

## A Simple Method for the Reduction of Carboxylic Acids to Aldehydes or Alcohols Using H<sub>2</sub> and Pd/C

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Aldehydes are versatile compounds in organic synthesis. Despite their intrinsic benefits, there are relatively few methods for their preparation.<sup>1</sup> A common approach to obtain aldehydes is in fact the oxidation of primary alcohols<sup>2</sup> or the reduction of carboxylic acids and their derivatives.<sup>3</sup> This last transformation is particularly useful for the preparation of *N*-protected  $\alpha$ -amino aldehydes<sup>4</sup> that are valuable intermediates for the synthesis of biologically active compounds.<sup>5</sup> Several methods employed for the preparation of protected amino aldehydes make use of complex metal hydrides as the reducing agents and esters or amides as the starting material (for example DIBAL-H on methyl esters<sup>6</sup> and LiAlH<sub>4</sub> on particularly reactive amides<sup>7</sup>).

All these approaches suffer from several disadvantages: metal hydrides are generally highly reactive or expensive, some problems may occur during the separation of the aldehyde from the reaction mixture after the quench of the metal hydride, and the reaction conditions can produce sometimes racemization of the formed aldehyde. Consequently, a practicable alternative for the large-scale preparation of amino aldehydes is the reduction of the carboxylic acid to alcohol followed by reoxidation of the alcohol to aldehyde.<sup>8</sup>

Except for the classical Rosenmund catalytic hydrogenation of acyl chlorides and some related reactions,<sup>9</sup> few reports describe the direct reduction of carboxylic acid

and their derivatives using hydrogen and a catalyst.<sup>10</sup> For example, in a Rosenmund type reduction a couple of the major problems are the stereochemical lability of the acyl chlorides and the difficulties in their preparation in the presence of acid labile groups or protections.<sup>11</sup>

Following our interest in the use of [1,3,5]triazine derivatives in organic synthesis,<sup>12</sup> we discovered that the activated ester of *N*-Boc amino acids with 2-chloro-4,6-dimethoxy[1,3,5]triazine (**1**) can be reduced into the corresponding aldehydes in good yields with H<sub>2</sub> on catalytic Pd/C.

Treating a carboxylic acid **3** with the complex formed by 2-chloro-4,6-dimethoxy[1,3,5]triazine (**1**) and *N*-methylmorpholine in DME (adduct **2** in Scheme 1), the corresponding activated ester **4** is quantitatively formed.<sup>13</sup> A solution of this ester can be directly treated with H<sub>2</sub> (1 atm pressure) at room temperature in the presence of Pd catalyst (Pd/C 10%) to give the corresponding aldehyde **5**. After filtration of the catalyst and acidic work up to separate the [1,3,5]triazine byproducts, the aldehyde can be recovered practically pure by evaporation of the solvent or purified by standard methods. Consequently, aldehydes are obtained from carboxylic acids using a catalytic process and friendly reaction conditions.

This process, although simple, will require optimization of the solvent, reaction time, and H<sub>2</sub> pressure.

The best results for conversion and isolated yields of the aldehyde were obtained using DME or THF in the formation of the activated ester and EtOH in the reductive step.

On the other hand, when the reaction was carried out for longer times, the alcohol obtained from over-reduction of the aldehyde was the main component of the reaction mixture.

For example, in the case of the activated ester formed from acid **3i**, after 3 h of reduction at room temperature, we observed the formation of the aldehyde **5i** with a conversion of about 85%. On waiting one additional hour for the complete disappearance of the activated ester, we observed the formation of the corresponding alcohol **6i** that, after additional 4 h of reduction, became the predominant product. Nevertheless, as alcohol does not react with **4** in the absence of a proper activation,<sup>14</sup> we did not observe the formation of the symmetric ester as often happens in Rosenmund type reductions.<sup>15</sup>

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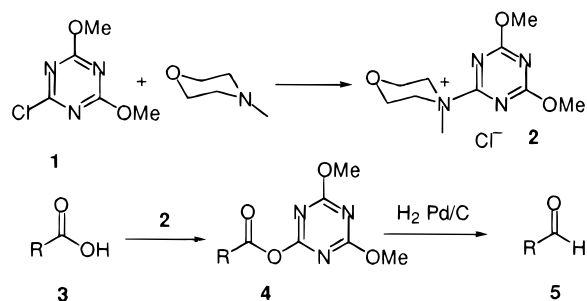
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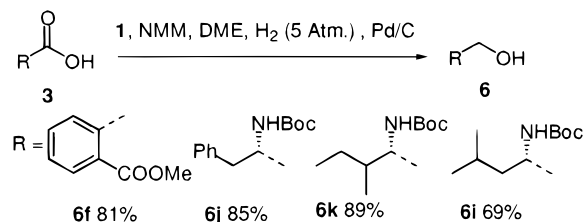
Scheme 1



Starting material	Yields of aldehyde	Starting material	Yields of aldehyde
	<b>5a</b> : 79%		<b>5h</b> : 79%
	<b>5b</b> : 75%		<b>5j</b> : 81%
	<b>5c</b> : 84%		<b>5k</b> : 77%
	<b>5d</b> : 88%		<b>5i</b> : 76% <sup>a</sup>
	<b>5e</b> : 32% <sup>a</sup>		<b>5l</b> : 84%
	<b>5f</b> : 30% <sup>a</sup>		<b>5m</b> : 72% <sup>b</sup>
	<b>5g</b> : 82%		<b>5n</b> : 76% <sup>c</sup>

a) Reduction carried out at 0 °C to prevent the contemporary formation of the alcohol. b) No significant debenzoylation was observed under our experimental conditions. c) Obtained as a 80:20 mixture of unsaturated: saturated aldehyde using Pd/BaSO<sub>4</sub> as the catalyst.

Scheme 2



The formation of the alcohol was also observed upon increasing the H<sub>2</sub> pressure. When the reaction was carried out in a Parr apparatus (3–5 atm of H<sub>2</sub>, room temperature) on compounds **3f,j–i**, the corresponding alcohols **6f,j–i** were obtained in high yield (Scheme 2). The direct conversion of a carboxylic acid into the corresponding alcohol by catalytic hydrogenation was thus achieved.

This methodology was applied to aliphatic acids and *N*-Boc-amino acids. When the reaction was carried out on aromatic carboxylic acids (**3e,f**), the main reaction product was the alcohol, even at low temperature and H<sub>2</sub> pressure. The use of a poisoned Pd catalyst did not improve the yields of the aldehyde.<sup>16</sup> Nevertheless, as the intermediate ester **4** is not consumed by the alcohol formed during the reaction, we were able to isolate a limited amount of the aldehyde at the end of the reaction.

The formation of the alcohol may happen also during the reduction of *N*-Boc amino acids. We observed that even in the case of similar substrates, different reaction times were needed for a satisfactory conversion to aldehydes. For example, the transformation of *N*-Boc-valine (**3l**) occurred after 3 h of reduction at room temperature, whereas *N*-Boc-leucine (**3i**) could be successfully reduced to aldehyde **5i** exclusively at 0 °C for 2 h. For this reason we suggest trying this procedure first on small amounts of the substrate to find the correct conditions before attempting the reduction of the whole material of interest. We also recommend use of a low pressure of H<sub>2</sub> (using an H<sub>2</sub> buret or a balloon) and eventually carrying out the reaction at 0 °C to prevent the formation of the alcohol.

On the other hand, if the alcohol is desired, the reduction under 5 atm of H<sub>2</sub> gives quantitative yields of the products.

Significant racemization of  $\alpha$ -amino aldehydes did not occur under these conditions, as revealed by the optical rotation values of the products and their derivatives (semicarbazones and dinitrophenyl hydrazones; see the Supporting Information).

We think that the method described in this note can be very useful for the preparation of aldehydes (and alcohols) in large scale, as it does not use anhydrous solvents, strong reaction conditions, or dangerous or expensive reagents. The main drawback (in the case of the aldehyde) is the necessity to monitor the reaction to prevent the formation of the alcohol, but we are currently trying to improve the conditions to avoid this trouble also.

## Experimental Section

All the solvents and the reagents (including Pd/C) were used in the commercially available grade purity. The protected amino acids were purchased and their purity was established before utilization by melting point and optical rotation. Although 2-chloro-4,6-dimethoxy[1,3,5]triazine is commercially available, we prepared it following a published procedure.<sup>17</sup>

**General Procedure for the Reduction of Carboxylic Acids to Aldehydes.** (*S*)-2-(*tert*-Butoxycarbonylamino)propanal (**5h**). To a solution of 2-chloro-4,6-dimethoxy[1,3,5]triazine (**1**) (0.93 g, 5.3 mmol) in DME (30 mL) cooled to 0 °C was added *N*-methylmorpholine (0.56 g, 5.4 mmol). A white precipitate was immediately formed and to this mixture a solution of (*S*) *N*-Boc-alanine **3h** (1.0 g, 5.3 mmol), dissolved in DME (10 mL), was slowly added. After stirring at 0 °C for 3 h, the solid formed was filtered off on Celite and the solution containing the activated ester transferred into a flask containing Pd/C 10% (0.10 g, 0.1 mmol of active Pd) dispersed in EtOH (20 mL). The flask was connected with a buret containing H<sub>2</sub>. After stirring at room temperature for 3 h (or until TLC analysis showed the disappearance of the activated ester spot (*R*<sub>f</sub> 0.6 with eluent: AcOEt/hexane 4/6) the catalyst was filtered on Celite and the solvent was evaporated and replaced with ethyl acetate (50 mL). The solution was washed three times with 1 M HCl (15 mL each) and three times with 5% NaHCO<sub>3</sub> (15 mL each).

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The ethereal layer was separated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> to give, after evaporation of the solvent, product **5h** (0.80 g, 79% yield) practically pure for any further transformation of the aldehyde group. An analytical sample was purified by column chromatography on silica gel.

The identity of the product was determined by comparison of <sup>1</sup>H NMR data, [α] values, and semicarbazone melting point with those previously described in the literature.<sup>18</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.53 (s-like, 1H), 5.05 (bs, 1H), 4.2 (m, 6 components visible, 1H), 1.42 (s, 9H), 1.32 (d, *J* = 7 Hz, 3H). [α]<sub>D</sub> = -25.0 (*c* = 1, MeOH); lit.<sup>18</sup> [α]<sub>D</sub> = -25.52 (*c* = 1, MeOH). Semicarbazone: [α]<sub>D</sub> = -24.3 (*c* = 1, MeOH); lit.<sup>18</sup> [α]<sub>D</sub> = -23.82 (*c* = 1, MeOH). Anal. Calcd for C<sub>9</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub> (250.17): C, 46.95; H, 7.87; N, 24.34. Found: C, 46.77; H, 7.88; N, 24.30.

**General Procedure for the Catalytic Reduction of Carboxylic Acids to Alcohols. (S)-2-(tert-Butoxycarbonylamino)-3-phenyl-1-propanol (6j).** A solution of the activated ester **3j** prepared as previously described was transferred into a flask containing Pd/C 10% (0.10 g, 0.1 mmol of active Pd) dispersed into DME (5 mL) and the flask connected with a Parr

apparatus filled with H<sub>2</sub>. The hydrogenation was carried at 5 atm of H<sub>2</sub> for 3 h, then the flask was purged with N<sub>2</sub> and the catalyst was filtered off on Celite. The solvent was evaporated and product **6j** was isolated by column chromatography on silica gel (eluent AcOEt/hexane 1/1) to yield 1.2 g (85% yield).

The identity of the product was determined by comparison of melting point, <sup>1</sup>H NMR data and the [α] values with those previously described in the literature.<sup>19,20</sup>

**6j:** mp 94–95 °C; lit.<sup>19</sup> mp 94–96 °C; [α]<sub>D</sub> = -20 (*c* = 1, MeOH); lit.<sup>20</sup> [α]<sub>D</sub> = -21.6. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.2 (m, 5H), 5.0 (bs, 1H), 4.4 (m, 4 components visible, 1H), 4.2 (m, 2H), 2.2 (m, 2H), 2.0 (bs, 1H), 1.45 (s, 9H).

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**Supporting Information Available:** <sup>1</sup>H NMR data for compounds **5d.g–n** and **6f.j–i**; [α] values for compounds **5g–m** and **6h–k**; and characterization of semicarbazones and 2,4 dinitrophenylhydrazones of all the aldehydes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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