A GENERAL PROCEDURE FOR MILD AND RAPID REDUCTION OF ALIPHATIC AND AROMATIC NITRO COMPOUNDS USING AMMONIUM FORMATE AS A CATALYTIC HYDROGEN TRANSFER AGENT

Siya Ram and Richard E. Ehrenkaufer
Cyclotron/PET Facility, Division of Nuclear Medicine
The University of Michigan Medical School, Ann Arbor, Michigan 48109

ABSTRACT

Various aliphatic and aromatic nitro compounds were selectively and rapidly reduced to their corresponding amino derivatives in very good yield using anhydrous ammonium formate as a catalytic hydrogen transfer agent.

Selective and rapid reduction of nitro compounds is still an area of considerable synthetic interest, particularly when a molecule has several other reducible moieties. Numerous new reagents have been developed for reduction of aromatic nitro compounds, however little attention has been paid to the reduction of aliphatic nitro compounds, which are traditionally reduced by high pressure catalytic hydrogenation. In the past 30 years catalytic transfer hydrogenation has demonstrated great potential value in organic and biological chemistry. Cyclohexene/Pd-C has been most widely studied. Recently, ammonium formate has been successfully employed as a catalytic hydrogen transfer agent in peptide chemistry for deprotection in stead of cyclohexene. Reduction of azides and cyano groups to the corresponding amines and methyl group has also been reported in the recent literature.

In our ongoing program, we were interested in the radiolabeled synthesis of 11C-amino acids (11C-half life = 20.4 min) via nitro acid intermediates. We have thus examined several classes of chemical reducing agents for e.g. FeSO4/NH4OH, Cyclohexene/Pd-C, NH2-NH2/Ra-Ni, Zn/AcOH, etc., however these systems failed to yield the amino acid. In this paper we wish to report a mild, simple, rapid and selective reduction of aliphatic and aromatic nitro compounds to the corresponding amino derivatives using ammonium formate (Scheme-I).

SCHEME I

\[
\begin{align*}
R - \text{NO}_2 + \text{HCO}_2\text{NH}_4 & \rightarrow R - \text{NH}_2 \\
10\% \text{Pd-C, CH}_3\text{OH} & \\
I & \rightarrow \text{II} & \\
R = \text{alkyl or aryl}
\end{align*}
\]

A typical experimental procedure for conversion of I to II is as follows.
TABLE I. Reduction of aliphatic and aromatic nitro compounds to corresponding amines.

<table>
<thead>
<tr>
<th>No.</th>
<th>Nitro Compound</th>
<th>Reaction time in min.</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CH₂CH₂NO₂</td>
<td>&lt; 30</td>
<td>CH₃CH₂CH₂NH₂.HCl</td>
<td>31&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CH₂CH₂CH₂NO₂</td>
<td>&lt; 20</td>
<td>CH₃CH₂CH₂CH₂NH₂.HCl</td>
<td>49&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>(CH₃)₂CHCH₂CH₂NO₂</td>
<td>&lt; 40</td>
<td>(CH₃)₂CHCH₂CH₂NH₂.HCl</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>C₂H₅O₂CCH₂NO₂</td>
<td>20</td>
<td>C₂H₅O₂CCH₂NH₂.HCl</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>HOOC(CH₂)₂NO₂</td>
<td>20</td>
<td>OOC(CH₂)₂NH₃⁺</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>CH₃O₂C(CH₂)₃NO₂</td>
<td>20</td>
<td>CH₃O₂C(CH₂)₃NH₂</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>CH₃O₂CCH₂CH₂CH(CH₃)NO₂</td>
<td>15</td>
<td>CH₃O₂CCH₂CH₂CH(CH₃)NH₂</td>
<td>75 and 5-methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>8</td>
<td>p-O₂NC₆H₄CO₂H</td>
<td>5-10</td>
<td>p-H₂NC₆H₄CO₂H</td>
<td>52&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>4-H₃COC₆H₃(3-No₂)CO₂H</td>
<td>5-10</td>
<td>4-H₃COC₆H₃(3-NH₂)CO₂H</td>
<td>75&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>p-O₂NC₆H₄CH₂CO₂H</td>
<td>5-10</td>
<td>p-H₂NC₆H₄CH₂CO₂H</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>p-O₂NC₆H₄CO₂CH₃</td>
<td>5-10</td>
<td>p-H₂NC₆H₄CO₂CH₃</td>
<td>89</td>
</tr>
<tr>
<td>12</td>
<td>C₆H₅NO₂</td>
<td>3-5</td>
<td>C₆H₅NH₂</td>
<td>76</td>
</tr>
<tr>
<td>13</td>
<td>o-FC₆H₄NO₂</td>
<td>3-5</td>
<td>o-FC₆H₄NH₂</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>p-H₃COC₆H₄NO₂</td>
<td>3-5</td>
<td>p-H₃COC₆H₄NH₂</td>
<td>93</td>
</tr>
<tr>
<td>15</td>
<td>4-H₃CC₆H₃(2-No₂)NH₂</td>
<td>3-5</td>
<td>3,4-(NH₂)₂C₆H₄CH₃</td>
<td>79</td>
</tr>
<tr>
<td>16</td>
<td>p-O₂NC₆H₄CH₂C=N</td>
<td>120</td>
<td>p-H₂NC₆H₄CH₂C=N</td>
<td>85</td>
</tr>
<tr>
<td>17</td>
<td>2-H₂NC₆H₃(5-No₂)COC₆H₅</td>
<td>15</td>
<td>2,5-(NH₂)₂C₆H₃COC₆H₅</td>
<td>91</td>
</tr>
<tr>
<td>18</td>
<td>m-O₂NC₆H₄CH₂NHCl(=NH)NH₂</td>
<td>25</td>
<td>m-H₂NC₆H₄CH₂NHCl(=NH)NH₂</td>
<td>70</td>
</tr>
<tr>
<td>19</td>
<td>2-I-C₆H₃(4-No₂)CONH₂</td>
<td>60</td>
<td>p-H₂NC₆H₄CONH₂</td>
<td>31&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td>2-H₃C-5-No₂-imidazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) Isolated yields are based on the single experiment and yields were not optimized;
(b) Products were characterized by comparison with authentic samples (IR, ¹H-NMR, TLC and m.p.);
(c) The low yields of aliphatic amines are due to low boiling points (n-propylamine b.p. 48°, n-butylamine b.p. 78°) and their volatile nature;
(d) These were obtained by trituration with small amount of water, the low yield in the case of p-aminobenzoic acid is due to its partial solubility in water. Modified workup is required for such water soluble products;
(e) No reaction takes place using Pd-C as the catalyst. When Raney-Nickel is used the resulting product is the deiodinated amine, p-aminobenzamide.
To a stirred suspension of an appropriate nitro compound (5 mmol) and 10% Pd-C (0.2 - 0.3 g) in dry methanol (10 mL), anhydrous ammonium formate was added (23 mmol) in a single portion. The resulting reaction mixture (slightly exothermic and effervescent) was stirred at room temperature for 3-40 min under argon, the catalyst was removed by filtration through a celite pad and washed with dry methanol (10 mL). The filtrate was evaporated either under reduced or at normal pressure. The resulting residue was triturated with water (10 mL - 25 mL), product was extracted with an organic solvent (i.e. ether, CH₂Cl₂ or CHCl₃) and dried over Na₂SO₄. The organic layer on evaporation gave the desired amino derivative. Some products were directly converted into the HCl-salt with ethereal-HCl without evaporation of ether layer.

The scope of this new general procedure is shown in Table I. In most cases the reaction is over within 3-40 min, however for p-nitrobenzyl cyanide 16, the reaction completion time was 120 min. In cases of iodinated aromatic systems, 2-iodo-4-nitrobenzamide 19 and 1-iodo-3-nitrobenzene no reaction was observed, however using Raney-Nickel as catalyst with 19, reduction of the nitro group as well as deiodination occurred, yielding p-aminobenzamide. These observations suggest that iodinated compounds may deactivate the Pd-C catalyst.

m-Nitrobenzylguanidine 18, which was unable to be reduced to the corresponding m-amino-benzylguanidine in the variety of conditions 27, was successfully reduced by 10% Pd-C/HCO₂NH₄ - CH₃OH system in 70% yield. Although methyl-4-nitropentanoate 7 was successfully reduced to corresponding amino acid ester, partial cyclization also occurred yielding 5-methyl-2-pyrolidine-none, which was confirmed by IR and ¹H-NMR spectroscopic data.

These results demonstrate a rapid versatile and selective reducing system for wide variety of nitro-compounds in the presence of other functional groups for e.g. -C ≡ N, > C = O, etc. Ammonium formate also has the advantages of being readily available, inexpensive, stable and nontoxic and can be used in conjunction with either Pd-C or Raney-Nickel catalysts. Moreover, it may be added to the reaction in a single portion and products can be easily separated from the reaction mixture. This procedure will therefore be of general use for the preparation of amines specifically in cases where rapid mild reduction is required.

ACKNOWLEDGMENTS

Research was supported by NCI Training Grant #5-T32-CA09015-08 and by NINCDS grant #PO1 NS15655-04.

REFERENCE

8) J. George and S. Chandrasekaran; Synthetic Commun. 13, 495 (1983).
27) H. Lee and D. Wieland. University of Michigan, Division of Nuclear Medicine. Personal Communication. Reduction of compound 18 using following three conditions was unsuccessful: 
(a) Raney-Nickel-H_2O in Parr apparatus (b) Fe powder - aqueous acetic acid (c) SnCl_2·2H_2O - conc. HCl:CH_3OH.

(Received in USA 11 April 1984)