NOVEL METHOD FOR REDUCTION OF NITRO- AROMATICS AND HETEROCYCLICS WITH HYDRAZINE HYDRATE AND SODIUM ACETATE

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Abstract : A new and efficient method has been developed for the reduction of aromatic and heterocyclic nitro compounds with hydrazine hydrate and sodium acetate in methanol. In this method, the reduction is chemoselective in the presence of different functional groups and the process has not used heavy metals, corrosive acids, pyrophoric reagents. The reduction products were purified using column chromatography and they were characterized using ^{1}H NMR and mass spectroscopy.

IndexTerms- Reduction, Nitroarenes, Nitro heterocyclics, Hydrazine hydrate, Sodium acetate

I. INTRODUCTION

The reduction of nitroarenes and nitroheterocycles to corresponding anilines and heterocyclic amines represents one of the most significant reactions in organic chemistry. The industrial importance of anilines is high demand for those pharmaceuticals, polymers [1], polyurethanes synthesis [2], agrochemical production [3], coloring agents [4], rubber materials [5], dyes and other industrial items as antioxidants. Alkylation of ammonia [6], reductive amination [7], reduction of azides [8], amides [9], nitriles [10], or nitro compounds are all used to make these amines. Standard procedures such as hydrogenation [11], electrochemistry [12], electron transfer [13] and hydrogen transfer conditions [14] are used to decrease nitro precursors. This is because the nitro group rapidly deactivates the electrophilic aromatic substitution of benzene ring.

Some n - heterocyclic compounds are intentionally sprayed into the environment as pesticides, and others have been released into the environment due to improper handling or storage procedures. Reduction of nitro heterocyclics to their corresponding amine groups is a fundamental conversion in the pharmaceutical industry, for the synthesis of important metabolites and active pharmaceutical components. In most of these methods, nitro reduction is carried out by catalytic hydrogenation [11], Iron in acidic media [15], stannous chloride in acidic media [16] and using heavy metals like Iron [17] and Zinc [18]. Many of these harsh and strongly acidic conditions can cause sidereactions, when the molecule contains other sensitive functionalities. By-products of such condition reactions cause high environmental pollution [19].

Among the reductions, Bechamp reduction [20] is the oldest and most widely used approach, with a history of over 150 years. The first reduction of nitro functions to organic compounds by iron was described by Bechamp in 1854. The Bechamp process is still employed in aniline plants because it provides access to colored iron oxide pigments as by-products. Raney nickel **[21]** is the most pyrophoric, toxic and inconvenient to handle highly flammable hydrogen gas.

Another common method is reduction of aryl nitro compounds with hydrazine hydrate. The reduction of nitro groups-containing aromatic and heterocyclic compounds with hydrazine hydrate in the presence of sodium acetate (NaOAc) is optimized in the present study, with good conversion and produced excellent yields.

II. RESEARCH METHODOLOGY

1. OPTIMIZATION OF REACTION CONDITIONS

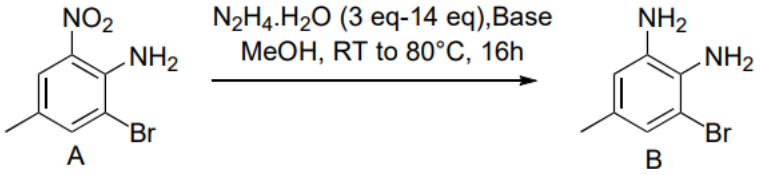


Figure 1. Reduction of nitro compound (A) to amine (B) with different Bases at various temperatures and changing the equivalents of Hydrazine hydrate.

Reduction of nitro compound (A) to amine (B) at different experimental parameters like different Bases, various temperatures and times and changing the equivalents of Hydrazine hydrate are listed in Table 1.

Table 1. Operative conditions for reduction of A to B with different Bases at various temperatures and changing the equivalents of Hydrazine hydrate

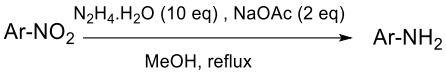
Entry	Reagent equivalents	Temperature	Time (h)	Yield (%)
1	$N_2H_2.H_2O$ (3 equiv.) NaOAc (2 equiv.)	80°C	16	6
2	$N_2H_2.H_2O$ (6 equiv.) NaOAc (2 equiv.)	80°C	16	41
3	$N_2H_2.H_2O$ (10 equiv.) NaOAc (2 equiv.)	80°C	16	92
4	$N_2H_2.H_2O$ (14 equiv.) NaOAc (2 equiv.)	80°C	16	92
5	$N_2H_2.H_2O$ (10 equiv.) KOAc (2 equiv.)	80°C	16	81
6	$N_2H_2.H_2O$ (10 equiv.) NaOAc (2 equiv.)	RT	24	0

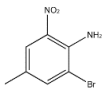
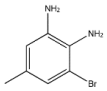
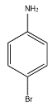
Entries 1 to 4 from Table 1. The studies found that 10 equivalents of Hydrazine hydrate were optimal for good reduction yields, and that less than 10 equivalents resulted in unsatisfactory reduction yields. It also showed that the conversion and rate of response between low and large levels of hydrazine hydrate did not differ significantly. There is no reduction at room temperature or at mild temperatures, with fixed hydrazine hydrate, sodium acetate, and solvent (Entry 6 from Table 1). It demonstrates that the process has only begun at extremely high temperatures. Subsequently, 10 equivalents of hydrazine hydrate and 2 equivalents of NaOAc at 80°C in methanol as a solvent for 18 - 24 h was shown to be an effective and efficient approach for reducing nitro groups including aromatic and heterocyclic compounds. The reduction was carried out with 2 equivalents of potassium acetate (KOAc) rather than NaOAc at fixed Hydrazine hydrate equivalents, temperature and duration (Entry 5 from Table 1).

In conclusion, an effective and efficient method for the reduction of nitro groups containing aromatic and heterocyclic compounds has been 10 equivalents of hydrazine hydrate, 2 equivalents of sodium acetate in methanol as a solvent at 80°C for 16 to 24 h. Then nitro aromatic compounds with various substituents were reduced under the optimized conditions as given in Table 2.

2. RESULTS AND DISCUSSION

Table 2. Reduction of aromatic nitro compounds employing Hydrazine hydrate and NaOAc under the conditions given in the equation



Entry	Substrate	Product	Time (h)	Yield (%)
1			16	92
2			16	91
3			16	93
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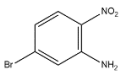
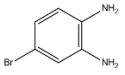
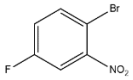
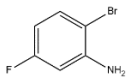
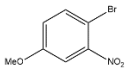
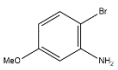
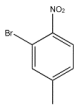
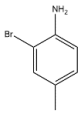
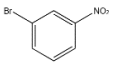
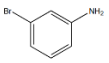
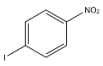
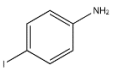
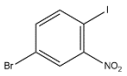
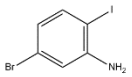
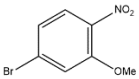
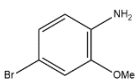
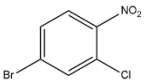
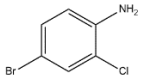
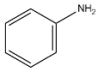
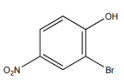
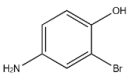
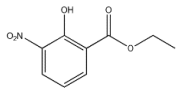
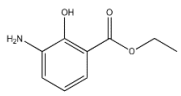
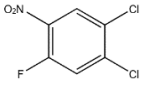
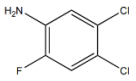
5			16	94
6			16	81
7			24	92
8			16	83
9			16	83
10			16	80
11			16	84
12			16	91
13			16	78
14			16	90
15			16	94
16			24	0

17			24	0
18			24	0

The chemo selectivity was observed in Entries [20, 21] [22]. the reduction of 1-bromo-4-(tert-butyl)-2-nitrobenzene [19] with 10% Pd/C, hydrazine hydrate (10 eq) in methanol at 80 °C in sealed tube for one hour has 80% conversion to 3-(tert-butyl) aniline [20], while the reduction of 1-bromo-4-(tert-butyl)-2-nitrobenzene [19] with hydrazine hydrate (10 eq.), sodium acetate (2 eq) in methanol refluxed for 16 h has given 85% conversion chemo selectively 2-bromo-5-(tert-butyl) aniline [21] [22].

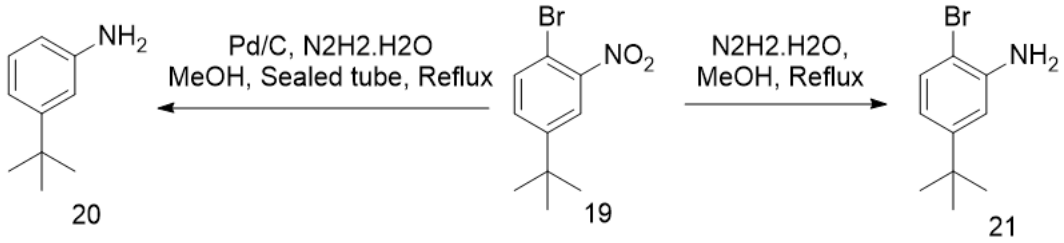
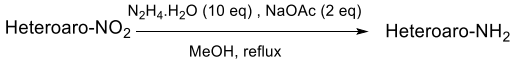
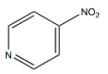
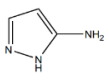
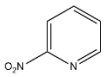
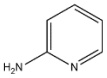


Figure 1. Chemo selective reduction

Comparison of Entries 3, 4 and 9 of Table 2: Reduction of 1-bromo-4-nitrobenzene (Entry 3) has given good yield (93%) in 16 h whereas 1-bromo-2-nitrobenzene (Entry 4) has given less yield. Comparison of Entries 6,11, 12 and 13 of Table 2: Reduction of 4-bromo-2-methoxy-1-nitrobenzene (Entry 12) has given good yield (91%) in 16 h, whereas 2-bromo-5-fluoroaniline (Entry 6) and (4-bromo-2-chloro-1-nitrobenzene (Entry 13) has given less yields, this indicates that electron donating groups at ortho position have significant effect on reduction. Similar variation is observed in other reactions (Entries 1, 2 from Table 2). There is no reduction of 2-bromo-4-nitrophenol (Entry 16**)** and ethyl 2-hydroxy-3-nitrobenzoate (Entry 17). It represents that the highly acidic groups show significant drawback for the reduction and surprisingly (Entry 18) has no conversion. Reduction of nitro heterocyclics in Entries 1 to 5 of Table 3 has given good conversion with excellent yields.

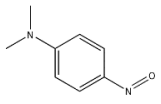
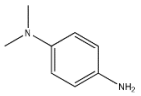
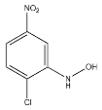
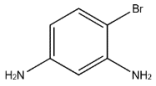
Table 3. Reduction of Hetero aromatic nitro compounds employing $N_2H_2.H_2O$ and NaOAc



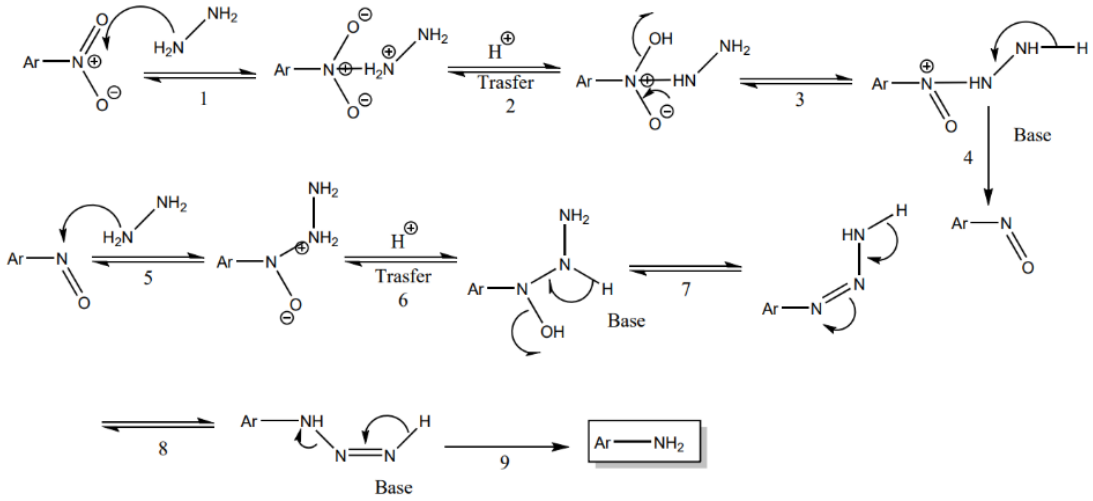
Entry	Substrate	Product	Time (h)	Yield (%)
1			16	91
2			16	88
3			16	80
4			16	91

3. MECHANISM

Table 4. Reduction of some common intermediates using optimized condition: Hydrazine hydrate (10 eq) and NaOAc (2 eq) in methanol solvent at 80°C

Entry	Substrate	Product	Time (h)	Conversion (%)
1			16	90
2			16	0

The amine was formed from Entry 1 but not from Entry 2 of Table 4 [23]. Reduction of the nitro proceeding via nitroso compounds was observed. From these experiments a mechanism for the reduction of the NO_2 group through reaction with hydrazine. Monohydrate was proposed (Scheme 1).



Scheme 1. Proposed mechanism for the reduction of nitro group using hydrazine.hydrate [23]

The first step of this reaction would involve nucleophilic attack of hydrazine on the nitro N atom to form a 1-hydroxy-1-aryltriazane-1-oxide. Attack of a hydroxyl anion results in the formation of a nitroso intermediate. A second hydrazine molecule shall attack the nitroso derivative to yield 1-hydroxy-1-aryltriazane which would undergo transformation into the anilino derivative. This hypothesis is in agreement with the positive results obtained with the nitroso (Entry 1 of Table 4) and lack of reactivity of the hydroxylamine (Entry 2 of Table 4).

III. MATERIALS AND METHODS

GENERAL PROCEDURE

A solution of the nitro compound (1 mmol) in methanol (2 mL) was treated with hydrazine hydrate (8-10 mmol equivalents) and sodium acetate (2 mmol equivalents), heated at the desired temperature for the set period of time, cooled to room temperature, quenched with water (10 ml) and extracted with dichloromethane, DCM (2 × 20 mL). The combined extracts were washed with water (2 × 5 mL), brine solution (2. 5 mL), dried (Na_2SO_4), and concentrated in vacuum to give the crude product. Crude residue was purified by silica gel column by eluting with proper solvents.

Preparation of 3-bromo-5-methylbenzene-1,2-diamine [24] [Entry 1 of Table 2]

A solution of 2-bromo-4-methyl-6-nitroaniline (100 mg, 0.41 mmol) in methanol (2 mL) was treated with hydrazine hydrate (217 mg, 4.34 mmol) and sodium acetate (68 mg, 0.833 mmol), heated to 80°C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with water (5 mL) extracted with DCM (2 x 10 mL), combined organic layers were washed with brine solution (5 mL), dried over sodium sulphate and evaporated under reduced pressure to afford crude. Crude residue was purified by silica gel column by eluting with 4% Methanol/DCM to afford 3-bromo-5-methylbenzene-1,2-diamine Entry 1 (80 mg, 92%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO): δ 6.48 (d, J = 1.2 Hz, 1H), 6.33 (d, J = 1.6 Hz, 1H), 4.76 (bs, 2H), 4.38 (bs, 2H), 2.05 (s_{br}, 3H). 13C NMR (DMSO): δ 136.34, 129.61, 127.06, 120.06, 114.20, 108.51. LCMS (EI) m/z 201.05 (M+H, 96%).

Preparation of 3-bromo-5-methoxybenzene-1,2-diamine [25] [Entry 2 of Table 2]

A solution of 3-bromo-5-methoxy-2-nitroaniline (100 mg, 0.4 mmol) in methanol (2 ml) was treated with hydrazine hydrate (203 mg, 4.06 mmol) and sodium acetate (68 mg, 0.8 mmol), heated to 80 °C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with water (5 mL) extracted with DCM (2 x 10 mL), combined organic layers were washed with brine solution (5 mL), dried over sodium sulphate and evaporated under reduced pressure to afford crude. Crude residue was purified by silica gel column by eluting with 4% Methanol/DCM to afford 3-bromo-5-methoxybenzene-1,2-diamine (2) (80 mg, 91%) as brown solid.

^{1}H NMR (400 MHz, DMSO): δ 6.26 (d, *J* = 2.8 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H), 4.92 (bs, 2H), 4.17 (s_{br}, 2H), 3.58 (s, 3H). 13C NMR (DMSO): δ 151.91, 137.54, 126.07, 108.62, 104.06, 100.49, 55.09. LCMS (EI) m/z 217.31 (M+H, 96%).

IV. CONCLUSIONS

A highly efficient and chemo selective method for reduction of nitroarenes and nitroheterocycles has been developed. Several advantages of the proposed method when compared to other methods are: (1) Methodology works on normal arenes and heteroarenes, (2) The chemo selective reduction can be conveniently controlled in the presence of bromo, chloro, iodo substituents, and (3) Most pyrophoric, toxic Raney nickel and corrosive hydrochloric acid are avoided.

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VI. SUPPORTING INFORMATION

Full experimental details, 1H and 13C NMR spectra and LCMS traces. This material can be found via the “Supplementary Content” section of this article’s webpage.

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