CHAPTER 1
FACILE TRANSFER REDUCTION OF NITRO ARENES
TO N-ARYLHYDROXYL AMINES

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INTRODUCTION

_N_-Arylhydroxylamines are reactive starting materials for the preparation of intermediates which find wide use in the manufacture of industrial chemicals. Substituted phenylhydroxylamines are generally formed as intermediate products during the reduction of substituted nitroarenes (Chart 1).\(^1\) _N_-Mono and \(N,N\)-disubstituted hydroxylamines are weakly acidic substances, but owing to their instability in strongly alkaline media, their acid strength does not appear to have been measured although they should be approximately in the range of 12-13.\(^2\) This property of substituted phenylhydroxylamines has been made use of in various chemical reactions to get valuable compounds. Substituted phenylhydroxylamines are good nucleophiles. The common structural feature of these nucleophiles is the nucleophilic centre is adjacent to an atom with lone pair of electrons, a phenomenon commonly known as \(\alpha\)-effect.\(^3\)

_N_-Phenylhydroxylamine was used mainly to get para-aminophenol via the well known Bambarger rearrangement.\(^4,5\) Para-aminophenol is a very important starting material for the preparation of dyes, drugs, photographic chemicals and analytical reagents.\(^5\)

_N_-Arylhydroxylamines readily undergo formylation, acetylation, or benzylation to yield the corresponding hydroxamic acids which have found a wide variety of uses. The hydroxamic acids can be ortho-halogenated to yield the corresponding orthohaloanilides.\(^6\) The orthohaloanilides are important starting materials for the synthesis of the
REDUCTION OF NITROARENE

Ref. 1.
antihypertensive drug Clonidine, and its analogues (Chart 2). Boudisch first prepared cupferron (ammonium salt of N-nitroso derivative of phenylhydroxylamine) as analytical precipitant for the quantitative estimation of metals like iron, titanium, zirconium, vanadium and tin. Because of the low stability of cupferron, benzoyl group was introduced in place of nitroso group in cupferron giving rise to a stable compound which could precipitate iron, aluminium and copper. The N-Benzoyl derivative of N-phenylhydroxylamine has been used as a reagent for the determination of tin. However, this compound had low solubility in water and its low basicity prevented the formation of an ammonium salt, properties which are essential for complex formation. Subsequently a number of N-benzoyl derivatives of N-substituted phenylhydroxylamines with appropriate substituents in both the phenyl rings were prepared and used as analytical precipitants for the quantitative determination of calcium cobalt, zinc, cadmium, manganese, nickel, magnesium, vanadium, copper, iron, tin, titanium, zirconium and hafnium. Thus, several N-benzoyl-N-arylhydroxylamines have found wide use as reagents for the quantitative determination of a variety of transition metals. Hydroxamic acids and N-phenylbenzohydroxamic acids have been tested for their antibacterial activity. The 5-bromosalicyclohydroxamic acid has antitubercular activity. A number of N-phenylbenzohydroxamic acids were prepared by Russian workers and tested for herbicidal activity. Eisai Co. Ltd. has used the N-phenylbenzohydroxamic acids and their analogues in deodorizing compositions. Amongst the number of N-substituted benzohydroxamic acids tested, N-substituted salicylohydroxamic acids have exhibited
promising activity as antibacterial, antitubercular, and anticancer agents. Salicyclohydroxamic acid, when tested as an anticancer agent, increased both inhibition of ribonucleotide reductase and life of L1210 leukaemia bearing mice.

Furancarboxamides of the general formula (Chart 3) used as herbicides, are prepared by treating N-arylhydroxylamines with 2-furoyl chloride and then methylating with dimethyl sulfate. At 1000 ppm, the compound (where $R = CH_3$; $R' = 3 - Cl$) controlled 87.5% powdery mildew on cucumbers. At 0.5 lb/acre the compound (where $R = H$; $R' = 3-N O_2$) completely controlled brome. At 100 lb/acre the compound (where $R = H$; $R' = 3,4$ diCl) controlled 93.5% rootnot mematoeles. The compound (where $R = Me$; $R' = Me_2CH$) controlled southern armyworms at 3500 ppm.

Para substituted N-arylhydroxylamines are used to make anti-inflammatory agents of the formula $p-RC_6H_4N(OH)CONHC_2R'$ (Chart 4).

N-Arylhydroxylamines are used to prepare compounds of the formula PhN(CO$_2$Pr-iso)OR, which are used as herbicides. The derivatives of N-carbalkoxyhydroxylamines are prepared by treatment of alkyl chlorocarbonates with aryl and haloarylhydroxylamines which have been reported to possess fungicidal activity. In fungicides and insecticides suitable for plant spray powder, phenylhydroxylamine oxalate or other salts of N-arylhydroxylamines with an acid are used as an active ingredient. Ethyl isocyanate reacted with N-(4-chlorophenyl)hydroxylamine and the product is treated with ethyl chloroformate.
to get a compound of the formula (Chart 5), which is used as a weedicide.  

Substituted phenylhydroxylamines are generally prepared by reduction of a nitrogen containing compound which is at a higher oxidation level than the phenylhydroxylamine itself. The compounds extensively used for this purpose are nitro compounds, oximes and to a lesser extent nitroso derivatives. In the case of reduction of nitro compounds, the most commonly used procedure involves the use of zinc in aqueous or alcoholic ammonium chloride.

\[ \text{N-Arylhydroxylamines are also synthesised by catalytic hydrogenation of nitroarene. The hydrogenation has to be done carefully, using mild conditions of temperature and pressure, because hydrogenation for longer time at higher temperature and pressure leads to the complete reduction of nitroarenes to the amines. The most commonly used catalysts are Raney nickel, }^{52-55} \text{ Skeletal nickel, }^{56,57} \text{ Palladium over charcoal, }^{58} \text{ Palladium over charcoal complexed with Co (edta)}_3 (\text{NO}_3)_2 \text{ and Co-Ph}_3\text{P, }^{60} \text{ Platinum, }^{62,63} \text{ Platinum oxide, }^{64} \text{ Platinum over charcoal, }^{64} \text{ and Platinum complexed with azo-dyes, }^{65} \text{ Iridium, }^{66} \text{ tin and bismuth fused with pottasium, }^{67,68} \text{ zinc or iron complexed with pyridinium salt of chloromethylated 6:94 divinylbenzene-styrene co-polymer. }^{69} \text{ The hydrogenation is done in organic solvents such as ethanol, aqueous ethanol, methanol, benzene, tetrahydrofuran, pyridine, piperidine, etc. The yields of the hydrogenation reactions are improved by addition of bases, aqueous solutions of alkaline metal sulphates or organic sulfides, disulfides and sulfoxides.} \]
Selective reduction of nitroarenes to \( \text{N-arylhydroxylamines} \) is done with different reagents like magnesium or zinc in liquid ammonia,\(^{70}\) ammonium hydrosulfide,\(^{71,72}\) ammonium hydrosulfide or sodium hydrosulfide and ammonium chloride,\(^{73-75}\) ascorbic acid,\(^{76,77}\) and ascorbic acid in the presence of iron.\(^{78}\)

Electrolytic reduction of nitroarene with controlled potential leads to its partial reduction to \( \text{N-arylhydroxylamines} \). The electrochemical reduction is generally done by using zinc or copper amalgam or mercury as cathode at room temperature or low temperature. The electrolytes mainly used are aqueous sulfuric acid, ethanol or methanol mixed with diluted sulfuric acid, liquid ammonia or dimethyl formamide. The electrolysis is done with or without diaphragm.\(^{79,92}\)

Oxidation of phenyl magnesium bromide with hydrogen peroxide to give phenylhydroxylamine is also reported to give more than 80% yield.\(^{93}\)

Catalytic transfer-reduction of nitroarenes to \( \text{N-arylhydroxylamines} \) is a very convenient process.\(^{94,99}\) The reaction is done at room temperature and atmospheric pressure. The reactions are clean and less tedious. In these reactions various hydrogen donating chemicals namely formic, phosphinic and phosphorus acids, and their salts, and hydrazine are used. The catalysts used are palladium, iridium and rhodium. The merits and demerits or the above catalytic reduction processes are discussed in greater detail in the section under \text{Present Work}.\(^{99}\)
PRESENT WORK

With a view to obtain pure ortho-halo aniline derivatives which are potentially important dye, drug and pesticide intermediates, a number of benzo and acetohydroxamic acids were synthesised from the corresponding nitroarenes via the intermediary of N-arylhydroxylamines in our laboratory. Since these preparations need suitable method for the reduction of nitroarenes selectively to N-arylhydroxylamines to produce them in high yields, a method for the partial reduction was reinvestigated in the light of earlier work done in our laboratory on catalytic reductions involving hydrazine hydrate. N-Arylhydroxylamines by themselves are reactive starting materials for the preparation of intermediates which find wide use in the manufacture of industrial chemicals (see Introduction).

Arylhydroxylamines have been traditionally synthesised by careful reduction of nitroarenes (see Introduction). However, these methods suffer from disadvantages such as cumbersome work-up procedures, inaccessibility to special equipment (special electrolytic cells, pressure autoclaves) and extra care for control of reactions. In order to overcome these difficulties, transfer hydrogenation methods have been developed which make use of various hydrogen sources namely, formic, phosphinic, and phosphorus acids and their salts, and hydrazine in presence of catalysts such as palladium, iridium and rhodium. Since these catalysts are expensive, the efficiency of their recovery for re-use decides the overall process economics. Although satisfactory yields of the N-arylhydroxylamines have been claimed, most of the reported methods have used either an excess or less than the theoretical requirement
of hydrazine for the partial reduction. The reaction temperature ranged from those of reflux of solvents such as methanol and tetrahydrofuran to boiling water bath. These temperatures are detrimental, particularly when the resulting hydroxylamines are explosive in nature.\textsuperscript{100} In one case the activity of the catalyst (5\% palladium on carbon) was not sufficient to carry out the reduction below 45\textdegree C.\textsuperscript{95} Solvent mixtures such as tetrahydrofuran/water and tetrahydrofuran/ethanol which shows selectivity to the formation of isolable hydroxylamines have been found to be hazardous.\textsuperscript{100} Moreover, some of these methods cause appreciable reductive elimination of halogen if it is present in the aromatic substrate.\textsuperscript{101}

It becomes pertinent here to briefly document the catalytic hydrogenations of nitroarenes using hydrazine as the hydrogen source which have been carried out in our laboratory. Reduction of nitroarenes and nitroalkanes by hydrazine hydrate is one of the most convenient processes which gives clean reduction of nitro group without side reactions provided other labile substituents are not present. Reduction of nitroarenes with hydrazine hydrate in presence of catalyst is smooth and faster than that without catalyst. Catalytic reduction of nitro compounds using hydrazine has been extensively reviewed.\textsuperscript{102} Reduction using hydrazine has been systematically discussed by House.\textsuperscript{103} The reductions with hydrazine in presence of catalyst are done at atmospheric pressure, avoiding the use of expensive pressure reactors. Hydrogenation catalysts generally used are palladium, platinum and nickel.\textsuperscript{104,105,106} The most widely used catalyst is Raney nickel. These reactions are generally
carried out in solvents such as ethanol, methanol, dioxane, xylene, toluene, tetrahydrofuran, dichloroethane, cyclohexane and n-hexane. However, the reduction of nitro compounds having limited solubility in solvents commonly used for the reduction with hydrazine, had not been systematically investigated. Recently, in our laboratory the reduction of difficultly soluble nitrocompounds such as 3,3'-dinitro and 4,4'-dinitrodiphenylsulphone with hydrazine hydrate was studied using different catalysts and solvent mixtures. It was found that reductions of such nitrocompounds with limited solubility could be achieved by using Raney nickel as catalyst in a solvent mixture of ethanol and dichloroethane in 1:1 proportions. The reactions could be done at 50-70°C within a short time of 2 to 6 h. Reduction of nitrocompound to the amines in almost quantitative yields could be achieved.

Under ideal conditions two molecules of hydrogen should be available from a molecule of hydrazine hydrate. However, in the presence of Raney nickel, hydrazine decomposes to give ammonia, in addition to nitrogen and hydrogen as shown below.

\[
\text{Raney nickel} \quad 3\text{N}_2\text{H}_4 \longrightarrow 2\text{NH}_3 + 2\text{N}_2 + 3\text{H}_2
\]

Thus, to reduce one nitro group to amine, three molecules of hydrazine are required. In case of reduction of dinitro compound nitroamines are obtained with three molecules of hydrazine and diamines are obtained with six molecules of hydrazine per molecule of dinitro compound. Hence the catalytic hydrogenation process developed in our laboratory was extended sucessfully to the
partial reduction of dinitro compounds to nitroamino compounds with required stoichiometric quantity of hydrazine hydrate in ethanol:1,1-dichloroethane (1:1) as solvent mixture in the presence of Raney nickel as catalyst. \textsuperscript{107}

In the above mentioned processes since three molecules of hydrazine hydrate are required to reduce one nitro group to amino group, we thought it prudent to use two molecules of hydrazines per nitro group and arrest the reaction at the intermediate stage of hydroxylamine.

The nitro compound 1 (Chart 6) was dissolved in 1:1 ethanol:dichloroethane (10 ml of solvent mixture for 1 g of nitro compound). Raney nickel catalyst (0.1 g of \textsuperscript{W}_4\textsuperscript{-type Raney nickel for 0.1 mol of the nitro compound) was added to it. Hydrazine hydrate (80\% aq. solution) (required stoichiometric amount) diluted with the same solvent was added dropwise to it. The reaction was followed by TLC by using benzene as an eluent with subsequent colour development of the eluted fractions by iodine vapours. When the reaction was done at room temperature without controlling the exothermicity, a spot corresponding to the hydroxylamine was seen initially along with a spot of amine and the starting nitro compound. As the reaction proceeded the spot corresponding to hydroxylamine went on reducing and the amine was formed in substantial amounts. However, the reactions could be successfully carried out to yield hydroxylamine in high selectivity by lowering the reaction temperature. It was found that, at 0-10\° we get major amount of hydroxylamine 2, a small amount of amine and a trace or nil amount of nitro compound in 2 - 5 h. The reaction could be
quenched by separating the catalyst by filtration. Distillation of the solvent mixture and crystallizing the residue in benzene or benzene/petroleum ether mixture gave the hydroxylamine 2 in 50-100% yields. The yield data of some isolable stable hydroxylamines are given in Table 1. They were characterised by undepressed mixed melting point with standard samples which were prepared by the classical method, micro analysis and mass spectral data. The hydroxylamines which are unstable and not easily isolable were benzyolated in situ to the corresponding stable benzohydroxamic acids 3 by reaction with benzoyl chloride in aqueous sodium bicarbonate solution at 0-5°C. The benzohydroxamic acids were characterised by undepressed mixed melting point with a standard sample, micro analyses and mass spectral data. The unknown benzohydroxamic acids were characterised by spectral data and elemental analyses. The yield data of the benzohydroxamic acids are given in Table 2.

The benzohydroxamic acids were insoluble in sodium bicarbonate solution. However, they were soluble in strongly alkaline sodium hydroxide solution. The alcoholic solution of the benzohydroxamic acid gave red, violet or brown colour with alcoholic ferric chloride solution.

IR spectra of all the isolated N-arylhydroxylamines showed strong absorption bands at 3420-3300 cm\(^{-1}\), 3260-3090 cm\(^{-1}\) due to OH and NH stretching vibrations. IR spectra of the N-(aryl)benzohydroxamic acids (3a-q) showed strong absorption in the range 3300-3100 cm\(^{-1}\) owing to the N-OH stretching vibrations. A prominent band appearing
<table>
<thead>
<tr>
<th>Substrate No.</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction Time [h]</th>
<th>Yield[^a] [%]</th>
<th>m.p. [°C]</th>
</tr>
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<tr>
<td></td>
<td>Ar</td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
</tr>
<tr>
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<td>C₆H₅</td>
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<td>81</td>
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<td>96</td>
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<td>2-Cl-5-CH₃-C₆H₃</td>
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<tr>
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<td>2o</td>
<td>4.0</td>
<td>65</td>
<td>121</td>
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<tr>
<td>1p</td>
<td>1-C₁₀H₇</td>
<td>2p</td>
<td>2.5</td>
<td>50</td>
<td>84</td>
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</table>

[^a]: Yield of isolated product
Table 2: Reduction of nitroarenes 1 to N-arylhydroxylamides 2 isolated as N-arylbenzohydroxamic acids 3 Ar-N(OH)COC₆H₄

<table>
<thead>
<tr>
<th>No.</th>
<th>Substrate I Ar.</th>
<th>Product 3</th>
<th>Time of reaction [h]</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Found</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
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<td>121</td>
<td>121⁶</td>
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<tr>
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<td>75</td>
<td>105</td>
<td>105⁶</td>
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<tr>
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<td>3c</td>
<td>2.5</td>
<td>60</td>
<td>119</td>
<td>119⁶</td>
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</tr>
<tr>
<td>1d</td>
<td>4-Cl-C₆H₄</td>
<td>3d</td>
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<td>60</td>
<td>157</td>
<td>157¹¹⁵</td>
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<tr>
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<td>3e</td>
<td>3.0</td>
<td>70</td>
<td>138</td>
<td>138⁶</td>
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<tr>
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<td>2-Br-C₆H₄</td>
<td>3f</td>
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<tr>
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<tr>
<td>1i</td>
<td>2-I-C₆H₄</td>
<td>3i</td>
<td>2.5</td>
<td>70</td>
<td>131</td>
<td>131⁶</td>
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<tr>
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<tr>
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<td>3k</td>
<td>2.5</td>
<td>65</td>
<td>105</td>
<td>105</td>
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<tr>
<td>1l</td>
<td>4-H₃C-C₆H₄</td>
<td>3l</td>
<td>2.5</td>
<td>65</td>
<td>108</td>
<td>108¹¹⁶</td>
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<td>2-CH₂CO-C₆H₄</td>
<td>3n</td>
<td>1.5</td>
<td>70</td>
<td>106</td>
<td>104⁶</td>
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<tr>
<td>1o</td>
<td>4-H₂CO-C₆H₄</td>
<td>3o</td>
<td>3.0</td>
<td>60</td>
<td>176</td>
<td>177¹¹⁷</td>
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<td>1p</td>
<td>3-O₂N-C₆H₄</td>
<td>3p</td>
<td>4.0</td>
<td>60</td>
<td>121</td>
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<tr>
<td>1q</td>
<td>1-C₁₀H₇</td>
<td>3q</td>
<td>2.5</td>
<td>45</td>
<td>164</td>
<td>164¹⁰</td>
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</table>

a Yield based on nitroarene 1
b Unreported benzohydroxamic acids 3
in the region 1645-1620 cm\(^{-1}\) is due to the stretching vibrations of amide carbonyl group. Earlier IR studies\(^{111,112}\) of hydroxamic acids are in agreement with the above observations. The mass spectra of all the hydroxylamines and \(\text{N-}(\text{aryl})\text{benzohydroxamic acids}\) showed a common peak at m/e (M-16)\(^{+}\) which is a characteristic peak for the hydroxamic acids.\(^{117}\) Mass spectra of \(\textbf{1m}, \textbf{3b}, \textbf{3c}, \textbf{3d}\) and \(\textbf{3m}\) gave two molecular ion peaks in the ratio of approximately 3:1 indicating the presence of one chlorine atom which has got two isotopes \(^{35}\text{Cl}\) and \(^{37}\text{Cl}\). The two molecular ion peaks of dichloro compounds \(\textbf{1e}\) and \(\textbf{3e}\) are in the proportion of 3:2 which is characteristic of the presence of two chlorine atoms.

The high yields of benzohydroxamic acids \(\textbf{3}\) based on the nitroarene used, indicate fairly good selectivity for the hydroxylamine formation after accounting for the formation of dibenzoyl derivative \(\textbf{4}\) (Chart-7) in about 10% yields. It is interesting to note that we could not detect any \(\text{o-}\)benzoylated derivatives in the product mixture by HPLC. Temperatures were strictly maintained below 10°C but too low a temperature (less than 0°C) rendered the reaction sluggish. In all cases, over reduction to the amine was prevented on quenching the reaction by filtering and removing the catalyst.

In a typical experiment, the crude product mixture obtained by \textit{in situ} benzoylation of \textit{N-}phenylhydroxylamine (\(\textbf{2a}\), partial reduction product of \(\textbf{1a}\)) was subjected to HPLC analysis. The analysis showed the presence of \textit{N-}phenylbenzohydroxamic acid (\(\textbf{3a}\); retention time 27.9 min) in 10% yield. \textit{O-}benzoyl-\textit{N-}phenylhydroxylamine was not detectable in the product chromatogram showing thereby that at first
instance the benzoylation exclusively occurs at the nitrogen of \textit{N}-phenyl-hydroxylamine. Further benzoylation on oxygen yields the dibenzoyl derivative 4. Some benzanilide (retention time 7.3 min) in 8.5\% yield formed by the benzoylation of the aniline, was also detected.

After confirming the high selective reducing ability of hydrazine hydrate in the presence of Raney nickel and ethanol/dichloroethane solvent mixture, the efficiency of this solvent was tested against others for which selectivity to hydroxylamine formation has been reported.\textsuperscript{95,97}

The partial reduction of nitrobenzene was carried out under identical conditions in ethanol/dichloroethane, ethanol and tetrahydrofuran, respectively. The hydroxylamine formed was converted \textit{in situ} to benzohydroxamic acid, again under identical conditions. The crude products isolated were subjected to HPLC analysis for estimating the benzohydroxamic acid content. The results are summarised in Table 3. It can be seen that our solvent system gave the highest yield of the phenylhydroxylamine as is evident from the benzohydroxamic acid formed.

In order to ascertain whether any reductive dehalogenation has occurred in this partial reduction, \textit{o}-chloronitrobenzene (1b) was subjected to partial reduction and benzoylation. The product mixture was then analysed by HPLC. Peaks corresponding to \textit{o}-chlorobenzohydroxamic acid (3b) and \textit{o}-chlorobenzanilide (5) (Chart 5) were identified by comparison with authentic samples. Using gradient elution, a small hump in the chromatogram could be detected which matched with the retention time of an authentic sample of benzohydroxamic acid (3a).
Table 3: Effect of solvent on the reduction of 1a to 2a isolated as 3a

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield [%]</th>
<th>HPLC analysis</th>
<th>Isolated</th>
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<tr>
<td>1:1 C₂H₅OH/ClCH₂CH₂Cl</td>
<td>93</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>89</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>69</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>
**CHART-5.**

$$\text{R}^* - \text{N} - \text{H} \xrightarrow{\text{i) C}_2\text{H}_5\text{NCO}} \text{R}^* - \text{N} - \text{C} = \text{O}$$

Ref.: 43

**CHART-6.**

$$\text{R} - \text{N} = \text{H} \xrightarrow{\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O} / \text{R.Ni} / \text{C}_2\text{H}_5\text{OH} / \text{ClCH}_2\text{CH}_2\text{Cl} / 0-10^\circ\text{C}} \text{R} - \text{N} = \text{H}$$

$$\xrightarrow{\text{C}_6\text{H}_5\text{COCl}} \text{R} - \text{N} - \text{C} - \text{CO}_2\text{C}_6\text{H}_5$$

**CHART-7.**

$$\text{N} - \text{H} \xrightarrow{\text{ClC}} \text{N} - \text{C} - \text{OH} + \text{N} - \text{C} - \text{CO}_2\text{C}_6\text{H}_5$$

**CHART-8.**

$$\text{Cl} - \text{N} - \text{H} \xrightarrow{\text{1) NH}_2\text{NH}_2 \cdot \text{H}_2\text{O} / \text{2) C}_6\text{H}_5\text{COCl}} \text{Cl} - \text{N} - \text{C} - \text{OH}$$

$$\xrightarrow{\text{Cl}} \text{N} - \text{C} - \text{OH} + \text{N} - \text{C} - \text{OH}$$
This amounted to a negligible yield (0.65%) of the total product mixture. No benzanilide could be detected.

\[
\text{N-(2-chloro-5-methylphenyl)hydroxylamine (2m, m.p. 92-3°C; dec) was obtained from 1m in quantitative yield. The compound was found to be stable during work-up. Earlier reports mention that the transfer-reduction of the nitroarene 1m using hydrazine in the presence of palladium on carbon as catalyst has resulted in a violent explosion. It is likely that this was due to the tendency of tetrahydrofuran to form hydroperoxides and not because of the accumulated hydroxylamine 2m. The hydroperoxide, if present even in minor quantities, will have initiated a free radical chain reaction leading to the explosion.}
\]

Features of the present method are as follows: (1) Raney nickel has been used as a catalyst for partial reduction of nitroarene to N-arylhydroxylamine, (2) The reaction conditions, especially temperatures, are sufficiently mild from the point of view of higher selectivity and are non-hazardous, (3) Use of selective, less expensive, and much less hazardous solvent system, and (4) Simple work-up procedures.
EXPERIMENTAL

1. Partial reduction of nitroarenes 1 to N-arylhydroxylamines 2:

   General Procedure:

   Nitroarene 1 (0.1 mol) was dissolved in 1:1 v/v ethanol/dichloroethane (10 ml per gram of nitroarene) and cooled to 0°C. Raney nickel (type W-4; 0.1 g) was added with stirring to the solution. Then 80% w/v hydrazine hydrate solution (6.25 ml, 0.1 mol) was added dropwise taking care to maintain the reaction temperature below 10°C. Complete or nearly complete conversion of the nitroarene was confirmed by TLC analysis on silica gel using benzene as eluent and colour development by iodine vapours (the order of elution being nitroarene 1, arylamine, and N-arylhydroxylamine 2). The catalyst was removed by filtration. The solvent was removed by distillation. The residual mass was crystallized from benzene or benzene/petroleum ether mixture to yield the corresponding N-arylhydroxylamine 2. In all except a few cases, the less stable N-arylhydroxylamines were converted in situ to the corresponding N-arylbenzohydroxamic acids 3. The yield data of the isolable N-arylhydroxylamines 2 are given in Table 1.

1.1 Analytical data for isolable N-arylhydroxylamines 2:

   N-Phenylhydroxylamine 2a

   White needles from benzene/petroleum ether mixture, m.p. 81°C (lit.46 m.p. 81°C); yield 9.5 g (87.5%); mixed melting point with a standard sample was undepressed.

   Anal.
   C_{6}H_{7}NO, Calc. C, 66.05; H, 6.42; N, 12.84%
   (109)  Found: C, 66.20; H, 6.50, N, 12.50%
N-(2,5-Dichlorophenyl)hydroxylamine 2e

White needles from benzene, m.p. 96°C (lit. m.p. 96-97°C); yield 12.5 g (70%); mixed melting point with a standard sample was undepressed.

Anal.

C_6H_3Cl_2NO  
Calc. C, 40.44; H, 2.80; N, 7.86; Cl, 39.88%  
Found: C, 40.40; H, 2.90; N, 8.00; Cl, 40.00%

N-(2-Chloro-5-methylphenyl)hydroxylamine 2m

White crystals from benzene, m.p. 92.3°C (dec.), yield 12.6 g (80%); IR (Nujol) \( \nu = 3300, 3100, 1610, 1590, 1500, 1470, 1420, 1380, 1290, 1250, 1150, 1070, 950, 885, 815, 775 \text{ cm}^{-1} \).

MS: m/e (rel. int., %) = 159 (18.5), 157(56), 142(37), 141(84), 140(86), 125(29), 113(43), 106(69), 99(13), 89(58), 77(100).

Anal.

C_7H_8ClNO  
Calc. C, 53.20; H, 5.08; N, 8.88; Cl, 22.60%  
Found: C, 52.87; H, 5.26; N, 8.35; Cl, 21.66%

N-(3-Nitrophenyl)hydroxylamine 2p

Yellowish white crystals from benzene, m.p. 121°C; (lit. m.p. 120-1°C); yield 9.2 g (60%).

IR: (Nujol) \( \nu = 3300, 3150, 1600, 1530, 1480, 1440, 1365, 1295, 1095, 1040, 900, 825, 800, 750 \text{ cm}^{-1} \).

MS: m/e (rel. int., %) = 154(100), 138(91), 122(51), 108(59), 91(66), 76(47).

Anal.

C_6H_6N_2O_3  
Calc. C, 46.75; H, 3.89; N, 18.18%  
Found: C, 46.80; H, 3.90; N, 18.20%
N-1-Naphthylhydroxylamine 2q

White needles from benzene, m.p. 84°C (lit. 85°C); yield 8g (50%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) \( \nu = 3420, 3270, 1600, 1520, 1465, 1410, 1390, 1055, 1030, 940, 850, 800, 770 \text{ cm}^{-1} \).

MS: m/e (rel. int., %) = 159(31), 143(100), 127(74), 115(79), 101(3), 89(34).

**Anal.**

C<sub>10</sub>H<sub>7</sub>NO  
Calc. C, 75.47; H, 5.66; N, 8.80%

(159)  
Found: C, 75.50; H, 5.63; N, 8.78%

2. **Conversion of N-arylhydroxylamines 2 to the corresponding N-arylbenzohydroxamic acids 3**

**General Procedure:**

The residue of N-arylhydroxylamine obtained by the evaporation of the solvents in the above procedure was redissolved in benzene (50 ml) and washed with ice-cold water (10 ml). This was added with stirring to a previously cooled solution (0°C) of sodium bicarbonate (10.1 g, 0.12 mol) in water (200 ml). Benzoyl chloride (14.05 g, 0.1 mol) in dry benzene (25 ml) was added dropwise to the well-stirred mixture in about 0.5 h taking care to maintain the temperature of the reaction mixture below 5°C. The mixture was stirred for 2 h at 0-5°C. The benzene layer was separated and the aqueous layer was extracted with benzene (100 ml). The combined benzene extract was shaken with 10% w/v sodium hydroxide solution (150 ml). The aqueous alkaline solution was separated and acidified with 10% w/v
hydrochloric acid solution when the colourless \( N \)-arylbenzohydroxamic acids 3 separated out. The products were crystallized from benzene or benzene/petroleum ether (1:1) mixture.

The unstable \( N \)-arylhydroxylamines 2 were benzoylated in situ by the above general procedure to their corresponding benzohydroxamic acids 3 and were characterised as follows.

\[ \text{N-(Phenyl)benzohydroxamic acid 3a} \]

White needles from benzene, m.p. 121°C (lit.\(^6\) m.p. 121°C); yield 16.1 g (77%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) \( \bar{\nu} = 3310, 1640, 1520, 1170, 920, 760, 710 \text{ cm}^{-1} \)

MS: \( m/e \) (rel. int. %) = 213(5), 167(7), 139(5), 105(100), 91(40), 77(96).

Anal.

\[ \text{C}_{13}\text{H}_{19}\text{NO}_{2} \]

Calc. C, 73.2; H, 5.1; N, 6.5%  
(213) Found: C, 72.75; H, 5.55; N, 6.66%

\[ \text{N-(2-Chlorophenyl)benzohydroxamic acid 3b} \]

Yellowish white crystals from benzene, m.p. 105°C (lit.\(^6\) m.p. 105°C); yield 18.5 g (75%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) \( \bar{\nu} = 3140, 1625, 1080, 1010, 915, 790, 770, 710 \text{ cm}^{-1} \)

MS: \( m/e \) (rel. int. %) = 247(44), 249(14), 231(17), 213(16), 196(100), 167(83), 153(25), 142(51), 125(87).

Anal.

\[ \text{C}_{13}\text{H}_{10}\text{ClNO}_{2} \]

Calc. C, 63.03; H, 4.04; N, 5.56%  
(247.5) Found: C, 63.10; H, 4.27; N, 5.51%
N-(3-Chlorophenyl)benzohydroxamic acid 3c

White crystals from benzene/petroleum ether mixture, m.p. 119°C (lit. m.p. 119°C), yield 14.8 g (60%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) \( \nu = 3135, 1625, 1090, 1020, 929, 880, 796, 755 \text{ cm}^{-1} \).

MS: m/e (rel. int. %) = 249(10); 247(29); 231(21); 167(21); 105(100); 77(94).

Anal.

\[ \text{C}_{13}\text{H}_{10}\text{ClNO}_2 \quad \text{Calc. C, 63.03; H, 4.04; N, 5.66\%} \]
\[ (247.5) \quad \text{Found: C, 62.9; H, 4.00; N, 5.6\%} \]

N-(4-Chlorophenyl)benzohydroxamic acid 3d

White needles from benzene, m.p. 157°C (lit. m.p. 158°C); yield 14.8 g (60%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) \( \nu = 3250, 1605, 1540, 1440, 1415, 1380, 1265, 1160, 1135, 1100, 1055, 870, 800, 745 \text{ cm}^{-1} \).

MS: m/e (rel. Int. %) = 249(10); 247(30); 231(15); 167(50); 105(100); 77(75).

Anal.

\[ \text{C}_{13}\text{H}_{10}\text{ClNO}_2 \quad \text{Calc. C, 63.04; H, 4.04; N, 5.66\%} \]
\[ (247.5) \quad \text{Found: C, 63.3; H, 4.30; N, 5.71\%} \]

N-(2,5-Dichlorophenyl)benzohydroxamic acid 3e

Pale yellow needles from benzene, m.p. 138°C (lit. m.p. 138°C); yield 19.7 g (70%); mixed melting point with a standard sample was undepressed.
IR: (Nujol) $\nu$ = 3150, 1630, 1150, 1090, 1010, 920, 800, 720 cm$^{-1}$.

MS: m/e (rel. int. %) = 281(10); 265(7); 230(24); 200(12); 178(18); 176(27);
146(64); 133(49); 124(69); 105(100); 77(100).

**Anal.**

$C_{13}H_{9}Cl_{2}NO_2$  Calc. C, 55.60; H, 3.19; N, 4.96; Cl, 25.00%
(281)  Found: C, 55.61; H, 3.44; N, 4.68; Cl, 24.54%

**N-(2-Bromophenyl)benzohydroxamic acid 3f**

Yellowish white needles from benzene/petroleum ether mixture, m.p. 109°C (lit.$^6$ m.p. 108°C); yield 17.5 g (60%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) $\nu$ = 3160, 1620, 1160, 1010, 910, 770, 710 cm$^{-1}$.

MS: m/e (rel. int. %) = 293(2); 291(3); 196(11); 167(12); 156(20); 105(100),
90(38); 77(89).

**Anal.**

$C_{13}H_{10}BrNO_2$  Calc. C, 53.44; H, 3.4; N, 4.82; Br, 27%
(292)  Found: C, 53.30; H, 3.60; N, 5.16; Br, 26.9%

**N-(3-Bromophenyl)benzohydroxamic acid 3g**

Yellowish white needles from benzene/petroleum ether mixture; m.p. 113°C; yield 16 g (55%).

UV: (CH$_3$OH) - $\lambda_{max}$ = 270 nm; Log 4.03.

IR: (Nujol) $\nu$ = 3260, 1630, 1600, 1590, 1480, 1460, 1370, 1290, 1180 cm$^{-1}$ (Fig.1-1).

MS: m/e (rel. int. %) = 293(23); 291(6); 277(5); 275(5); 197(12); 195(24);
187(2); 168(11) (Fig.1-2).

**Anal.**

$C_{13}H_{10}BrNO_2$  Calc. C, 53.44; H, 3.4; N, 4.82; Br, 27%
(292)  Found: C, 53.30; H, 3.60; N, 5.16; Br, 26.9%
N-(4-Bromophenyl)benzohydroxamic acid 3h

White crystals from benzene, m.p. 163°C; yield 17.2 g (59%).

UV: (CH$_3$OH) $\lambda_{\text{max}}$ = 272 nm; log 4.12.

IR: (Nujol) $\gamma$ = 3180, 1620, 1600, 1590, 1500, 1470, 1380, 1300, 1190 cm$^{-1}$. (Fig. 1-3).

MS: m/e (rel. int. %) = 293(23); 291(23); 277(9); 275(2); 197(12); 195(38); 188(8); 186(8); 171(17); 169(9); 158(16); 156(16); 168(11); 105(100) (Fig. 1-4).

Anal.

C$_{13}$H$_{10}$BrNO$_2$  Calc. C, 53.44; H, 3.42; N, 4.82; Br, 27.00%
(292)  Found: C, 53.34; H, 3.62; N, 4.76; Br, 26.8%

N-(2-Iodophenyl)benzohydroxamic acid 3i

Pale yellow needles from benzene, m.p. 131°C (lit. m.p. 131°C); yield 23.7 g (70%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) $\gamma$ = 3100, 1625, 1215, 1100, 1010, 726 cm$^{-1}$.

MS: m/e (rel. int. %) = 340(50); 339(100); 323(57); 219(30); 127(50); 105(97).

Anal.

C$_{13}$H$_{10}$INO$_2$  Calc. C, 46.00; H, 2.95; N, 4.1; I, 37.46%
(339)  Found: C, 46.28; H, 3.32; N, 4.21; Br, 37.84%

N-(4-Iodophenyl)benzohydroxamic acid 3j

White needles from ethanol/water mixture, m.p. 180°C; yield 22 g (65%).

UV: (CH$_3$OH) $\lambda_{\text{max}}$ = 276 nm, log 4.14.

IR (Nujol) $\gamma$ = 3180, 1620, 1590, 1500, 1470, 1410, 1380, 1200, 1060 cm$^{-1}$ (Fig. 1-5).

MS: m/e (rel. int. %) = 340(53); 339(100); 323(60); 242(49); 234(37); 219(33); 204(37); 196(88); 195(98); 127(56); 105(98) (Fig.1-6).
N-(2-Methylphenyl)benzohydroxamic acid 3k

White crystals from benzene/petroleum ether mixture, m.p. 105°C (lit. m.p. 104°C); yield 14.7 g (65%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) $\nu =$ 3145, 1622, 1180, 1156, 1120, 1000, 930, 720, 712 cm$^{-1}$.
MS: m/e (rel. int. %) = 227(24); 211(15); 180(10); 167(9); 152(7); 135(15); 106(100); 78(95).

N-(4-Methylphenyl)benzohydroxamic acid 3l

White needles from benzene/petroleum ether mixture, m.p. 108°C (lit. m.p. 108°C); yield 14.7 g (65%); mixed melting point with a standard sample was undepressed.

IR: (Nujol) $\nu =$ 3120, 1630, 1575, 1510, 1450, 1380, 1160, 1015, 920, 825, 788, 720, 700 cm$^{-1}$.
MS: m/e (rel. int. %) = 227(7); 211(9); 167(6); 132(9); 122(24); 105(100); 91(68); 77(99).
N-(2-Chloro-5-methylphenyl)benzohydroxamic acid 3m

White needles from benzene, m.p. 154°C; yield 21 g (80%); UV (CH₃OH): λ<sub>max</sub> = 262 nm, log 3.90.
IR: (Nujol): ν = 3180, 1645, 1610, 1585, 1495, 1360, 1170, 110 cm<sup>–1</sup> (Fig.1-7)
MS: m/e (rel. int. %) = 263(12); 261(40); 245(14); 210(60); 180(10); 141(32); 106(74); 105(100) (Fig.1-8).

Anal.

C<sub>14</sub>H<sub>12</sub>ClN<sub>2</sub>O<sub>2</sub>  Calc. C, 69.24; H, 4.50; N, 5.35; Cl, 13.57%
(261.5)  Found: C, 64.88; H, 4.67; N, 5.91; Cl, 13.52%

N-(2-Anisoyl)benzohydroxamic acid 3n

White crystals from benzene/petroleum ether mixture, m.p. 106° (lit. m.p. 104°); yield 17 g (70%); mixed melting point with a standard sample was undepressed.
IR: (Nujol) ν = 3205, 1630, 1120, 1020, 990, 880, 815, 720 cm<sup>–1</sup>.
MS: m/e (rel. int. %) = 243(82); 228(81); 196(13); 167(11); 149(12); 120(62); 105(100); 77(86).

Anal.

C<sub>14</sub>H<sub>13</sub>NO<sub>3</sub>  Calc. C, 69.13; H, 5.30; N, 5.7%
(243)  Found: C, 69.26; H, 5.48; N, 5.37%

N-(4-Anisoyl)benzohydroxamic acid 3o

White crystals from benzene, m.p. 176°C (lit. m.p. 177°C); yield 14.6 g (60%); mixed melting point with a standard sample was undepressed.
IR: (Nujol) ν = 3190, 1590, 1570, 1510, 1450, 1420, 1380, 1300, 1250, 1160, 1110, 1060, 1030, 925, 855, 820, 780, 700 cm<sup>–1</sup>.
MS: m/e (rel. int. %) = 243(4); 227(3.5); 149(1); 138(7); 121(10); 105(100); 77(100).

Anal.

C_{14}H_{13}NO_{3}  Calc. C, 69.13; H, 5.30; N, 5.76%
(243)  Found: C, 68.94; H, 5.68; N, 5.97%

N-(3-Nitrophenyl)benzohydroxamic acid \textit{3p}

White crystals from water, m.p. 121°C; yield 15.5 g (60%);
UV: (CH_{3}OH) \lambda_{\text{max}} = 266 nm, log \ 4.36
IR: (Nujol) \nu = 3200, 1630, 1615, 1590, 1500, 1420, 1360, 1300, 1060 cm^{-1} (Fig. 1-9).
MS: m/e (rel. int. %) = 258(1); 242(5); 241(37); 212(11); 152(9); 122(58); 105(100) (Fig. 1-10).

Anal.

C_{13}H_{10}N_{2}O_{4}  Calc. C, 60.46; H, 3.87; N, 10.85%
(258)  Found: C, 59.96; H, 3.82; N, 10.69%

N-(1-Naphthyl)benzohydroxamic acid \textit{3q}

White needles from benzene, m.p. 164°C (lit. 10 m.p. 164°C); yield 11.8 g (45%); mixed melting point with a standard sample was undepressed.
IR: (Nujol) \nu = 3260, 1630, 1600, 1580, 1500, 1470, 1410, 1380, 1250, 1150, 970, 910, 790, 770 cm^{-1}.
MS: m/e (rel. int. %) = 263(60); 247(50); 127(65); 105(100); 77(35).

Anal.

C_{17}H_{13}NO_{2}  Calc. C, 77.56; H, 4.94; N, 5.32%
(263)  Found: C, 77.29; H, 5.05; N, 5.18%
Partial reduction of orthochloronitrobenzene

Extent of dechlorination:

Orthochloronitrobenzene (1b) (15.7 g, 0.1 mol) was dissolved in 1:1 ethyl alcohol/ethylene dichloride mixture (157 ml) and was reduced to N-(2-chlorophenyl)hydroxylamine (2b). The N-(2-chlorophenyl)hydroxylamine (2b) was benzoylated in situ to N-(2-chlorophenyl)benzohydroxamic acid (3b) and the reaction mixture was subjected to HPLC analysis to estimate quantitatively the formation of the dechlorinated product that is N-(phenyl)benzohydroxamic acid (3a).

HPLC Evaluations:

The combined benzene extract before the alkaline extraction of the hydroxamic acid was subjected to HPLC analysis in every case. A Waters Model ALC/GPC-202R 401 liquid chromatograph with a Model 440 UV detector operated at 254 nm connected to a model 730 data module was used. The column used was Radial Pak C18 cartridge (10 cm x 8 mm) installed in Model RCM-100 hydraulic compression module. A mobile phase of 55% methanol in water buffered with phosphoric acid to pH 3 was used at a flow rate of 1.0 ml/min. for the quantitative estimation of benzohydroxamic acid residue. A linear gradient of methanol to water (15 to 80%) over 15 min. was used at a flow rate of 1.0 ml/min. to quantitatively determine the product distribution in the crude mixture arising out of the partial reduction and subsequent in situ benzoylation of orthochloronitrobenzene.
FIG. 1-2.

Relative Intensity (%)
FIG. 1-4.
REFERENCES


7. E. Bamberger and O. Boudisch, Ber., 42, 3568 (1909).


40. All-Union Scientific Research Institute of Chemical for Plant Protection *Belg.*, 659,351 (1963); C.A: **64**, 642 (1966).


42. William P. Ter Host, US 2,311,585 (1943); C.A: **37** 4526 (1943).


44. Bamberger, E; *Ber.; 42*, 3568 (1948).


47. Gustav E. Utzinger; *Ann.*, **556**, 50 (1944).


58. I.K. Brand and Joseph Steiner, Ber., 55B, 875
63. Le Ludec Joe; Ger Offen, 2,455,238 (1975).
77. Richard Kuhn; Hellmuth Vetter and Pierre Desnulle; Ber., 70B, 1314 (1937).
85. Staal, Phillip W; Fr., 1,500,879 (1968); C.A: 70, 63588p (1969).


91. Michel Le Guyader; Andre Tallec and Raymond Legoff; Compt. Rend., 258(25), 6175 (1964).


