PPh3)4-catalyzed hydrogenation of a mixed-anhydride produced from a carboxylic acid in situ,1 Pd/BaSO4-catalyzed hydrogenation of acid chloride (Rosenmund reaction),2 and reduction of acid halide with aluminum hydride, boron hydride, or tin hydride.3 The stabilization strategy includes hydride reduction of esters with aluminum hydride,4 DIBALH,5 lithium aluminum hydride,6 lithium tri-n-butoxyaluminum hydride,7 sodium aluminum hydride,8 sodium diethylpiperidinohydroaluminate,9 or sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH).10,11 Although many aldehydes were prepared by these methods, few reactions have been applied for the reduction of diesters (or their derivatives) to obtain corresponding dialdehydes successfully.

2,6-Naphthalenedicarboxaldehyde (1) has important applications i.e. as fluorine contained resins,12 fluorescent whitening dyes,13 food dye and cosmetic colorant,14 anticancer drugs,15 and optically active bis-β-amino acid.16 Fabrication of efficient blue and green light-emitting diodes is also suggested.17 In spite of these utilities only a few synthetic methods of 1 have been reported.18–20 In these reports, 1 was prepared from 2,6-dimethylnaphthalene18 or 2,6-naphthalenedicarboxylic acid.19,20 Among potential precursors of 1, we propose here dimethyl 2,6-naphthalenedicarboxylate (2,6-NDCM), known as a monomer of polyethylene naphthalate, which is the most favorable compound due to its availability, and thus the development of an industrially applicable method for the transformation of 2,6-NDCM to 1 has been sought.

We demonstrate here that SMEAH reduction gives 1 selectively from 2,6-NDCM in the presence of amine such as N-methylpiperazine (Scheme 1). Several other aromatic dicarboxylic esters are reduced to their corresponding dialdehydes using this newly developed system.

Scheme 1

Reduction of 2,6-NDCM

Hydride reduction of 2,6-NDCM to the corresponding dialdehyde is usually accompanied by formation of several naphthalenes (2–5) as shown in Scheme 2. The yield of 1 depends on the reaction temperature and the mode of the reduction system employed. In order to establish a selective and efficient conversion to dialdehyde 1, further reduction of 1 should be avoided.

We first examined DIBALH and SMEAH, which are popular reagents for the reduction of esters to aldehydes, but obtained unsatisfactory results. The reaction of 2,6-NDCM employing DIBALH in n-hexane or toluene did not proceed at –78 ºC because of the low solubility of 2,6-NDCM in these solvents. Elevation of the temperature to room temperature gave only dialcohol 5, while 33% of the employed 2,6-NDCM was consumed within 4 hours. SMEAH also gave only 5 at 5 ºC in toluene after 0.5 hours.

We then studied an amine-modified SMEAH reducing system. Among evaluated amines, morpholine and N-methylpiperazine gave the most satisfactory results for the conversion of 2,6-NDCM to 1. Results generated from the optimization research are summarized in Table 1.

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The reducing reactions of 2,6-NDCM were carried out as follows: a mixture of SMEAH (2.5 equivalents) and an amine (2.75 equivalents) was added to a 2,6-NDCM solution at 5 ºC, and the reaction solution was kept at the same temperature for 0.5–1.5 hours. An extract of the reaction mixture was analyzed by GC to determine the product distribution. The diethylamine-SMEAH system gave dialdehyde 1 in 66.2% yield; however, the reaction proceeded slowly and 25.7% of 2,6-NDCM was remained (Table 1, entry 1). When dicyclohexylamine was employed as a modifying agent, only over-reduced dialcohol 5 was produced, which was the same result obtained without an amine (entry 3). We assume that the steric hindrance of bulky dicyclohexylamine prevents the interaction between SMEAH and the amine moiety.

Table 1  Reduction of 2,6-NDCM with Amine-Modified SMEAH Under Various Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Conditions</th>
<th>Yield (%) a,b</th>
<th>2,6-NDCM</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Others d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diethylamine</td>
<td>Toluene/5 ºC</td>
<td>25.7</td>
<td>–</td>
<td>66.2</td>
<td>5.5</td>
<td>–</td>
<td>–</td>
<td>2.6</td>
<td>62.4</td>
</tr>
<tr>
<td>2</td>
<td>Pyrrolidine</td>
<td>Toluene/5 ºC</td>
<td>0.9</td>
<td>10.4</td>
<td>26.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>81.4</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Dicyclohexylamine</td>
<td>Toluene/5 ºC</td>
<td>18.6</td>
<td>–</td>
<td>15.4</td>
<td>20.6</td>
<td>11.8</td>
<td>3.5</td>
<td>30.0</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>N-Methylaniline</td>
<td>THF/5 ºC</td>
<td>–</td>
<td>18.7</td>
<td>96.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>Morpholine</td>
<td>Toluene/5 ºC</td>
<td>–</td>
<td>–</td>
<td>96.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>N-Methylpiperazine</td>
<td>Toluene/5 ºC</td>
<td>–</td>
<td>–</td>
<td>97.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>7</td>
<td>N-Methylpiperazine</td>
<td>Toluene/5 ºC</td>
<td>–</td>
<td>–</td>
<td>96.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>8</td>
<td>N-Methylpiperazine</td>
<td>Toluene/20 ºC</td>
<td>–</td>
<td>12.4</td>
<td>80.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>9</td>
<td>N-Methylpiperazine</td>
<td>Toluene/40 ºC</td>
<td>–</td>
<td>16.7</td>
<td>44.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>10</td>
<td>N-Methylpiperazine</td>
<td>Anisole/5 ºC</td>
<td>–</td>
<td>6.8</td>
<td>84.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>11</td>
<td>N-Methylpiperazine</td>
<td>Disopropylether/5 ºC</td>
<td>11.0</td>
<td>5.6</td>
<td>53.8</td>
<td>2.3</td>
<td>–</td>
<td>–</td>
<td>27.3</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>N-Methylpiperazine</td>
<td>Dimethoxyethane/5 ºC</td>
<td>–</td>
<td>5.6</td>
<td>85.0</td>
<td>4.9</td>
<td>–</td>
<td>–</td>
<td>4.5</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>N-Methylpiperazine</td>
<td>THF/5 ºC</td>
<td>0.4</td>
<td>38.9</td>
<td>60.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.6</td>
<td>–</td>
</tr>
</tbody>
</table>

a  Determined by GC.
b  Products were determined by GC-MS.
c  4.5 equivalents of amine-modified SMEAH were used.
d  Most of the other products were amine/amide 6.

The reducing reactions of 2,6-NDCM were carried out as follows: a mixture of SMEAH (2.5 equivalents) and an amine (2.75 equivalents) was added to a 2,6-NDCM solution at 5 ºC, and the reaction solution was kept at the same temperature for 0.5–1.5 hours. An extract of the reaction mixture was analyzed by GC to determine the product distribution. The diethylamine-SMEAH system gave dialdehyde 1 in 66.2% yield; however, the reaction proceeded slowly and 25.7% of 2,6-NDCM was remained (Table 1, entry 1). When dicyclohexylamine was employed as a modifying agent, only over-reduced dialcohol 5 was produced, which was the same result obtained without an amine (entry 3). We assume that the steric hindrance of bulky dicyclohexylamine prevents the interaction between SMEAH and the amine moiety. N-Methylaniline or pyrrolidine gave amine and amide 6 as major products (entries 2 and 4). A system modified with morpholine or N-methylpiperazine gave significant yields of 1 (96.2% or 97.2%, respectively) without the accompanying by-products 2–5 (entries 5 and 6). An increase in the amount of N-methylpiperazine-modified SMEAH (NMP-SMEAH) in the reduction did not affect the result (entry 7). At higher
reaction temperatures, lower selectivity was observed (entries 8 and 9). We also obtained unsatisfactory results using other solvents such as anisole, diisopropylether, dimethoxyethane, or THF (entries 10–13).

Recently, Abe and co-workers reported improved conditions for monoester conversion to monoaldehyde in a pyrrolidine-modified SMEAH reduction system in \( \text{t}-\text{butyl methyl ether} \).\(^{11} \) In their method, potassium \( \text{t}-\text{butoxide} \) was described as an indispensable component to suppress formation of the by-product alklypyrrolidine, derived from pyrrolidine attack at the ester. Such a basic additive is not required in our present method. In toluene, amine attack at the ester is suppressed at lower temperature, while in ethers significant amounts of by-products derived from amine attack at the ester was observed. The increased nucleophilicity of the amine is attributable to the interaction between the oxygen lone pair on the ether and NMP-SMEAH. Here we demonstrated that hydrogen attack dominates in NMP-SMEAH in the toluene system, while amine attack at the ester is suppressed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>NMP-SMEAH (equiv)</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2.5</td>
<td>![Image]((\text{MeOOC} - \text{COOMe} - \text{CHO}))</td>
<td>83.8</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2.5</td>
<td>Complex mixture(^a)</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2.5</td>
<td>![Image]((\text{COOMe} - \text{COOMe} - \text{CHO}))</td>
<td>65.6</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2.5</td>
<td>![Image]((\text{MeOOC} - \text{COOMe} - \text{CHO}))</td>
<td>66.3</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2.7</td>
<td>![Image]((\text{MeOOC} - \text{COOMe} - \text{CHO}))</td>
<td>76.8</td>
</tr>
<tr>
<td>6(^b)</td>
<td></td>
<td>3.0</td>
<td>![Image]((\text{EtOOC} - \text{COOH} - \text{CHO}))</td>
<td>93.5</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2.5</td>
<td>![Image]((\text{MeOOC} - \text{N} - \text{COOMe} - \text{CHO}))</td>
<td>30.3 (62.5(^c))</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2.5</td>
<td>![Image]((\text{MeOOC} - \text{COOMe} - \text{CHO}))</td>
<td>31.5 (77.6(^c))</td>
</tr>
<tr>
<td>9(^b)</td>
<td></td>
<td>2.0</td>
<td>![Image]((\text{N} - \text{COOEt} - \text{CHO}))</td>
<td>62.8</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>2.5</td>
<td>Complex mixture</td>
<td>–</td>
</tr>
</tbody>
</table>

All reactions were carried out at 5 °C unless otherwise stated.
\(^a\) Most of the side products are various carboxylic acids.
\(^b\) Carried out at 25 °C.
\(^c\) Determined by GC (reaction mixture).
Reduction of Various Aromatic Diesters

The present method was applied to various kinds of aromatic diesters to evaluate its scope and limitation. Results of the preparative evaluation are listed in Table 2.

From 2,6-NDCM, 2,6-naphthalenedicarboxaldehyde (1) was obtained in 83.8% yield, while the reduction of dimethyl 1,2-benzenedicarboxylate was unsuccessful giving substantial amounts of carboxylic acids as major products accompanied with a trace of the corresponding dialdehyde (entry 2). Dimethyl 1,3-benzenedicarboxylate and dimethyl 1,4-benzenedicarboxylate gave dialdehydes 8 and 9 in moderate isolated yields showing partial formation of over-reduced alcohols (entries 3 and 4). We obtained dialdehyde 10 from ethylene glycol bis[4-(ethoxycarbonyl)phenyl] ether in a significant isolated yield of 93.5% (entry 6). In case of heterocyclic diesters we only isolated the corresponding dialdehydes in low yield, although GC analyses of the reaction mixtures showed moderate formation of dialdehydes 11 and 12 (entries 7 and 8). The dialdehydes formed were decomposed by oxidation during the isolating procedure. During the reaction of 4-methyl-5-thiazolecarboxylate, the corresponding monaldehyde 13 was obtained in 62.8% yield (entry 9). Reduction of dimethyl adipate gave various reduced forms (entry 10). We assume that the aliphatic ester is more labile than the aromatic ones under these reaction condition because the aliphatic ester and its reaction intermediates can rotate freely.

Conclusion

In summary, we have developed a plain and efficient reduction system employing NMP-SMEA for the conversion of aromatic diesters to dialdehydes. The system uses commercially available and easy to handle SMEA, and can be carried out under mild and operationally simple conditions applicable to large scale productions.

All reactions were carried out under positive pressure of dry nitrogen unless otherwise stated. Chemicals were obtained from Mitsubishi Gas Chemical Company, Aldrich, Kanto Chemicals, or Tokyo Chemical Industry. Reduction products were characterized by $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR using a JEOL Excaliber-400 spectrometer, and by IR with a Shimadzu 8200PC spectrometer. Analytical GC was concluded on a Shimadzu GC14A or GC17A, and GC-MS was obtained on a Shimadzu 8200PC spectrometer. Elemental analyses were performed with a Perkin-Elmer CHNS/O Analyser 2400. Melting points were obtained on a Mettler melting point apparatus FP62, and are uncorrected.

Reduction of 2,6-NDCM (Table 1); General Procedure

To a mixture of a toluene solution of SMEA (65%, 15.0 mL, 50 mmol) and toluene (25 mL) at 10–20 ºC, and the resulting mixture was stirred for 15–30 min at the same temperature. The prepared reagent was added drop-wise to 2,6-NDCM (4.88 g, 20 mmol) in the solvent (90 mL) at the specified temperature. After stirring for 0.5–1.5 h, the reduction was interrupted by drop-wise addition of H$_2$O (50 mL), and then ethyl acetate (50 mL) was added. The organic layer was separated and subjected to GC analysis.

Synthesis of Various Aldehydes (Table 2)

Preparation of the NMP-SMEA Solution; Typical Procedure

To a mixture of a toluene solution of SMEA (65%, 75.0 mL, 250 mmol) and toluene (125 mL) was added drop-wise N-methylpiperazine (27.55 g, 275 mmol) below 10 ºC, and the resulting mixture was stirred for 30 min to give a clear solution of NMP-SMEA.

2,6-Naphthalenedicarboxaldehyde (1)

To a solution of 2,6-NDCM (24.42 g, 100 mmol) in toluene (450 mL) was added drop-wise the NMP-SMEA solution (250 mmol) at 5 ºC, and the resulting mixture was stirred for 1 h. The reaction was quenched with H$_2$O (300 mL), and then extracted with EtOAc (600 mL) at r.t. The organic layer was washed with H$_2$O (600 mL), dried over anhyd Na$_2$SO$_4$ (100 g), and then concentrated in vacuo. The residue was dissolved in acetone (400 mL) while heating, crystallized by adding H$_2$O (1600 mL), and then stirred for 2 h at 5 ºC. The filtered solid was dried under reduced pressure to give 15.41 g (83.8%) of 2,6-naphthalenedicarboxaldehyde as a white solid.

Mp 173.4–174.0 ºC.

IR (KBr): 1682, 1601, 1506, 1400, 1337, 1231, 1159, 1113, 908, 818, 770 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta$ = 10.20 (s, 2 H), 8.40 (d, $J$ = 1.0 Hz, 2 H), 8.12 (d, $J$ = 8.3 Hz, 2 H), 8.05 (dd, $J$ = 8.3, 1.0 Hz, 2 H).

$^{13}$C NMR (CDCl$_3$): $\delta$ = 191.62, 136.11, 135.65, 133.62, 120.54, 124.06.

MS (El, 70 eV); $m/z$ (%): 184 (100) [M$^+$/z, 155 (59), 127 (36), 75 (30), 63 (32), 50 (30).

Anal. Calcd for C$_{12}$H$_{10}$O$_2$: C, 78.25; H, 4.38. Found: C, 78.41; H, 4.54.

1,3-Benzenedicarboxaldehyde (7)

To a solution of dimethyl 1,3-benzenedicarboxylate (5 g, 25.7 mmol) in toluene (128.5 mL) was added drop-wise the NMP-SMEA solution (64.3 mmol) at 5 ºC, and the resulting mixture was stirred for 1 h. The reaction was quenched with H$_2$O (40 mL), and then extracted with EtOAc (30 mL) at r.t. The organic layer was washed with H$_2$O (100 mL), dried over anhyd Na$_2$SO$_4$, and then concentrated in vacuo. The residue was dissolved in acetone (10 mL) while heating, crystallized by adding H$_2$O (50 mL), and then stirred for 2 h at 5 ºC. The filtered solid was dried under reduced pressure to give 2.26 g (65.6%) of 1,3-benzenedicarboxaldehyde as a white solid.

Mp 87.7–88.0 ºC.

IR (KBr): 1695, 1605, 1585, 1288, 1140, 939, 799, 677, 638 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta$ = 10.10 (s, 2 H), 8.36 (s, 1 H), 8.14 (d, $J$ = 7.3 Hz, 2 H), 7.71 (t, $J$ = 7.3 Hz, 1 H).

1,4-Benzenedicarboxaldehyde (8)

To a solution of dimethyl 1,4-benzenedicarboxylate (5 g, 25.7 mmol) in toluene (128.5 mL) was added drop-wise the NMP-SMEA solution (64.3 mmol) at 5 ºC, and the resulting mixture was stirred for 1 h. The reaction was quenched with H$_2$O (40 mL), and then extracted with EtOAc (30 mL) at r.t. The organic layer was washed with H$_2$O (100 mL), dried over anhyd Na$_2$SO$_4$, and then concentrated in vacuo. The residue was dissolved in acetone (10 mL) while heating, crystallized by adding H$_2$O (50 mL), and then stirred for 2 h at 5 ºC. The filtered solid was dried under reduced pressure to give 2.29 g (66.3%) of 1,4-benzenedicarboxaldehyde as a white solid.
Aromatic Dialdehydes from Diesters via the Amine-Modified SMEAH Reduction System

To a solution of dimethyl 2,6-pyridinedicarboxylate (2 g, 10.2 mmol) in toluene (51 mL) was added drop-wise the NMP-SMEAH solution (20.0 mmol) at 5 °C, and the resulting mixture was stirred for 3 h. The reaction was quenched with H₂O (20 mL), and then extracted with EtOAc (20 mL) at r.t. The organic layer was washed with H₂O (50 mL), dried over anhyd Na₂SO₄, and then concentrated in vacuo. The residue was dissolved in acetone (20 mL) while heating, crystallized by adding H₂O (80 mL), and then stirred for 2 h at 5 °C. The filtered solid was dried under reduced pressure to give 1.19 g (76.8%) of [1,1′- Biphenyl]-4,4′-dicarboxaldehyde as a white solid.

Mp 120–140 °C.

IR (KBr): 3295, 1720, 1695, 1350, 1261, 1209, 912, 770, 683 cm⁻¹.

Anal. Calcd for C₁₆H₁₄O₄: C, 71.10; H, 5.22. Found: C, 70.81; H, 3.90; N, 10.27.

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References


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(12) Teshima, S.; Asako, Y. Jpn. Kokai Tokkyo Koho JP 2001031598, **2001**.
(14) Gruetzmacher, G. D. U. S. Pat. US 4567048, **1986**.
(18) Taussig, P. R.; Storms, P. W. U. S. Pat. US 3448156, **1969**.