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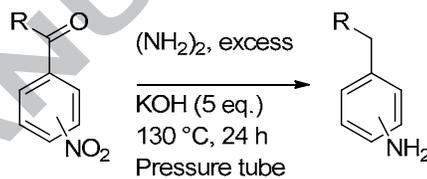
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## Graphical Abstract

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## One-step double reduction of aryl nitro and carbonyl groups using hydrazine

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**Abstract**— Single-step reduction of aryl nitro and carbonyl groups to the corresponding synthetically useful alkyl-anilines occurs with excellent yields by treatment with hydrazine and a base in a solvent-free reaction. The method has been applied to a broad range of compounds with different properties. Investigations into the mechanism of the reduction reveal that each group is reduced independently. A mechanism is proposed for this novel reduction of aromatic nitro groups. © 2011 Elsevier Science. All rights reserved.

**Keywords:** Reduction, nitro, carbonyl, hydrazine

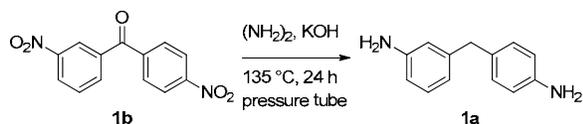
Although many methods exist for the reduction of aromatic nitro derivatives to anilines and of carbonyl groups to the corresponding deoxygenated alkyl derivatives, their simultaneous reduction, which has not been reported, would be of significant synthetic utility. The methods most commonly used for deoxygenation of carbonyl groups to alkanes are the Clemmensen reduction,<sup>1</sup> the Wolff-Kishner reaction,<sup>2,3</sup> and the Mozingo reduction.<sup>4</sup> Although both the Clemmensen and Wolff-Kishner conversions work well, they are carried out under strongly acidic and basic conditions respectively. The Mozingo reduction of dithioketals using Raney-Nickel overcomes some of these problems but requires formation of the dithioketal and the undesirable use of a heavy metal.

Raney-Nickel can also be used as a catalyst for the hydrogenation of aryl-nitro compounds to aryl-amines;<sup>5</sup> however, no conditions exist for the simultaneous reduction of carbonyl and nitro groups under Mozingo conditions. Similarly, Zn can be used for the reduction of aromatic nitro compounds to anilines, but still requires the use of a heavy metal.<sup>6</sup> Moreover, when attempted in the present work, the concurrent reduction of carbonyl and nitro groups with Zn, using Clemmensen conditions (as described in reference 6), was not achieved.

Aromatic nitro groups can readily be reduced to anilines by several methods such as catalytic hydrogenation with Pd-carbon,<sup>7</sup> Pt(IV) oxide<sup>8</sup> or Raney-Nickel.<sup>9</sup> Reductions using metals such as Fe or Zn powder in acidic media are also widely used.<sup>10</sup> Among other nitro reducing agents, sodium sulfide has been applied successfully in our laboratory.<sup>11</sup> However, none of these methods is capable of reducing a carbonyl group to an alkane.

The Wolff-Kishner reaction has long been used for the full reduction of carbonyls to alkanes. This reaction which proceeds via the formation of a hydrazone, generally requires hydrazine hydrate and a strong base such as KOH in a polar solvent like propan-1,3-diol or triethylene glycol at high temperature (>200 °C).<sup>12</sup> We report here the reduction of nitro and carbonyl aromatic groups to the corresponding aniline and alkyl-aromatics using hydrazine under modified Wolff-Kishner conditions. Moreover, we show that the simultaneous double reduction can take place to afford alkyl-anilines in high yield and in only one step.

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Scheme 1

When trying to obtain compound **1a** from **1b** (Scheme 1), the reduction of the carbonyl group under Wolff-Kishner conditions was first attempted with the intention of subsequently trying to reduce the aromatic nitro groups. However, formation of **1a** was observed in a single step and it was decided to optimize this transformation by modifying the reaction conditions.

**Table 1.** Conditions and yields of the double reduction of compound **1b** with and without solvent.

Solvent (mL)	(NH <sub>2</sub> ) <sub>2</sub> (eqv.)	KOH (eqv.)	T (°C)	t (h)	Conv. (%) <sup>a</sup>	Yield (%) <sup>b</sup>
Propan-1,3-diol (5)	1.1	1.2	220 reflux	4	0	0
Triethylene glycol (1)	2	2.2	220 reflux	4	0	0
Triethylene glycol (1)	10	10.2	220 reflux	24	>60	<10
None	41	8.3	130 <sup>c</sup>	24	>90	88

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy.

<sup>b</sup>Pure isolated compound.

<sup>c</sup>Reaction was run in a pressure tube.

The polar solvents usually required in the Wolff-Kishner reduction have limited the utility of this transformation as the products obtained are highly polar and proved difficult to extract from the solvent. Thus, conversion to the product as adjudged by <sup>1</sup>H-NMR spectroscopy was low (0-60%) in a variety of solvents (Table 1) and overall yields were less than 10%. Although conversion was improved by increasing the equivalents of hydrazine and base and the reaction time, the problem of product isolation persisted and to circumvent it, hydrazine was used as the solvent in a pressure tube at 135 °C. For our test compound (**1b**, Table 1), conversion into the totally reduced product was increased to over 90%, and an overall yield of 88% was obtained.

Using these conditions, this method was subsequently investigated for a wide range of aryl nitro carbonyl substrates and proved to be applicable to different systems including heterocyclic derivatives. Only slight variations in yield, associated with the relative stability of the intermediate benzylic anion species in the carbonyl reduction, were observed (see Table 2).

From these reactions it was possible to deduce a number of mechanistic details. First, in the case of compound **1b**, the NO<sub>2</sub> group was reduced before the CO since the *bis*-anilino carbonyl derivative was isolated when only 2 equiv. of hydrazine were added. Further evidence was obtained from the isolation of dimeric hydrazones when aryl aldehyde substrates were used. Formation of these products could only be explained by the simultaneous presence of the amine and aldehyde groups.

**Table 2.** Double reduction using hydrazine.

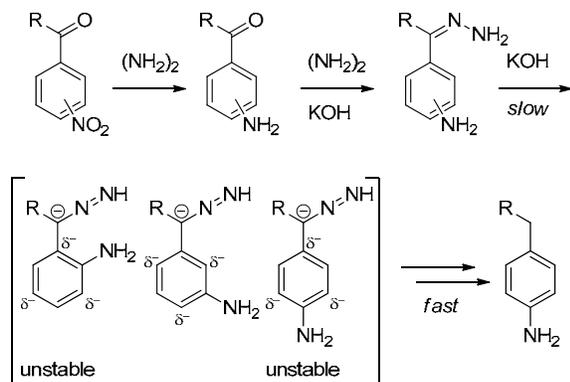
Entry	Substrate	Conversion <sup>a</sup> (%)	Yield <sup>b</sup> (%)
1		>90	88
2		>40	30
3		>90	83
4		>70	65
5		> 40	33
6		>90	97
7		>80	76
8		>90	87

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy.

<sup>b</sup>Pure isolated compound.

Differences in yield between the *ortho*, *meta* and *para*-substituted substrates can be rationalized by the relative

stability of the intermediate benzylic anion (Scheme 2). The formation of this anion is thought to be the rate determining step of the reaction. The first deprotonation of the anilino-hydrazone intermediate is more difficult for the *ortho* and *para*-substituted substrates, since conjugative electron donation by the N lone-pair makes the *ipso*-carbon more electron-rich destabilizing the benzylic anion (Scheme 2). It is assumed that re-protonation of this C atom by a water molecule and subsequent deprotonation of the azine with loss of nitrogen gas are fast processes, giving the alkane product.



Scheme 2

Reduction of NO<sub>2</sub> groups to NH<sub>2</sub> following this method has not been reported; hence, we have explored a possible mechanism for the transformation. First, to check if the reduction of the aromatic nitro was influenced by the presence of the carbonyl group, the reduction of 1-chloro-3-nitrobenzene (**2**) was attempted. This reduction yielded the corresponding amine, showing that the nitro reduction was independent of the presence of a CO group.

Second, we explored the effect of the base, KOH, on the double reduction. Substrate **2** was reduced in the absence of base, suggesting that other species such as water or OH groups formed during the course of the reaction were sufficient to complete the reduction. Furthermore, when **1b** was reacted in the absence of base, reduction of the NO<sub>2</sub> group was observed, but not the CO group.

Considering the intermediates reported in the literature,<sup>13</sup> for alternative nitro reductions and to explore if the present conditions could also work on these intermediates, representative aromatic nitroso **3**, azide **4** and hydroxylamine **5** substrates were synthesised according to literature procedures,<sup>12,14,15</sup> and were subjected to our reduction conditions (Table 3).

The corresponding amine was obtained from both compounds **3** and **4** but not from the hydroxylamine **5**.

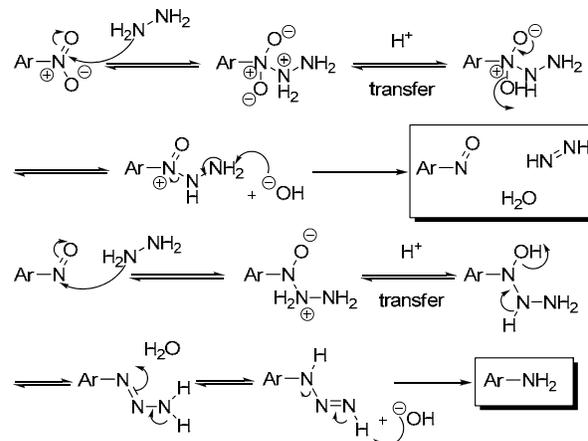
Furthermore, to confirm that hydrazine was involved in the reductive process, derivatives **2**, **3** and **4** were reacted in its absence under the same conditions and no reduction was observed. In addition, reactions were carried out with hydrazine but without hydroxide, and reduction of the nitro **2** and nitroso **3** compounds was observed. Importantly, the azide derivative **4** was not reduced under these conditions. These results seem to suggest that reduction of the nitro group proceeds *via* a nitroso intermediate.

**Table 3.** Reduction of common nitro intermediates using the optimized conditions (2 mL NH<sub>2</sub>NH<sub>2</sub>, 5 equiv. KOH, 135 °C in a pressure tube, 24 h).

Substrate	Product	Yield (%) <sup>a</sup>
		98
		93
		100
		0

<sup>a</sup>Isolated yield of purified compound

From these experiments a mechanism for reduction of the NO<sub>2</sub> group through reaction with hydrazine can be proposed (Scheme 3).



Scheme 3

The first step of this reaction would involve nucleophilic attack of hydrazine on the nitro N atom to form a 1-hydroxy-1-aryltriazone 1-oxide. Attack of a hydroxyl anion results in the formation of a nitroso intermediate and the release of diazene and water. A second hydrazine molecule can attack the nitroso derivative to yield a 1-hydroxy-1-aryltriazone which would undergo transformation into the anilino derivative, water and nitrogen. This hypothesis is in agreement with the lack of reactivity of the hydroxylamine derivative **5** and the positive results obtained with the nitroso compound **3**. In addition, this mechanism would explain why the reduction of derivatives **3** and **4** could be performed in the absence of KOH.

The first objective of this project was to develop a methodology for reduction of a problematic diaryl carbonyl **1b** to the corresponding diaryl alkane. In the process we achieved not only this reduction but also the simultaneous reduction of two aryl-nitro groups to the corresponding anilines **1a**. This method of double reduction proved to be applicable to a variety of molecules and is a valuable route to alkyl-substituted anilines.

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#### References

1. Clemmensen, E. *Chem. Ber.*, **1913**, *46*, 1837.
2. Kishner, N. *J. Russ. Chem. Soc.*, **1911**, *43*, 582.
3. Todd, D. *Org. React.*, **1948**, *4*, 378.
4. Mozingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. J. *J. Am. Chem. Soc.*, **1946**, *65*, 1013.
5. Allen, C. F. H.; VanAllan, J. *Org. Synth. Coll. Vol.* **3**, **1955**, 63.
6. Burdon, J.; Price, R. C. *J. Chem. Soc., Chem. Commun.*, **1986**, 893.
7. Dewar, M. J. S.; Mole, T. *J. Chem. Soc.*, **1956**, 2556.
8. Kuhn, L. P. *J. Am. Chem. Soc.*, **1951**, *73*, 1510.
9. Raney M., U.S. Patent 1,628,190, 1927; *Chem. Abstr.* **1927**, *21*, 17120.
10. Binz, A.; Schickh, O. V. *Chem. Ber.*, **1935**, *68*, 315.
11. Cope, O. J.; Brown, R. K. *Can. J. Chem.*, **1961**, *39*, 1695.
12. Durham, L. J.; McLeod, D. J.; Cason, J. *Org. Synth. Coll. Vol.* **4**, **1963**, 510.
13. Ung, S.; Falguieres, A.; Guy, A.; Ferroud, C. *Tetrahedron Lett.*, **2005**, *46*, 5913.
14. Wu, G.; Zhu, J.; Mo, X.; Wang, R.; Terskikh, V. *J. Am. Chem. Soc.*, **2010**, *132*, 5143.
15. Samet, A. V.; Kislyi, K. A.; Marshalkin, V. N.; Strelenko, Y. A.; Nelyubina, Y. V.; Lyssenko, K. A.; Semenova, V. V. *Russ. Chem. Bull. Int. Ed.*, **2007**, *56*, 2089.

#### Supplementary Material

Supplementary material is available. Synthesis and spectroscopic data and HPLC information of all compounds obtained.

Scheme 1.- One-pot preparation of N-substituted N'-Boc protected thioureas.

Scheme 2.- Synthesis of N,N'-disubstituted N''-Boc protected guanidines.

Scheme 3.- Preparation of the corresponding N,N'-disubstituted guanidinium chlorides by Boc deprotection.

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