Pergamon

Tetrahedron Letters 42 (2001) 5601–5603

TETRAHEDRON LETTERS

Simple and chemoselective reduction of aromatic nitro compounds to aromatic amines: reduction with hydriodic acid revisited

J. S. Dileep Kumar, ManKit M. Ho and Tatsushi Toyokuni*

Crump Institute for Molecular Imaging, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, 700 Westwood Plaza, Los Angeles, CA 90095, USA

Received 10 May 2001; revised 15 June 2001; accepted 19 June 2001

Abstract—Reduction of aromatic nitro compounds to amines with hydriodic acid was reinvestigated. Under a milder non-refluxing condition (at 90°C for 2–4 h), the reduction proceeded efficiently with excellent chemoselectivity without affecting other functional groups including nitrile, ester, halide, carbonyl, amide, sulfonamide, imidazole and methylthio groups.

Reduction of aromatic nitro compounds to the corresponding amines is an important chemical transformation in synthetic organic chemistry. This is because the nitro group is often used to activate the aromatic nucleus for nucleophilic substitution reactions but the amino group often serves as a site for further derivatisation towards final products. Indeed, aromatic amines are important intermediates for a number of valuable compounds such as pharmaceuticals, agrochemicals and dyes. A variety of methods have so far been reported for this transformation, many of which employ metallic reagents.[1] More chemoselective and efficient methods are constantly being developed.[2–4]

In 1947 Bruce and Perez-Medina observed that refluxing hydriodic acid (HI)[†] efficiently reduced the nitro group in pyridine rings to give aminopyridines.[5] In 1971 Krasnec reported some chemoselectivity in the HI-mediated reduction of aromatic nitro compounds to aromatic amines.[6] Thus, by refluxing with 57% HI the nitro group was reduced as well as a double bond with a high chemoselectivity over chloride and carbonyl groups. However, acid-labile nitrile and ester groups resulted in complete hydrolysis. Since then very little attention has been paid to this potentially useful method, particularly in terms of simplicity, ready availability of the reagent and the use of water as the solvent.[4,7] Therefore, we have reinvestigated this decades-old method under a milder non-refluxing condition which might improve its chemoselectivity.

Treatment of aromatic nitro compounds with 57% HI at 90°C for 2–4 h yielded the corresponding amines with excellent chemoselectivity over various functional groups that are often present in the substrate (Table 1). Moreover, acid-labile nitrile and ester groups did not undergo hydrolysis (entries 5 and 9, respectively). Boiling HI has been used to replace the halogen atom in pyridine[5] and pyridazine[8] rings with iodine. It is also reported that such halogen exchange was possible without reducing the nitro group by heating just below the boiling point.[5] Under our condition the aromatic nitro group was reduced exclusively without any halogen exchange reactions (entries 2, 3 and 10). It is worth mentioning that extraction of the reaction mixture generally yielded the product with a >95% purity (by ^{1}H NMR analysis) without purification by column chromatography (entries 1–5 and 11). The lower yields (entries 6–10) were attributed to the incomplete reactions.

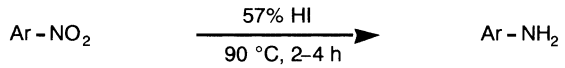
A typical reaction procedure is described below. All starting compounds are known (entries 2[9] and 3[10]) or commercially available (entries 1 and 4–11). A suspension of an aromatic nitro compound (1 mmol) in unstabilized 57% HI (3 mL) was heated at 90°C for 2–4 h. The reaction mixture became homogeneous as the reaction progressed. After cooling to room temperature, the dark purple mixture was diluted with EtOAc (50 mL)

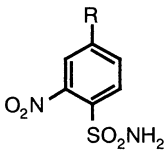
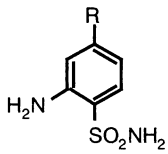
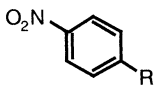
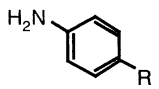
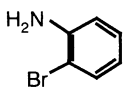
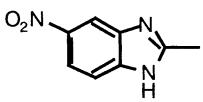
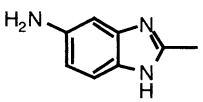
* Corresponding author. Tel.: (310) 206-1675; fax: (310) 206-8975; e-mail: ttoyokuni@mednet.ucla.edu

† 57% HI boils constantly at 127°C.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01083-8

Table 1. Chemoselective reduction of aromatic nitro compounds with 57% HI at 90°C



Entry	Substrate	Product	Time h	Yield %
				
1	2-nitrobenzenesulfonamide (R = H)	2-aminobenzenesulfonamide (R = H)	2	90
2	4-chloro-2-nitrobenzenesulfonamide (R = Cl)	2-amino-4-chlorobenzenesulfonamide (R = Cl)	2	95
3	4-bromo-2-nitrobenzenesulfonamide (R = Br)	2-amino-4-bromobenzenesulfonamide (R = Br)	2	90
				
4	4-nitroacetophenone (R = Ac)	4-aminoacetophenone (R = Ac)	4	80
5	4-nitrobenzonitrile (R = CN)	4-aminobenzonitrile (R = CN)	4	85
6	4-(methylthio)nitrobenzene (R = SMe)	4-(methylthio)aniline (R = SMe)	3	55
7	4-nitrobenzamide (R = $CONH_2$)	4-aminobenzamide (R = $CONH_2$)	3	60
8	4-nitrotoluene (R = Me)	*p*-toluidine (R = Me)	3	60
9	ethyl 4-nitrobenzoate (CO_2Et)	ethyl 4-aminobenzoate (CO_2Et)	3	60
				
10	1-bromo-2-nitrobenzene	2-bromoaniline	2	60
				
11	2-methyl-5-nitrobenzimidazole	5-amino-2-methylbenzimidazole	2	80

and washed successively with saturated aq $Na_2S_2O_3$ (for the destruction of iodine formed), saturated aq $NaHCO_3$ and brine. The colorless organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The crude product was further purified by silica-gel column chromatography to give the product amine. All products are known (entries 2[11] and 3[10]) or commercially available (entries 1 and 4–11) and gave ^1H NMR and MS spectra consistent with the assigned structures.

In conclusion, the use of 57% HI at 90°C is a simple and chemoselective means for reducing aromatic nitro compounds to the corresponding amines.

Acknowledgements

We thank Jennifer Leung for technical assistance. This work was supported by a research grant from the National Institutes of Health (CA86306). J.S.D.K. was supported by a fellowship through the Norton Simon Fund at UCLA.

References

1. Some reviews: (a) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035–2052; (b) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, 121–136.

2. Some recent examples: (a) Lee, J. G.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Kang, Y.; Cho, Y. S. *Synthesis* **2001**, 81–84; (b) Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett*. **2001**, *42*, 167–170; (c) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem*. **2001**, *66*, 919–924; (d) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955–977; (e) Pradhan, N.; Pal, A.; Pal, T. *Langmuir* **2001**, *17*, 1800–1802.
3. Solid-phase compatible methods are being developed: (a) Hari, A.; Miller, B. L. *Tetrahedron Lett*. **1999**, *40*, 245–248; (b) Scheuerman, R. A.; Tumelty, D. *Tetrahedron Lett*. **2000**, *41*, 6531–6535.
4. Methods are being developed to carry out the reduction in water without any organic solvent: (a) Boix, C.; Poliakoff, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1487–1490; (b) Tsukinoki, T.; Tsuzuki, H. *Green Chem*. **2001**, *3*, 37–38.
5. Bruce, W. F.; Perez-Medina, L. A. *J. Am. Chem. Soc*. **1947**, *69*, 2571–2574.
6. Krasnec, L. *Z. Chem*. **1971**, *11*, 110–111.
7. (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, 1997; (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie/Thomson Science: London, 1998.
8. (a) Horning, R. H.; Amstutz, E. D. *J. Org. Chem*. **1955**, *20*, 707–713; (b) Coad, P.; Coad, R. A.; Clough, S.; Hyepock, J.; Salisbury, R.; Wilkins, C. *J. Org. Chem*. **1963**, *28*, 214–218; (c) Maes, B. U. W.; Lemière, G. L. F.; Dommisse, R.; Augustyns, K.; Haemers, A. *Tetrahedron* **2000**, *56*, 1777–1781.
9. Daly, W. H.; Hölle, H. J.; Fouad, F. M. *J. Org. Chem*. **1974**, *39*, 1600–1603.
10. Hayman, D. F.; Petrow, V.; Stephenson, O. *J. Pharm. Pharmacol*. **1962**, *14*, 522–533.
11. Fedenko, V. S.; Avramenko, V. I.; Khmel, M. P.; Solomko, Z. F. *Zh. Org. Khim*. **1979**, *15*, 1673–1676.