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RAPID CATALYTIC TRANSFER REDUCTION OF AROMATIC NITRO COMPOUNDS TO HYDROXYLAMINES

IAN D. ENTWISTLE and TERRY GILKERSON
Shell Biosciences Laboratory, Sittingbourne, Kent ME9 8AG, England

ROBERT A. W. JOHNSTONE* and ROBERT P. TELFORD
The Robert Robinson Laboratories, The University, Liverpool L69 3BX, England

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Abstract—A general method has been developed for the rapid, metal-catalysed transfer reduction of nitro compounds to N-substituted hydroxylamines.

In the course of our work on catalytic transfer reduction[1-4] we found that, during conversion of aromatic nitro compounds to anilines, intermediate compounds could be observed on monitoring the course of the reduction by thin-layer chromatography. It is known[5] that reduction of nitro compounds to amines proceeds through intermediate stages involving nitroso compounds and hydroxylamines (1),

$$RNO_2 \rightarrow RNO \rightarrow RNHOH \rightarrow RNH_2 \qquad (1)$$

Examination of individual steps in this sequence (1; R=Ph) has shown[5] that the rates of reduction of the various intermediates are arranged, nitrosobenzene > N-phenylhydroxylamine > nitrobenzene so that it is not difficult to comprehend the main reason for the difficulty in stopping reduction at either the nitroso or hydroxylamine stage. Although catalytic transfer reduction may proceed via discrete steps (1), it is possible that conversion into amines could proceed on the catalyst surface without release of intermediates at any stage. Alternatively, the heterogeneous interaction of catalyst and intermediates could alter the reduction rates usually observed in solution. This seems to have been the case in the successful reduction of nitro compounds to hydroxylamines using molecular hydrogen and a specially prepared iridium catalyst[6] but no other metal was found which allowed reduction to be stopped at this intermediate stage.

Reduction of nitro compounds to hydroxylamines can be effected by a wide variety of non-catalytic methods.[7] Although none of them seems general, perhaps the most widely applicable is that using zinc, ammonium chloride and an aqueous suspension or alcoholic solution of the nitro compound. Over-reduction occurs frequently and can be prevented more sucessfully by employing a two-phase ether–water system[8] but the method is still exothermic and requires careful temperature control. Of the other methods known[7] for the formation of hydroxylamines from nitro compounds, only one other,[9] an isolated instance of the preparation of one hydroxylamine using hydrazine and a palladium metal catalyst, appears to be catalytic and bears resemblance to the work described here; in all the other examples described,[9] further reduction to amine occurred. The observation by thin-layer chromatography of intermediates in our work prompted an investigation into their nature and led to this new general method for the preparation of aromatic hydroxylamines, many of industrial interest.

In our work on transfer reduction, the reaction of *m*-dinitrobenzene with cyclohexene and palladium–charcoal catalyst was monitrored by tlc and found to produce N-3-nitrophenyl hydroxylamine as an intermediate which could not be isolated because of its rapid further reduction to *m*-nitroaniline; this procedure did allow half-reduction of dinitro compounds to nitro, amino compounds.[1] Similarly, the vigorous reaction of *m*-dinitrobenzene with formic acid in the presence of palladium[3] also gave clear evidence by tlc for the intermediate formation of the hydroxylamine.

The vigorous transfer reduction of *m*-dinitrobenzene with formic acid and palladium was moderated by changing the hydrogen-donor to hydrazine and using a rhodium-charcoal catalyst. Under these conditions, tlc showed that the intermediate observed during the earlier reductions under more vigorous conditions was only slowly reduced further to *m*-nitroaniline and *m*-phenylene diamine. The intermediate was isolated and shown to be N-3-nitrophenylhydroxylamine. Similarly, other aromatic nitro compounds gave hydroxylamines but, although the reducing conditions had been moderated, in some instances hydroxylamines were obtained in modest yield (Table 1). Some formation of azoxybenzenes was occasionally observed, possibly because of the alkalinity[10] of the reducing medium.

Alternative mild transfer reduction to hydroxylamines was achieved on changing the hydrogen donor to phosphinic acid or its sodium salt and using a two-phase solvent system, frequently tetrahydrofuran–water, with a palladium–charcoal catalyst. Hydroxylamines produced in this way are shown in Table 2. Yields quoted in Table 2 are for isolated hydroxylamines but some of these are extremely labile (other than to further reduction) and any low yields reported were frequently the result of difficulties in work-up. Some hydroxylamines were too labile even for isolation in a pure state and were further characterized by oxidation with ferric chloride to the corresponding nitroso compounds (Table 3).

The two methods of reduction appear complementary.

Table 1. N-Arylhydroxylamines from aryl nitro compounds by reduction with rhodium and hydrazine

Hydroxylamine (R)[a]	Yield %	Mp[b] (solvent)	Analytical Data[b]
3-NO_2	55	120–121 (EtOH) lit., 118–119 (benzene)[12]	-
3-Me	77	65–67 (benzene) lit., 68 (benzene/pet. ether)[13]	-
4-Me	24	81–85 (benzene) lit., 93–94 (benzene/pet. ether)[13]	-
4-Cl	72	89–90[c] lit., 86[4]	-
4-trans-CH=CHCO$_2$Me	52	124–125 dec. (benzene)	m/e 193($M^{+\cdot}$); ν 3200–3300, 1690, 1630 cm^{-1}; δ 3.72(s,3H), 6.34(d,1H,20 Hz), 6.98(d,2H, 8 Hz), 7.52(d,2H,8 Hz), 7.59(d,1H,20 Hz), 7.94(s,1H), 8.16(s,1H).
2-Cl, 5-CF_3	45	50–51 (benzene)	m/e 211($M^{+\cdot}$); ν 3200–3400 cm^{-1}; δ 5.4–6.1 (broad H), 6.9–7.9(m,4H became 3H after D_2O shake)
2,5-(OMe)$_2$	33	69–71 dec. (benzene)	m/e 169($M^{+\cdot}$); ν 3400 cm^{-1}; δ 3.75(s,6H), 6.0–7.3(m,5H became 2H after D_2O shake)
3-Cl, 4-Me	77	101–102[c]	C, 54.1(53.3); H, 4.8(5.0); N, 8.6(8.8)%.

[a] All of type, ArNHOH, in which Ar = R-substituted phenyl.

[b] Analytical data for new compounds. See Table 2 for other elemental analyses, listed as required percentages in parentheses immediately following the percentages found for each element.

[c] See comment c in Table 2.

Table 2. Hydroxylamines from nitro compounds by reduction with palladium and phosphinite

Hydroxylamine (R or other)[a]	Yield (%)	Mp[b] (solvent)	Elemental analysis or Reference[b]
2-$CO_2C_2H_5$	30	oil[c]	-
3-NO_2	84	119–120 (benzene)	12
3-OH	70	oil[c]	-
3-Br	50	64–66 (benzene)	14
3-trans-CH=CHPh	52	149–150 dec. (benzene)	C, 79.9(79.6); H, 6.3(6.2); N, 6.4(6.6)%
3-OCO.NHPh	85	129–130[c]	C, 63.9(63.9); H, 5.0(4.9); N, 11.5(11.5)%
3-OCO.NHC$_6$H$_4$Me(m)	74	85–86[c]	C, 64.9(65.1); H, 5.5(5.5); N, 10.3(10.8)%
3-OCO.NH-cycloC_6H_{11}	93	127–128[c]	C, 64.1(62.4); H, 7.6(7.2); N, 11.1(11.2)%
3-NHCOCH$_2$Cl	75	oil[c]	-
4-NO_2	78	106–107 (benzene)	15
4-trans-CH=CHCO$_2$Me	64	181–183 dec. (benzene)	C, 62.0(62.2); H, 5.7(5.7); N, 7.3(7.3)%
4-Cl	75	85–86 (benzene)	16
2-CN, 3-Cl	90	182–187[c]	C, 50.3(49.9); H, 2.7(3.0); N, 16.3(16.6)%
2-Cl, 5-CF_3	90	55–88[c]	C, 39.8(39.7); H, 2.4(2.6); N, 5.4(6.6)%
	49	55–56 (CH_2Cl_2)[d]	C, 36.2; H, 3.11; N, 6.2. $C_7H_5ClF_3NO.H_2O$ requires C, 36.6; H, 3.1; N, 6.1%
2-Cl, 5-NHCONMe$_2$	74	97–98[c]	C, 47.5(47.6); H, 5.8(5.2); N, 17.5(18.3)%
4-nitropyridine-N-oxide[*]	70	222 dec (EtOH)	17
2-chloro-3-nitropyridine[*]	66	115–116[c]	C, 41.5(42.4); H, 3.4(3.5); N, 24.5(23.9)%
5-nitro-2,1,3-benzthiadiazole[*]	44	115–116 (benzene)	C, 43.6(43.1); H, 3.2(3.0); N, 24.7(25.1)%

[a] These are all of type, ArNHOH, in which Ar = R-substituted phenyl except for the last three named heteroaromatic (*) examples. The hydroxylamines, ArNHOH, were obtained from the corresponding nitro compounds, $ArNO_2$.

[b] For brevity, analyses are presented with the required percentages in parentheses immediately following the percentages found for each element. A reference is given for known compounds.

[c] These hydroxylamines were labile and difficult or impossible to recrystallize for analysis. Reported analyses in these cases refer to material isolated from column chromatography by elution and low temperature evaporation of solvent.

[d] Comment c applies but this example gave recrystallized material in greatly reduced yield in which a molecule of water appeared to be incorporated.

Table 3. Aryl nitroso compounds obtained from N-arylhydroxylamines by oxidation with ferric chloride

Nitroso compound (R) [a]	Yield (%)	Mp[b]	Elemental analysis [b]
3-OCO.NHPh [c]	93	143–144 (lit. 133–4)[18]	C, 64.4(64.5); H, 4.1(4.2); N, 11.6(11.6)%.
3-NHCOCH$_2$Cl [d]	75	131–132	C, 48.1(48.4); H, 3.6(3.5); N, 14.3(14.1)%.
3-OH [c]	60	104 (lit. 104–105)[18]	
4-Cl [d]	100	88–89 (lit., 89.5)[19]	
3-OCO.NHC$_6$H$_4$(m-Me) [c]	89	94–95	C, 65.8(65.6); H, 4.5(4.7); N, 10.6(10.8)%
2-CN, 3-Cl	36	220–222	C, 50.4(50.5); H, 1.7(1.7); N, 16.7(16.8)%
2-Cl, 5-NHCONMe$_2$ [d]	70	93–95	C, 46.6(47.4); H, 4.4(4.4); N, 17.2(18.5)%
2-Cl, 5-CF$_3$ [c]	25	243–245	C, 39.8(40.1); H, 2.3(1.4); N, 5.0(6.7)%
3-Cl, 4-Me [d]	91	66–67	C, 55.2(55.0); H, 4.0(3.8); N, 8.8(9.0)%

[a] All of type, ArNO, in which Ar = R-substituted phenyl

[b] Elemental analyses given as percentages of elements found with required values in parentheses.

[c] Green monomer

[d] Yellow dimer

Thus, 2-chloro-5-trifluoromethyl-nitrobenzene gave only a 45% yield of the hydroxylamine using Rh/hydrazine but with Pd/phosphinite it yielded 90%.

Use of rhodium-charcoal catalyst with phosphinic acid as a reducing medium proved to be slower than other reagents.

EXPERIMENTAL

Compounds were identified by three or more of m.p., ms, PMR and IR. Hydroxylamines have very characteristic mass spectral fragmentation, showing losses of H_2, O and OH from the molecular ion.[11] Further checks on purity were obtained by tlc on silica gel using chloroform as mobile phase. The course of reduction was monitored by tlc in the same system.

Reduction with rhodium and hydrazine. To a stirred solution of *m*-dinitrobenzene (1.0g) in THF (10 ml) was added 5% rhodium-charcoal catalyst (15–20 mg) followed by the gradual dropwise addition of hydrazine (65% w/w aqueous soln); the reaction was monitored by tlc until most of the starting material had disappeared. After 90 min, the mixture was poured into water and extracted with ether to give N-3-nitrophenylhydroxylamine.

The other hydroxylamines listed in Table 1 were obtained similarly. In some instances, azoxy compounds were produced through reaction of the intermediate hydroxylamine with intermediate nitroso compound, a known reaction.[10]

Reduction with palladium and phosphinic acid or sodium phosphinite. To a stirred mixture of sodium phosphinite (4g) in water (25 ml) with THF (25 ml) containing 3-bromonitrobenzene (3g) was added 5% Pd-C catalyst (commercial grade; 0.3g). The reduction was monitored by tlc and continued until amost all the nitro compound had reacted. The upper layer was separated, diluted with ether washed with water, and dried ($MgSO_4$) to give N-3-bromophenylhydroxylamine.

The other hydroxylamines in Table 2 were obtained similarly. The following compounds, $ArNO_2$, gave only anilines, $ArNH_2$, and not hydroxylamines: Ar = 4-isopropyl-3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 2,5-dimethoxyphenyl.

Preparation of nitroso compounds from hydroxylamines. To a stirred soln $FeCl_3$ (9g) in water (400 ml) was added N-3-α-chloroacetamidophenylhydroxylamine(2g) in EtOH (80 ml) over a period of 10 min. After stirring for a further 30 min, the product was extracted with diethyl ether and chromatographed on silica gel, eluting with methylene chloride to give N-3-α-chloroacetamidonitrosobenzene (1.5g; 75% yield), m.p. 131–132°. The other nitrosbenzenes listed in Table 3 were obtained similarly.

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