19-44 The Reduction of Nitriles to Aldehydes

Hydro,oxy-de-nitrilo-tersubstitution

$$\mathrm{R{-}C{\equiv}N} \xrightarrow[\text{2. hydrolysis}]{\text{1. HCl, SnCl}_2} \mathrm{RCH{=}O}$$

There are two principal methods for the reduction of nitriles to aldehydes.[1179] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form an iminium salt, **47**.

$$\mathrm{RCCl} = \overset{\oplus}{\mathrm{N}}\mathrm{H_2} \quad \overset{\ominus}{\mathrm{Cl}}$$

47

Iminium salt **47** is reduced with anhydrous $SnCl_2$ to RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (**16-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[1180] It is also possible to prepare **47** in a different way, by treating ArCONHPh with PCl_5, which can then be converted to the aldehyde. This is known as the *Sonn–Müller method*. Aqueous formic acid in the presence of PtO_2, followed by treatment with aqueous acid, converts aryl nitriles to aryl aldehydes.[1181]

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 equivalent of hydrogen and hydrolysis, *in situ*, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[1182] $LiAlH(NR_2)_3$,[1183] and DIBALH.[1184] The metal hydride method is useful for aliphatic and aromatic nitriles.

OS **III**, 626, 818; **VI**, 631.

19-45 Reduction of Nitro Compounds to Amines

$$\mathrm{RNO_2} \xrightarrow[\text{HCl}]{\text{Zn}} \mathrm{RNH_2}$$

Both aliphatic[1185] and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro

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[1179] For a review, see Rabinovitz, M., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, p. 307. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1271–1272.

[1180] Zil'berman, E.N.; Pyryalova, P.S. *J. Gen. Chem. USSR* ***1963***, *33*, 3348.

[1181] Xi, F.; Kamal, F.; Schenerman, M.A. *Tetrahedron Lett.* ***2002***, *43*, 1395.

[1182] Brown, H.C.; Shoaf, C.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1079. For a review of reductions with this and related reagents, see Málek, J. *Org. React.* ***1988***, *36*, 249, see pp. 287–289, 438–448.

[1183] Cha, J.S.; Lee, S.E.; Lee, H.S. *Org. Prep. Proceed. Int.* ***1992***, *24*, 331. Also see, Cha, J.S.; Jeoung, M.K.; Kim, J.M.; Kwon, O.O.; Lee, J.C. *Org. Prep. Proceed. Int.* ***1994***, *26*, 583.

[1184] Miller, A.E.G.; Biss, J.W.; Schwartzman, L.H. *J. Org. Chem.* ***1959***, *24*, 627; Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. *J. Org. Chem.* ***1970***, *35*, 858.

[1185] For a review of selective reduction of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe, S.L.; Tartakovskii, V.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1966***, *35*, 19.

compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe (or sometimes other metals) and acid, and catalytic hydrogenation.[1186] Indium metal in aqueous ethanol with ammonium chloride[1187] or with water in aq. THF[1188] also reduces aromatic nitro compounds to the corresponding aniline derivative. Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.[1189] Samarium and a catalytic amount of iodine also accomplishes this reduction,[1190] as does Sm with a bipyridinium dibromide in methanol.[1191] Samarium metal in methanol with ultrasound also reduces aryl nitro compounds.[1192] Sodium sulfide (NaHS) on alumina with microwave irradiation reduces aryl nitro compounds to aniline derivatives.[1193] A mild reduction uses Al(Hg) in aq. THF with ultrasound.[1194] An $Al/NiCl_2$ reagent was used to reduced the nitro group of a polymer-bound $CH_2OCH_2C_6H_4NO_2$ moiety.[1195] Some other reagents used[1196] were $Et_3SiH/RhCl(PPh_3)_3$,[1197] $AlH_3{-}AlCl_3$, Mn with $CrCl_2$,[1198] nanoparticulate iron in water at 210°C,[1199] formic acid and Pd–C[1200] for formic acid with Raney nickel in methanol,[1201] and sulfides, such as NaHS, $(NH_4)_2S$, or polysulfides. The reaction with sulfides or polysulfides is called the *Zinin reduction*.[1202] Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with $HCOONH_4{-}Pd{-}C$.[1203] Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (although ketones are reduced, see **19-33**). With optically active alkyl substrates this method gives

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[1186] For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 104–116, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 168–202. See Deshpande, R.M.; Mahajan, A.N.; Diwakar, M.M.; Ozarde, P.S.; Chaudhari, R.V. *J. Org. Chem.* ***2004***, *69*, 4835; Wu, G.; Huang, M.; Richards, M.; Poirer, M.; Wen, X.; Draper, R.W. *Synthesis* ***2003***, 1657.

[1187] Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1028; Banik, B.K.; Suhendra, M.; Banik, I.; Becker, F.F. *Synth. Commun.* ***2000***, *30*, 3745.

[1188] Lee, J.G.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Kang, Y.; Cho, Y.S. *Synthesis* ***2001***, 81.

[1189] Kim, B.H.; Han, R.; Piao, F.; Jun, Y.M.; Baik, W.; Lee, B.M. *Tetrahedron Lett.* ***2003***, *44*, 77.

[1190] Banik, B.K.; Mukhopadhyay, C.; Venkatraman, M.S.; Becker, F.F. *Tetrahedron Lett.* ***1998***, *39*, 7243; Wang, L.; Zhou, L.; Zhang, Y. *Synlett* ***1999***, 1065.

[1191] Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* ***2001***, *66*, 919.

[1192] Basu, M.K.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 5603.

[1193] Kanth, S.R.; Reddy, G.V.; Rao, V.V.V.N.S.R.; Maitraie, P.; Narsaiah, B.; Rao, P.S. *Synth. Commun.* ***2002***, *32*, 2849.

[1194] Fitch, R.W.; Luzzio, F.A. *Tetrahedron Lett.* ***1994***, *35*, 6013.

[1195] Kamal, A.; Reddy, K.L.; Devaiah, V.; Reddy, G.S.K. *Tetrahedron Lett.* ***2003***, *44*, 4741.

[1196] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 821–828.

[1197] Brinkman, H.R. *Synth. Commun.* ***1996***, *26*, 973.

[1198] Hari, A.; Miller, B.L. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2777.

[1199] Wang, L.; Li, P.; Wu, Z.; Yan, J.; Wang, M.; Ding, Y. *Synthesis* ***2003***, 2001.

[1200] Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 443. See also, Terpko, M.O.; Heck, R.F. *J. Org. Chem.* ***1980***, *45*, 4992; Babler, J.H.; Sarussi, S.J. *Synth. Commun.* ***1981***, *11*, 925.

[1201] Gowda, D.C.; Gowda, A.S.P.; Baba, A.R.; Gowda, S. *Synth. Commun.* ***2000***, *30*, 2889.

[1202] For a review of the Zinin reduction, see Porter, H.K. *Org. React.* ***1973***, *20*, 455.

[1203] Ram, S.; Ehrenkaufer, R.E. *Tetrahedron Lett.* ***1984***, *25*, 3415.

retention of configuration.[1204] Ammonium formate in methanol reduces aromatic nitro compounds.[1205] Lithium aluminum hydride reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (**19-80**). Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, although both aliphatic and aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts, such as $NiCl_2$ or $CoCl_2$[1206] phthalocyanine iron (II),[1207] and $ZrCl_4$.[1208] Borohydride exchange resin in the presence of $Ni(OAc)_2$, however, gives the amine.[1209] Treatment of aromatic nitro compounds with $NaBH_4$ alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[1210] or in cleavage of the nitro group from the ring.[1211] With $(NH_4)_2S$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.[1212] The nitro groups of *N*-nitro compounds can also be reduced to amino groups, for example, nitrourea $NH_2CONHNO_2$ gives semicarbazide $NH_2CONHNH_2$. Bakers yeast reduces aromatic nitro compounds to aniline derivatives.[1213] A combination of $NaH_2PO_2/FeSO_4$ with microwave irradiation reduces aromatic nitro compounds to aniline derivatives.[1214] Hydrazine on alumina, with $FeCl_3$ and microwave irradiation accomplishes this reduction.[1215] Hydrazine–formic acid with Raney nickel in methanol reduces aromatic nitro compounds.[1216] Heating aromatic nitro compounds with 57% HI reduces the nitro group to the amino group.[1217]

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (**19-46**), hydrazobenzenes, azobenzenes (**19-80**), and azoxybenzenes (**19-79**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates. Reduction by metals in mineral acids cannot be stopped, but always produces the amine.

[1204] Barrett, A.G.M.; Spilling, C.D. *Tetrahedron Lett.* ***1988***, *29*, 5733.

[1205] Gowda, D.C.; Mahesh, B. *Synth. Commun.* **2000**, *30*, 3639.

[1206] See, for example, Osby, J.O.; Ganem, B. *Tetrahedron Lett.* ***1985***, *26*, 6413; Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* ***1987***, 713; He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun.* ***1989***, *19*, 3047. See also, references cited therein.

[1207] Wilkinson, H.S.; Tanoury, G.J.; Wald, S.A.; Senanayake, C.H. *Tetrahedron Lett.* ***2001***, *42*, 167.

[1208] Chary, K.P.; Ram, S.R.; Iyengar, D.S. *Synlett* ***2000***, 683.

[1209] Yoon, N.M.; Choi, J. *Synlett* ***1993***, 135.

[1210] Severin, T.; Schmitz, R. *Chem. Ber.* ***1962***, *95*, 1417; Severin, T.; Adam, M. *Chem. Ber.* ***1963***, *96*, 448.

[1211] Kaplan, L.A. *J. Am. Chem. Soc.* ***1964***, *86*, 740. See also, Swanwick, M.G.; Waters, W.A. *Chem. Commun.* ***1970***, 63.

[1212] This result has also been achieved by hydrogenation with certain catalysts [Lyle, R.E.; LaMattina, J.L. *Synthesis* ***1974***, 726; Knifton, J.F. *J. Org. Chem.* ***1976***, *41*, 1200; Ono, A.; Terasaki, S.; Tsuruoka, Y. *Chem. Ind. (London) 1983*, 477], and with hydrazine hydrate and Raney nickel: Ayyangar, N.R.; Kalkote, U.R.; Lugad, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3159.

[1213] Baik, W.; Han, J.L.; Lee, K.C.; Lee, N.H.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.* ***1994***, *35*, 3965.

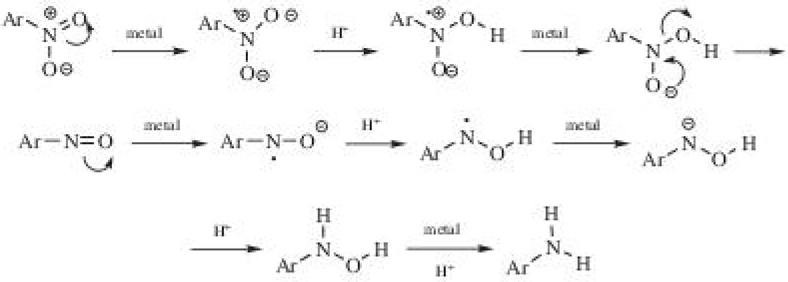
[1214] Meshram, H.M.; Ganesh, Y.S.S.; Sekhar, K.C.; Yadav, J.S. *Synlett* ***2000***, 993.

[1215] Vass, A.; Dudás, J.; Tóth, J.; Varma, R.S. *Tetrahedron Lett.* ***2001***, *42*, 5347.

[1216] Gowda, S.; Gowda, D.C. *Tetrahedron* ***2002***, *58*, 2211.

[1217] Kumar, J.S.D.; Ho, M.M.; Toyokuni, T. *Tetrahedron Lett.* ***2001***, *42*, 5601.

The mechanisms of these reductions have not been studied much, although it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (**19-47**), and hydroxylamines can be isolated (**19-46**). With metals and acid the following path has been suggested:[1218]



Certain aromatic nitroso compounds (Ar—NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 *M* aq. KCN with uv light.[1219] The reaction has also been performed electrochemically.[1220] When nitro compounds are treated with most reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated.

Reductive alkylation of aromatic nitro compounds is possible. The reaction of nitrobenzene with allylic or benzyl halides in the presence of an excess of tin metal in methanol, leads to the *N,N*-diallyl or dibenzyl aniline.[1221] A similar reaction occurs with nitrobenzene, allyl bromide, and indium metal in aq. acetonitrile.[1222]

OS **I**, 52, 240, 455, 485; **II**, 130, 160, 175, 254, 447, 471, 501, 617; **III**, 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV**, 31, 357; **V**, 30, 346, 552, 567, 829, 1067, 1130; **81**, 188.

19-46 Reduction of Nitro Compounds to Hydroxylamines

$$\mathrm{ArNO_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{Zn}} \mathrm{ArNHOH}$$

When aromatic nitro compounds are reduced with zinc and water under neutral conditions,[1223] hydroxylamines are formed. Among other reagents used for this

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[1218] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 211.

[1219] Petersen, W.C.; Letsinger, R.L. *Tetrahedron Lett.* ***1971***, 2197; Vink, J.A.J.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1971***, 90, 1333.

[1220] Lamoureux, C.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1988***, 59.

[1221] Bieber, L.W.; da Costa, R.C.; da Silva, M.F. *Tetahedron Lett.* ***2000***, *41*, 4827.

[1222] Kang, K.H.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Chung, B.Y.; Cho, Y.S. *Synth. Commun.* ***2001***, *31*, 2277.

[1223] For some other methods of accomplishing this conversion, see Rondestvedt Jr., C.S.; Johnson, T.A. *Synthesis* ***1977***, 850; Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* ***1978***, *34*, 213.