Selective Rapid Transfer-hydrogenation of Aromatic Nitro-compounds

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Reduction of mono- and poly-nitro-aromatic compounds was effected rapidly, selectively, and in high yield by transfer of hydrogen from cyclohexene to the substrate *via* palladium–charcoal catalyst. The usefulness of the method is not affected by the presence of a variety of other functional groups, except for halogen which is removed during hydrogenation and sulphur-containing systems which retard and sometimes stop the reaction.

THE effectiveness of transfer-hydrogenation of aromatic nitro-compounds to produce amino compounds was demonstrated over 20 years ago,[1] but subsequent general application of this mild, convenient technique in synthesis has not followed.[2] Under the earlier reported optimum reaction conditions, refluxing the nitro-compound in ethanol with cyclohexene and Pd–C catalyst (catalyst: substrate ratio 10^{-2} : 1), inordinately long reaction times were recorded and many non-specific reductions noted;[1] this has resulted in the method receiving little attention as an alternative to ordinary catalytic hydrogenation or metal–acid reductions of nitro-groups. That the selective reduction of aromatic nitro-compounds is still of considerable interest is shown by recent communications.[3]

Our interest in this transfer-hydrogenation was occasioned by one of its reported [1] but little studied advantages namely, the mono-reduction of polynitrobenzenes. Under the modified conditions reported here, *o*-, *m*-, and *p*-dinitrobenzene are rapidly and efficiently reduced to the corresponding *o*-, *m*-, and *p*-nitroaniline, contrary to an earlier report that only *m*-dinitrobenzene could be reduced successfully. Similarly, we have reduced other mono- and di-nitro-aromatic compounds.

Typically, the nitro-compound is refluxed in ethanol with a large excess of cyclohexene in the presence of Pd–C catalyst (catalyst : substrate ratio 1 : 2). Generally, formation of product was observed almost immediately after refluxing commenced and the reactions were stopped when starting material was not detected by t.l.c. The used catalyst could generally be re-used up to six times before there was a noticeable deterioration in its efficiency. The short reaction times and the reduction of many different types of nitro-compound indicate that when large catalyst : substrate ratios are used, as in these experiments, the transfer of hydrogen does not involve specific donor–acceptor relationships as suggested earlier.[1] Rather, the reaction seems to be one involving separate donor dehydrogenation and acceptor hydrogenation. In agreement with the earlier work,[1] the nature of the hydrogen donor seems critical as shown for example by the inferior donor properties of cyclohexa-1,3-diene in comparison with cyclohexene.

Transfer-hydrogenation under the conditions reported here can achieve, in a more controlled and rapid manner, many reductions effected by catalytic hydrogenation.

[1] E. A. Braude, R. P. Linstead, and K. R. H. Wooldridge, *J. Chem. Soc.*, 1954, 3586.

[2] G. Brieger and T. J. Nestrick, *Chem. Rev.*, 1974, **74**, 567.

[3] R. E. Lyle and J. L. LaMattina, *Synthesis*, 1974, 726; T.-L. Ho and C. M. Wong, *ibid.*, p. 45.

Thus, large quantities of 3,6-dimethoxy-2-nitroaniline were conveniently obtained by transfer-hydrogenation of the readily available 4-methoxy-2,3-dinitroanisole.[4]

Although reduction of dinitroanilines was slower than for other nitro-compounds (Table), we did not experience the difficulties reported earlier.[1] A particularly interesting example was the initial conversion of 2-(2,6-dinitroanilino)-*N*-methylpropionamide (I; R = Me, R′ = NH_2) into the aniline (II; R = Me, R′ = NH_2) followed by cyclisation to 3,4-dihydro-3-methyl-5-nitroquinoxalin-2(1*H*)-one (III; R = Me) under the reaction conditions. This reduction–cyclisation is a possible alternative to an earlier described method of peptide end-group analysis.[5] The general applicability of this reaction was indicated by the conversion of *N*-2,6-dinitrophenyl derivatives of amino-acid methyl esters (I; R = amino-acid side-chain, R′ = OMe) into the corresponding quinoxalinones (III). The common amino-acids contain a variety of side-chains (*e.g.* R = CH_2·OH, CH_2·SH, CH_2·CH_2·SMe, CH_2Ph, CH_2-indol-3-yl, and CH_2-imidazol-2-yl), but only in the case of cysteine was difficulty encountered in that the CH_2·SH group was reduced to CH_3, thereby yielding the quinoxalinone (III; R = Me) rather than (III; R = CH_2·SH). The reaction sequence (I) ⟶ (III) was examined as a means of sequencing amino-acid residues in a peptide and these results are to be reported more fully in a later communication.

The hydrogen-transfer process was noticeably slower but went to completion with the sulphur-containing compounds (I; R = CH_2·SH or CH_2·CH_2·SMe). However, with 2-nitrothiophen and 6-nitrobenzothiadiazole no reduction was observed.

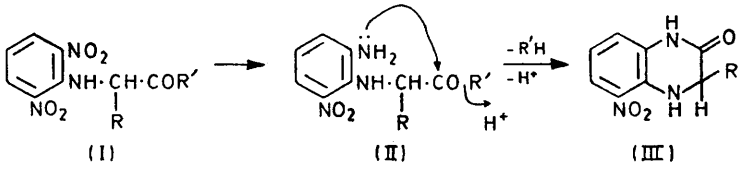
Nitro-heterocyclic systems without sulphur were reduced normally, *e.g.* the conversions of 6-nitroindazole into 6-aminoindazole and of *N*-(3-nitro-2-pyridyl)-tryptophan methyl ester into *N*-(3-amino-2-pyridyl)-tryptophan methyl ester.

Transfer-hydrogenation was very effective in removing halogeno-substituents as demonstrated by the formation of 2-amino-*N*-methyl-6-nitroaniline from 4-chloro-*N*-methyl-2,6-dinitroaniline.

Nitro-compounds reduced by transfer-hydrogenation

Nitro-compound	Product	Yield (%)	M.p. (°C)	Reaction time (min)
4-Methoxy-2,3-dinitroanisole	3,6-Dimethoxy-2-nitroaniline	85	76—77	10
4-Methoxy-2,5-dinitroanisole	3,6-Dimethoxy-4-nitroaniline	85	152—153	10
4-Methoxy-2,6-dinitroanisole	2,5-Dimethoxy-3-nitroaniline	70	88—89	15
2,6-Dinitroaniline	2-Amino-6-nitroaniline	95	158—159	30
4-Chloro-*N*-methyl-2,6-dinitroaniline	2-Amino-*N*-methyl-6-nitroaniline	85	75—76	30
3,6-Dimethoxy-2-nitroaniline	2,3-Diamino-4-methoxyanisole	70	86—87	120
3,6-Dimethoxy-*N*-methyl-2-nitroaniline (m.p. 80—81°)	2-Amino-4-methoxy-3-methylaminoanisole (as hydrochloride)	80	decomp. 150	120
6-Nitroindazole	6-Aminoindazole	90		60
2-(2,6-Dinitroanilino)-*N*-methylpropionamide	3,4-Dihydro-3-methyl-5-nitroquinoxalin-2(1*H*)-one	60	222—223	60
	2-(2-Amino-6-nitroanilino)-*N*-methylpropionamide	30	169—170	

* Satisfactory spectral and analytical data have been obtained.



EXPERIMENTAL

All the compounds reported are either known or simply derived from known compounds; new compounds were identified by elemental analysis and mass and n.m.r. spectra. In a typical reaction 4-methoxy-2,5-dinitroanisole was mixed with 10% Pd–C catalyst (0.5 mol. equiv.; ordinary commercial material) and cyclohexene (5—6 mol. equiv.) in ethanol. The solution was refluxed vigorously on a steam-bath for 10 min. After filtration from catalyst, which was washed with ethanol and re-used, the solution was evaporated to give 3,6-dimethoxy-2-nitroaniline. Typical reaction times are shown in the Table.

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[4] R. Nietzki and F. Rechberg, *Ber.*, 1890, **23**, 1216.
[5] M. Jutisz and W. Ritschard, *Biochem. Biophys. Acta*, 1955, **17**, 548; V. M. Ingram, *ibid.*, 1956, **20**, 577.