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SELECTIVE REDUCTION OF NITROARYLALKYLNITRILES WITH HYDRAZINE AND A METAL CATALYST

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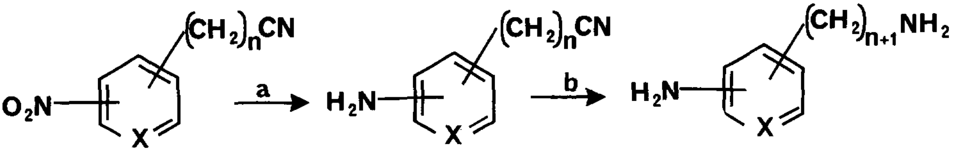
Abstract: The selectivity in the catalytic reduction of nitroarylalkylnitriles with hydrazine and metal catalysts was studied.

The reduction of aromatic nitro compounds to the corresponding amine can be accomplished using hydrazine in the presence of several catalysts, for example Palladium-Charcoal, Platinum-Charcoal or Raney Nickel[1]. The reduction of aliphatic nitriles to the corresponding primary amine using hydrazine in the presence of Raney Nickel has also been reported[2, 3]. Very little work, however, has been done regarding the selectivity of such reductions. The only reported examples are concerned with haloaromatic nitro compounds[4] and with aromatic nitro compounds containing O- and N-benzyl groups[5]. It has been found that the selective reduction of aromatic nitro compounds to the corresponding amine can be achieved with or without concomitant reduction of an alkylnitrile side chain depending on the conditions employed. These findings are summarised in Scheme I.



X = N or CH

a. $N_2H_4.H_2O$ - PALLADIUM/CARBON OR RANEY NICKEL

b. $N_2H_4.H_2O$ - RANEY NICKEL

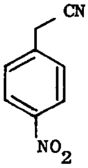
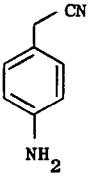
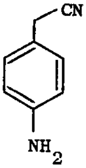
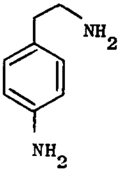
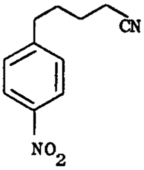
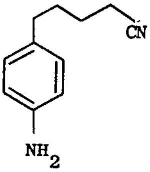
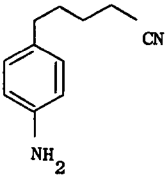
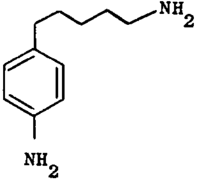
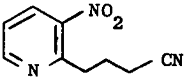
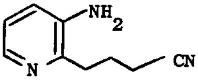
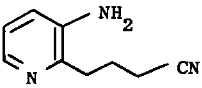
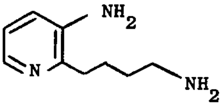
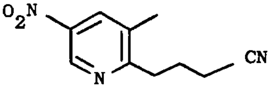
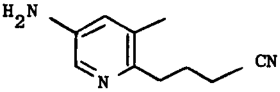
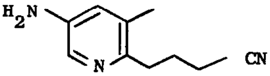
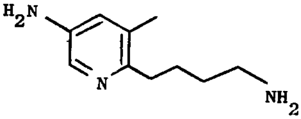
SCHEME I

Thus it has been found that if an ethanolic solution of the nitroarylalkylnitrile in the presence of a catalytic quantity of Raney Nickel is treated with hydrazine hydrate (2 - 3 equivalents) keeping the temperature in the range 20 - 25°, the nitro group is rapidly and cleanly reduced to afford the corresponding aminoarylalkylnitrile. Removal of the Raney Nickel by filtration over celite followed by evaporation of the solvent affords the aminoarylalkylnitrile in virtually quantitative yield. Alternatively, after complete reduction of the nitro group as evidenced by TLC, the mixture is warmed to 50 - 55° and a further quantity of hydrazine hydrate (4 - 5 equivalents) is added slowly. Under these conditions the nitrile group is rapidly and cleanly reduced. Removal of the catalyst by filtration over celite followed by evaporation of the solvent affords the aminoarylalkylamine in virtually quantitative yield. Although this procedure is suitable for small scale work it was found that reduction of the nitro group is highly exothermic. On scale-up, temperature control was difficult and this resulted in the intermediate aminoarylalkylnitrile being contaminated with the aminoarylalkylamine. This problem was simply overcome by using Palladium-Charcoal as the catalyst for the first reduction. Using this system the nitrile group was completely inert to reduction even under reflux conditions. The catalyst is then removed by filtration as before and evaporation of the solvent affords the required aminoarylalkylnitrile. Alternatively Raney Nickel is added after filtration and the second reduction is carried out as before to afford the aminoarylalkylamine on workup. It has been found that this procedure can be scaled up to multikilogramme quantities without problem. Yields are virtually quantitative and the products are essentially pure by HPLC and spectroscopic analysis. The advantages of this procedure are the avoidance of strong acid media, no pressure apparatus is required, the reduction of the nitrile group is uncomplicated by secondary amine formation (often a problem under classic hydrogenation conditions) and no reduction of aromatic rings takes place, sometimes a problem with pyridines.

The reduction of p-nitrophenylacetonitrile provides an example of the method: To a magnetically stirred solution of p-nitrophenylacetonitrile (1.62 g, 10 mm) in ethanol (10 ml) was added 10% Palladium-Charcoal catalyst (160 mg). Hydrazine hydrate (1 - 1.5 g) was added dropwise maintaining the temperature in the range 20 - 25°. When effervescence had ceased the catalyst was removed by filtration over celite. Evaporation of the filtrate afforded p-aminophenylacetonitrile. The yield was 1.32 g, 100%. Alternatively, Raney Nickel (160 mg) was added to the filtrate which was warmed to 50 - 55° and with magnetic stirring hydrazine hydrate (2 - 2.5 g) was added at such a rate as to maintain the temperature in the 50 - 55° range. When effervescence had ceased the catalyst was removed by filtration over celite. Evaporation of the filtrate afforded 2-(p-aminophenyl) ethylamine. The yield was 1.36 g, 100% Similar results were obtained with other nitroarylalkylnitriles (Table I). The products were identified by elemental analysis, IR, NMR and MS. The purity of the products was confirmed by TLC and HPLC.

TABLE I

Reduction Of Nitroarylalkylnitriles With Hydrazine And A Catalyst

Compound	Catalyst	Product	% yield	m.pt or b.pt
	Pd-C		100	44-45 (m.pt.)
	Ra-Nickel		100	62-63 (m.pt.)
	Pd-C		93	160-163 (b.pt,0.5mm)
	Ra-Nickel		95	33-34 (m.pt.)
	Pd-C		97	66-68 (m.pt.)
	Ra-Nickel		96	98-100 (b.pt.0.1mm)
	Pd-C		98	130-132 (b.pt.0.1mm)
	Ra-Nickel		95	104-106 (b.pt.0.1mm)

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