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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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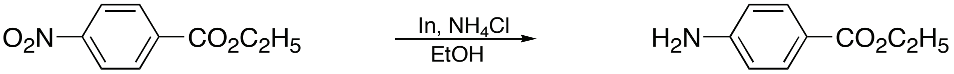
# INDIUM/AMMONIUM CHLORIDE-MEDIATED SELECTIVE REDUCTION OF AROMATIC NITRO COMPOUNDS: ETHYL 4-AMINOBENZOATE

## (Benzoic acid, 4-amino-, ethyl ester)



Submitted by Bimal K. Banik[1], Indrani Banik, and Frederick F. Becker.
Checked by Weiqiang Huang and Marvin J. Miller.

## 1. Procedure

*Ethyl 4-aminobenzoate.* A 1000-mL, round-bottomed flask equipped with a magnetic stirbar is charged with a suspension of 10 g (51 mmol) of ethyl 4-nitrobenzoate in 250 mL of ethanol, and a solution of 27.4 g (510 mmol) of ammonium chloride in 125 mL of water is then added (Note 1). Indium powder (23.5 g, 205 mmol) (Note 2) is added, and the resulting mixture is heated at reflux for 2.5 hr. The reaction mixture is allowed to cool to room temperature, diluted with 350-400 mL of water, and filtered under vacuum. The filtrate is extracted with 6-8 portions of 50-60 mL of dichloromethane, and the combined organic phases are washed with 100 mL of brine and dried over anhydrous sodium sulfate. The resulting solution is concentrated under reduced pressure and the crude product is dissolved in 100 mL of dichloromethane. The solution is concentrated by warming, and 50 mL of hexane is then added. The resulting solution is allowed to stand in a refrigerator overnight and then filtered under vacuum to give 7.63 g (90%) of ethyl 4-aminobenzoate (Note 3).

## 2. Notes

1. Ethyl 4-nitrobenzoate, ammonium chloride, ethanol were purchased from Aldrich Chemical Company and used as received.
2. Indium powder (99.99%) was obtained from Aldrich Chemical Company.

3. The spectral properties of ethyl 4-aminobenzoate are as follows: IR (film) $cm^{-1}$: 3424, 3345, 3224, 1685, 1636, 1598, 1515, 1367, 1312, 1281, 1173, 773; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.36 (3 H, t, J = 6), 4.04 (2 H, brs), 4.31 (2 H, q, J = 7), 6.63 (2 H, d, J = 9), 7.85 (2 H, d, J = 9); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 14.6 ($CH_3$), 60.4 ($CH_2$), 114.0 (Ar-CH), 120.5 (Ar-q), 131.7 (Ar-CH), 151.0 (Ar-q), 166.9 (Ar-q = quaternary carbon atom); *m/e*: 166 (M+H); exact mass: m/e ($M^+$): 165.0764 (measured), 165.0790 (theoretical).

### Waste Disposal Information

All toxic materials were disposed of in accordance with the policy of UTMDACC to handle and dispose of hazardous waste, which is in accordance with the regulations of the Environmental Protection Agency, Occupational Safety and Health Administration, Federal Department of Transportation, Texas Department of Health, and the Texas Water Commission.

## 3. Discussion

The synthesis of aromatic amines is an active and important area of research.[2] Many methods are available in the literature for the synthesis of these compounds. Though some of these are widely used, still they have limitations based on safety or handling considerations. For example, catalytic hydrogenation[3] of nitro or azido compounds in the presence of metals such as palladium on carbon or Raney nickel require stringent precautions because of their flammable nature in the presence of air. In addition, these methods require compressed hydrogen gas and a vacuum pump to create high pressure within the reaction flask. To overcome these difficulties, several new methods have been reported in the recent literature[4] involving such reducing agents as decaborane,[5] electrochemically generated Raney nickel,[6] dimethyl hydrazine/ferric chloride,[7] hydrazine hydrate/ferric oxide-magnesium oxide,[8] diethyl chlorophosphite,[9] and sodium borohydride-sodium-methoxide in methanol[10] In general, the main drawbacks of these methods are long reaction time and non-chemoselectivity. The submitters[11] have also described new methods for the reduction of aromatic nitro compounds and imines to aromatic amines by novel samarium-induced iodine catalyzed and ammonium chloride mediated reduction.[12] While our samarium-induced reduction of aromatic nitro compounds works well in the polycarbocyclic series, similar reaction with several heteroaromatic nitro compounds results in a mixture of products under identical conditions. Moreover, samarium-induced reduction of the nitro compounds requires anhydrous reaction conditions.

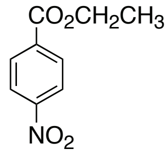
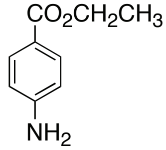
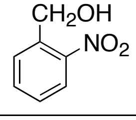
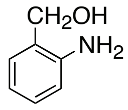
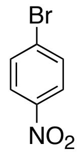
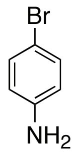
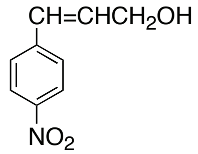
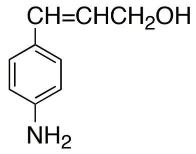
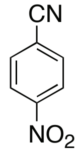
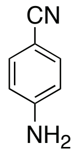
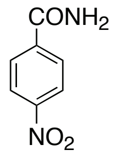
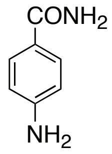
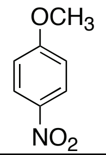
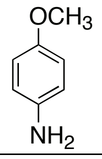
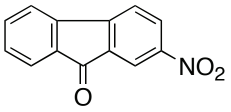
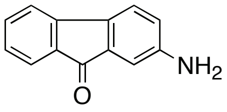
The submitters have been actively involved in the use of polyaromatic amines for the development of anticancer agents.[13] Therefore, the submitters began a research program aimed at developing methods to synthesize several aromatic amines rapidly and in high selectivity, by using ecologically friendly reagents. The present study describes a method for the selective reduction of aromatic nitro compounds to the corresponding amines by indium in the presence of ammonium chloride in aqueous ethanol.[14]

The chemistry of indium metal is the subject of current investigation, especially since the reactions induced by it can be performed in aqueous solution.[15] The selective reductions of ethyl 4-nitrobenzoate (entry 1), 2-nitrobenzyl alcohol (entry 2), 1-bromo-4-nitrobenzene (entry 3), 4-nitrocinnamyl alcohol (entry 4), 4-nitrobenzonitrile (entry 5), 4-nitrobenzamide (entry 6), 4-nitroanisole (entry 7), and 2-nitrofluorenone (entry 8) with indium metal in the presence of ammonium chloride using aqueous ethanol were performed and the corresponding amines were produced in good yield. These results indicate a useful selectivity in the reduction procedure. For example, ester, nitrile, bromo, amide, benzylic ketone, benzylic alcohol, aromatic ether, and unsaturated bonds remained unaffected during this transformation. Many of the previous methods produce a mixture of compounds. Other metals like zinc, tin, and iron usually require acid-catalysts for the activation process, with resultant problems of waste disposal.

Because of the non-flammable nature of the process and ready availability of indium and ammonium chloride, the submitters believe this method is practical for the preparation of several aromatic amines. Further, this method is performed in aqueous ethanol, is extremely safe from the environmental point of view, and should prove useful in organic chemistry.

TABLE 1

## SELECTIVE REDUCTION OF AROMATIC NITRO COMPOUNDS BY INDIUM METAL IN THE PRESENCE OF $NH_4Cl/H_2O/EtOH$

| Entry | Nitro compound | Product | Reduction time (h) | %Yield | mp °C |
|---|---|---|---|---|---|
| 1 |  |  | 2.5 | 94 | 88<br>(lit. 88-90) |
| 2 |  |  | 2h, 5 min | 68.5 | 84<br>(lit. 83-85) |
| 3 |  |  | 1.5 | 80 | 59<br>(lit. 60-64) |
| 4 |  |  | 1 | oil | oil |
| 5 |  |  | 2 | 75 | 85<br>(lit 83-85) |
| 6 |  |  | 1.75 | 71 | 182<br>(lit. 181-183) |
| 7 |  |  | 5 | 90 | 58-60<br>(lit. 57-60) |
| 8 |  |  | 8 | 80 | 157-160<br>(lit. 160) |

**1.** The University of Texas, M. D. Anderson Cancer Center, Department of Molecular Pathology, Box 89, 1515 Holcombe Blvd., Houston, TX 77030.

**2.** For a recent reference, see: Main, B. G.; Tucker, H. In *Medicinal Chemistry*, 2nd Ed.; Genellin, C. R.; Roberts, S. M.; Academic Press: New York, **1993**, p187.

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*Media*; J. Wiley & Sons: New York, **1997**. (b) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. (c) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023.

## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

Ethyl 4-aminobenzoate: Benzoic acid, 4-amino-, ethyl ester; (94-09-7)
Ethyl 4-nitrobenzoate: Benzoic acid, 4-nitro-, ethyl ester; 99-77-4)
Ammonium chloride (NH4Cl); (12125-02-9)
Indium; (7440-74-6)

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JZ, 1H parametrs for robot

exp1  s2pul

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date   Jun 11 2002  dfrq        299.701
solvent      CDC13  dn               H1
file           exp  dpwr             30
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sfrq       299.701  dm              nnn
tn              H1  dmm               c
at           4.683  dmf             200
np           32000  dseq
sw          3416.5  dres            1.0
fb            2000  homo              n
bs               4       PROCESSING
tpwr            59  wtfile
pw             9.0  proc             ft
d1           0.500  fn         not used
tof          145.8  math              f
nt               4
ct               4  werr
alock            n  wexp
gain      not used  wbs
      FLAGS         wnt
il               n
in               n
dp               y
hs              nn
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sp           -14.8
wp          2720.6
vs             133
sc               0
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is          148.29
rfl           63.8
rfp              0
th               2
ins        100.000
nm  cdc  ph
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