Pergamon

Tetrahedron Letters 41 (2000) 5603–5606

TETRAHEDRON LETTERS

Ultrasound-promoted highly efficient reduction of aromatic nitro compounds to the aromatic amines by samarium/ammonium chloride

Manas K. Basu, Frederick F. Becker and Bimal K. Banik*

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

Received 5 June 2000; accepted 6 June 2000

Abstract

Ultrasound-promoted, highly efficient reduction of several aromatic nitro compounds to the aromatic amines was achieved by samarium/ammonium chloride mediated reaction.

The synthesis of aromatic amines by various methods has been an active area of research for many years. As a result, many methods are currently available in the literature.[1] Some of these have significant limitations based on safety and handling considerations.[2] Further, the reaction conditions of many of these methods can destroy many sensitive functional groups. Catalytic hydrogenation[3,4] and catalytic transfer hydrogenation[5] are the most common of these methods for the synthesis of aromatic amines by the reduction of nitro compounds. However, metals such as palladium and Raney nickel used for this purpose, in the presence of hydrogen gas or a hydrogen donor, are flammable when exposed to air and, in many cases, the use of a vacuum pump and high temperature are necessary.

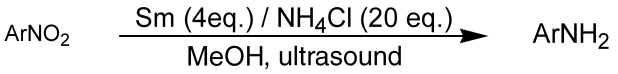
Recently, many novel reducing agents have been reported in the literature, such as decaborane in methanol,[6] electrochemically generated Raney nickel,[7] indium–ammonium chloride in ethanol,[8] samarium iodine in methanol,[9] *N*,*N*-dimethylhydrazine/ferric chloride,[10] hydrazine hydrate/ferric oxide–magnesium oxide,[11] diethyl chlorophosphite,[12] and sodium borohydride–sodium methoxide in methanol.[13] In general their main drawbacks are long reaction time, non-chemoselectivity and the requirement of reflux temperature.

We have been engaged in the use of polycyclic aromatic amines for the development of anti-cancer agents and towards this goal we have already reported the biological effects of a large number of polyaromatic compounds.[14] However, the supply of many of the parent amines from

* Corresponding author. Fax: +1 713 792 5940; e-mail: banik@mdanderson.org

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00917-5

different vendors is erratic. Therefore, we began a research program aimed at developing methods to synthesize the starting polycyclic amines rapidly and in high yield, by using ecologically friendly reagents. In this paper, we have developed a highly effective reducing agent by combining samarium metal[15] with ammonium chloride under sonication (Scheme 1).[16]

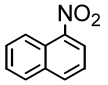
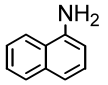
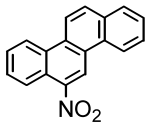
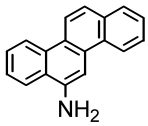
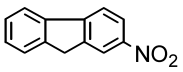
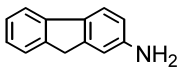
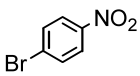
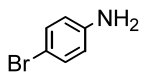
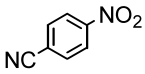
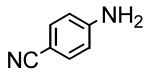
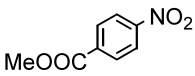
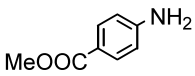
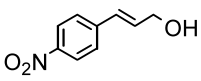
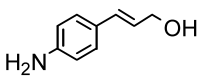
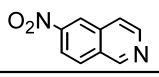
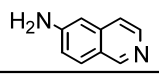


Scheme 1.

We believe that no other methods in the literature[1–13] can produce the aromatic amines by the reduction of aromatic nitro compounds within this time frame and under such mild conditions.

A wide variety of aromatic nitro compounds were reacted by samarium metal and ammonium chloride in methanol using ultrasound at room temperature (Table 1). For example, 6-nitro chrysene (entry 2) was reduced to the 6-amino chrysene in only 10 min by this method in excellent yield (86%). No reaction was observed in the absence of sonication.

Table 1
Ultrasound-promoted reduction of various aromatic nitro compounds by Sm/NH_4Cl

Entry	Starting Material	Product	Time (min)	Yield (%)
1			10	88
2			10	86
3			10	92
4			10	88
5			10	87
6			10	74
7			10	90
8			25	56

Similarly, nitrofluorene (entry 3) was reduced to the amino fluorene within 10 min. Indium/ammonium chloride reduction of the 2-nitro fluorene in the presence of sonication gave no reduction at room temperature even after 30 min. By following one reported method[8] we were able to prepare 2-aminofluorene by the reduction of 2-nitro fluorene at reflux temperature for 10 h using methanol in the presence of indium/ammonium chloride. Iron powder in the presence of ammonium chloride under sonication failed to produce traces of the amino compound. This indicates that samarium/ammonium chloride has a much greater reducing ability than the indium/ammonium chloride or iron/ammonium chloride combination, for the reduction of aromatic nitro group. We have further verified this conclusion by the facile chemoselective reduction of a number of other aromatic nitro compounds by using samarium/ammonium chloride under identical conditions. The reduction sensitive groups, such as bromo (entry 4), cyano (entry 5), ester (entry 6), unsaturated bond (entry 7) and heterocyclic ring (entry 8) remained unaffected during this transformation.

From a series of experiments, we found that 4-equiv. of samarium were required for completion of the reaction. An increase in the amount of samarium did not reduce the time required. We found that ammonium chloride was necessary since the reduction did not proceed in the presence of samarium and methanol only.

The mechanism of this new reducing system is unknown to us. In an effort to find the mechanistic path, reduction of 6-nitro chrysene was carried out by reacting it with samarium trichloride and samarium metal in methanol under sonication, since one can question the involvement of samarium dichloride. We found that the progress of this reaction was slow in comparison to the reaction when samarium metal and ammonium chloride were used. Therefore, we cannot exclude the involvement of samarium dichloride as the reactive species. We observed the critical role of methanol in this reaction as the reduction failed to produce amino compounds with any of these substrates under identical conditions with other solvents, such as ethanol and tetrahydrofuran.

In conclusion, we have shown an expeditious method for the synthesis of aromatic amines by the reduction of aromatic nitro compounds via samarium-induced ultrasound-promoted reaction at room temperature within a few minutes.[17]

Acknowledgements

We gratefully acknowledge the funding support received for this research project from the Hubert L. and Olive Stringer Chair and NIH Cancer Center Support Grant, 50P30-CA-16672-25, in particular the shared resources of the Pharmacology and Analytical Center Facility.

References

1. For example, see: (a) Coleman, G. H.; Blomquist, R. F. *J. Am. Chem. Soc*. **1941,** *63,* 1692. (b) Beak, P.; Kokko, B. *J. Org. Chem*. **1982**, *47,* 2822. (c) Kokko, B.; Beak, P. *Tetrahedron Lett*. **1983**, *24,* 561. (d) Beak, P.; Basha, A.; Kokko, B.; Loo, B. *J. Am. Chem. Soc*. **1986,** *108,* 6016. (e) Guram, A. S.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl*. **1995**, *34,* 1348. (f) Louie, J.; Hartwig, J. F. *Tetrahedron Lett*. **1995**, *36,* 3609. (g) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **1996**, *61,* 1133.
2. Synthesis of the aromatic amines by the reduction of aromatic azides is known. For some recent examples: (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev*. **1988**, *88*, 297. (b) Benati, L.; Montevecci, P. C.; Nanni, D.; Spagnolo, P.; Volta, M. *Tetrahedron Lett*. **1995,** *36*, 7313. (c) Goulaouic-Dubois, C.; Hesse, M. *Tetrahedron Lett*. **1995**, *36*, 7427. (d) Capperucci, A.; Degl'Innocenti, A.; Funicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org.*

Chem. **1995**, *60,* 2254. (e) Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Synlett* **1996**, 1193. Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett*. **1997**, *38,* 1065. (f) Kabalka, G.; Li, G. *Tetrahedron Lett*. **1997**, *38*, 5777. (g) Hays, D. S.; Fu, G. C. *J. Org. Chem*. **1998**, *63*, 2796.

3. For example, see: Johnstone, R. A. W.; Wilby, A. H.; Entistle, I. D. *Chem. Rev*. **1985**, *85*, 129.
4. For example, see: Greenspoon, N.; Keinan, E. *J. Org. Chem*. **1988**, *53*, 3723.
5. For example, see: Rajagopal, S.; Spatola, A. F. *J. Org. Chem*. **1995**, *56*, 4481.
6. Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C. M. *Tetrahedron Lett*. **2000**, *41*, 175.
7. Yasuhara, A.; Kasano, A.; Sakamoto, T. *J. Org. Chem*. **1999**, *64*, 2301.
8. Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1028.
9. Banik, B. K.; Mukhopadhyay, C.; Venkatraman, M. S.; Becker, F. F. *Tetrahedron Lett*. **1998**, *39*, 7243.
10. Boothroyd, S. R.; Kerr, M. A. *Tetrahedron Lett*. **1995**, *36*, 2411.
11. Kumbhar, P. S.; Sanchez-Valente, J.; Figueras, F. *Tetrahedron Lett*. **1998**, *39*, 2573.
12. Fisher, B.; Sheihet, L. *J. Org. Chem*. **1998**, *63*, 393.
13. Suwinski, J.; Wagner, P.; Holt, E. M. *Tetrahedron* **1996**, *52*, 9541.
14. Becker, F. F.; Banik, B. K. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2877.
15. (a) Ghatak, A.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett*. **2000**, *41*, 3793. (b) Banik, B. K., Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F. F. *Tetrahedron Lett*. **1999**, *40*, 6731
16. For an example, see: Han, B. H.; Boudjouk, P. *J. Org. Chem*. **1982**, *47*, 5030.
17. A representative procedure is given below: To a solution of the nitro compound (0.5 mmol) in methanol (5 mL) (for those compounds which are not completely soluble in methanol, a few drops of dichloromethane was added to make it soluble), solid ammonium chloride (10.0 mmol) and samarium metal (2.2 mmol, 40 mesh) were added and the reaction mixture was sonicated[18] at room temperature for 10–20 min (Table 1). The reaction started immediately as indicated by the evolution of gas, an increase in the internal temperature and by the change in the color of the mixtures. After the reaction was over, as indicated by TLC, water (5 mL) was added and then it was extracted with dichloromethane, dried over sodium sulfate and concentrated. The pure product was isolated by filtration through a short column over silica gel using ethyl acetate and hexanes as the solvent. The reaction can be carried out with 1–2 g nitro compound. All products have been characterized through a comparison of mp, TLC and NMR with authentic compounds.
18. A Bransonic Model 2210R-DTH was used for sonication.