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A simple synthesis of anilines by $LiAlH_4/TiCl_4$ reduction of aromatic nitro compounds

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ABSTRACT

A rapid and efficient single-step synthesis of substituted anilines has been developed. The aromatic nitro compounds were reduced by using reducing systems generated by the action of an excess of $LiAlH_4$ on $TiCl_4$. Anilines substituted with different functional groups were synthesized in high yields and purity starting from the corresponding nitro compounds. The developed procedure is applicable to nitroaromatics containing both electron withdrawing and electron donating substituents. Substrates with electron donor substituents require a larger excess of $LiAlH_4$. The reducing power of the prepared reactant systems depends on the used molar ratio of $LiAlH_4$ and $TiCl_4$.

Reduction of aromatic and aliphatic nitro compounds is one of the most important methods for preparing amines in the organic synthesis. The synthesis of aromatic amines is widely studied and represents an important research area.[1] They in fact, are important intermediates in the preparation of dyes, antioxidants, pharmaceuticals, and agrochemicals.[2]

Several methods have been employed for the reduction of aromatic nitro compounds,[3] some of these procedures use alcohols, hydrazine hydrates, silanes, and formates as hydrogen sources.[4] Substituted anilines are usually obtained through catalytic hydrogenation under pressure of the corresponding nitro compounds.[5]

The use of sodium borohydride ($NaBH_4$) in combination with metal nanoparticles represents an important reagent system for the reduction of functional groups in modern preparative chemistry. Under normal conditions[6] $NaBH_4$ does not work to convert nitro compounds into amines, instead, when it is used together with transition metal halides such as $CoCl_2$, $FeCl_2$, $CuSO_4$ is able to reduce successfully aromatic nitro compounds.[7–9]

$NaBH_4$, in protic solvents, reduces transition metal ions, with evolution of hydrogen gas, by producing metal boride nanoparticles that allow the rapid conversion of nitro compounds into their corresponding anilines.[10]

This methodology has been extensively studied, as regards preparation and characterization of reducing agent, although applications to organic substrates were negligible. The complex preparation of the reduction system represents an important limitation of this procedure.

Lithium aluminum hydride ($LiAlH_4$) represents a very versatile reducing agent that is extremely useful in synthetic organic chemistry. It is a more powerful reducing agent than sodium borohydride and reduces aromatic nitro compounds affording their corresponding azo compounds.[11] The reaction most likely proceeds, in analogy with the catalytic hydrogenation of nitro compounds,[12] through electron transfer, in an aprotic solvent, from hydride to nitro group with the formation of a radical intermediate that dimerizes by providing the azo-derivative (Scheme 1).

The activation of nitro compounds with titanium tetrachloride ($TiCl_4$) or even the formation of mixed hydrides, generated by the action of $LiAlH_4$ on $TiCl_4$, could change the reaction course, furthermore, the use of an excess of $LiAlH_4$ could provide directly the corresponding amine. In the literature[13] it is reported that $LiAlH_4$ reacts with $TiCl_4$ with hydrogen gas evolution and by forming, depending on the used molar ratio of $LiAlH_4$ and $TiCl_4$, a reducing system characterized by the presence of aluminum and titanium metal nanoparticles.

In an attempt to use this system for the reduction of aromatic nitro compounds, *N*,*N*-diethyl-4-nitrobenzensulfonamide (**1a**) (1 mmol) was added portionwise to a reducing system obtained by adding $LiAlH_4$ (1 mmol) to a suspension of $TiCl_4$ (1 mmol) in

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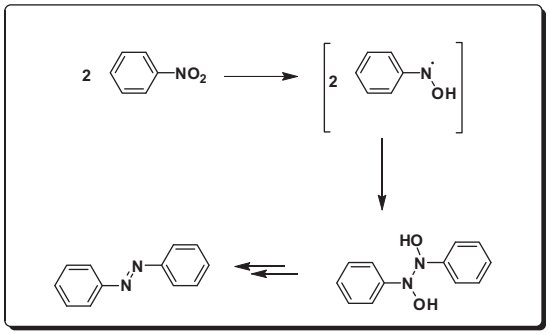


Scheme 1. Probable formation mechanism of azo compounds.

Table 1
Results of reduction of substituted nitrobenzenes with the reducing system $LiAlH_4$/$TiCl_4$ in molar ratio 5:1

Entry	R_1	R_2	R_3	Yield[a] **2** (%)	Yield[a] **3** (%)	Reaction time
a	SO_2NEt_2	H	H	92	—	15 min
b	H	SO_2NEt_2	H	89	—	25 min
c	H	H	SO_2NEt_2	90	—	25 min
d	F	H	H	98	—	45 min
e	Cl	H	H	91	—	45 min
f	Br	H	H	94	—	45 min
g	H	H	H	48	25	15 h
h	CH_3	H	H	45	28	26 h
i	OCH_3	H	H	43	20	29 h

[a] Isolated yield.

tetrahydrofuran (THF). The reaction mixture was kept stirring at room temperature for 48 h. After this time the starting *N*,*N*-diethyl-4-nitrobenzensulfonamide was recovered unchanged. The formation of reduction products was not even observed with the substrates 1-chloro-4-nitrobenzene (**1e**), nitrobenzene (**1g**), and 1-methoxy-4-nitrobenzene (**1i**) when they were treated under the same reaction conditions of **1a**. Even the reducing system, prepared by using $LiAlH_4$ and $TiCl_4$ in the molar ratio 2:1, was not effective in reducing the same substrates (**1a**, **1e**, **1g,** and **1i**).

After several attempts, a reducing system able to reduce efficiently nitro aromatic derivatives to amines has been found. It was prepared by adding $LiAlH_4$ (5 mmol) to a stirred suspension of $TiCl_4$ (1 mmol) in diethyl ether. The reaction mixture was stirred at room temperature for 15 min. As a result of filtration the obtained black suspension was recovered as a black solid which, when it is dry, burns mildly in air and reacts with water with moderate and constant evolution of hydrogen.

The so prepared reagent system was tested to reduce *N*,*N*-diethyl-4-nitrobenzensulfonamide (**1a**) chosen as a model substrate. In a typical experiment **1a** (1 mmol), was added slowly to the obtained black reducing suspension in diethyl ether.[14] The reaction was completed in 15 min and, after work up of the reaction mixture, 4-amino-*N*,*N*-diethylbenzenesulfonamide (**2a**) was recovered in 92% yield (Scheme 2, Table 1). Also 3-amino-*N*,*N*-diethylbenzenesulfonamide (**1b**) and 2-amino-*N*,*N*-diethylbenzenesulfonamide (**1c**), treated under the same reaction conditions of **1a**, afforded the corresponding amines **2b** and **2c** in high yields (Scheme 2, Table 1). In all cases the reduction reaction provided, at room temperature and within very short reaction times, the corresponding amines as unique reaction products.

1,4-Dinitrobenzene (**4**) was also particularly reactive in fact, in just 15 min was reduced into the corresponding diamine, 1,4-phenylenediamine (**5**), in quantitative yield (98%). Subsequently we investigated the reaction of nitrobenzenes substituted with electron-withdrawing groups using the above optimized conditions. The reduction of halogen substituted nitrobenzenes proceeded without dehalogenation. The reduction of 1-fluoro-4-nitrobenzene (**1d**), 1-chloro-4-nitrobenzene (**1e**), and 1-bromo-4-nitrobenzene (**1f**), was, in all cases, completed in 45 min and provided the corresponding aniline derivatives **2d–f** in excellent yields (Scheme 2, Table 1). All the recovered products did not require further purification and their structures were assigned based on ^1H and ^{13}C NMR spectra.

On the contrary the reaction of nitrobenzene (**1g**) with the same reducing system went to completion in 15 h at room temperature as detected by TLC. After this time, aniline (**2g**, 48% yield), 1,2-diphenyldiazene (**3g**, 25% yield), and benzidine (**6**, 5% yield) were recovered after short column chromatography (diethyl ether/petroleum ether 60:40 v/v). Long reaction times were also required for the reduction of 1-methyl-4-nitrobenzene (**1h**), that, after 26 h, afforded *p*-toluidine (**2h**, 45% yield), 4,4′-dimethylazobenzene (**3h**, 28% yield).

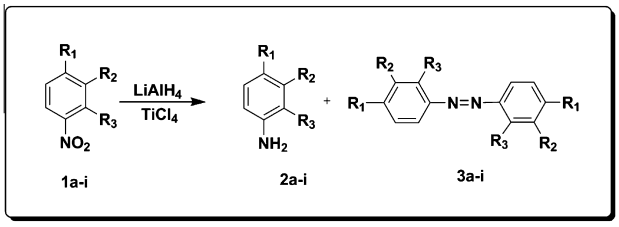
The treatment of 1-methoxy-4-nitrobenzene (**1i**) provided, after 29 h and separation of the reaction mixture by short column chromatography (diethyl ether/petroleum ether, 60:40 v/v), 4-methoxyaniline (**2i**, 43% yield) and 1,2-bis(4-methoxyphenyl) diazene (**3i**, 20% yield).

The reduction of nitrobenzenes **1h–i**, bearing electron-donor substituents in the 4-position, gave a mixture of azobenzene and aniline derivatives and reaction times became significantly longer (Scheme 2, Table 1).

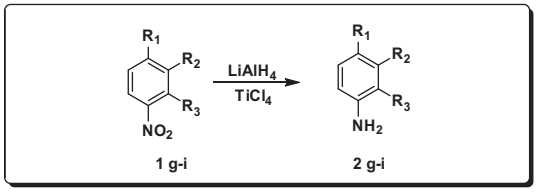
Additional experiments were performed in order to explore the reaction progress for the synthesis of aromatic amino compounds under modified reaction conditions. Nitrobenzene (**1g**, 1 mmol), 1-methyl-4-nitrobenzene (**1h**, 1 mmol) and 1-methoxy-4-nitrobenzene (**1i**, 1 mmol) were treated with a different reducing system prepared by adding $LiAlH_4$ (10 mmol) to a suspension of $TiCl_4$ (1 mmol) in diethyl ether at room temperature.

The reaction went to completion after about 30 min of stirring, then a NaOH aqueous solution was added and the phases were separated. The resulting organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to give the corresponding substituted anilines **2g–i** in very high yields (86–90%) (Scheme 3, Table 2), reaction by-products were not observed.

The results of reduction reactions of substrates **1g–i** suggested that azobenzenes could be key intermediates of the reduction process. In order to gain a better understanding of the reduction



Scheme 2. Reduction of substituted nitrobenzenes with the reducing system $LiAlH_4$/$TiCl_4$ in molar ratio 5:1.



Scheme 3. Reduction of nitrobenzene and nitrobenzenes bearing electron donor substituents with the reducing system $LiAlH_4$/$TiCl_4$ in molar ratio 10:1.

Table 2
Results of reduction of nitrobenzenes **1g–i** with the reducing system $LiAlH_4/TiCl_4$ in molar ratio 10:1

Entry	R_1	R_2	R_3	Yield[a] **2** (%)	Reaction time (min)
g	H	H	H	90	25
h	CH_3	H	H	88	30
i	OCH_3	H	H	86	30

[a] Isolated yield.

reaction progress, symmetrical azobenzenes **3d**, **3g,** and **3h** were prepared by using a classical procedure.[11a] To this aim 1-fluoro-4-nitrobenzene (**1d**, 1 mmol), nitrobenzene (**1g**, 1 mmol), and 1-methyl-4-nitrobenzene (**1h**, 1 mmol), were treated separately with 5 mmol of $LiAlH_4$. In all cases, after about 15 min, the reaction was completed with the formation of a single product, the corresponding substituted azobenzene **3** (Scheme 4, Table 3).

The formation of azobenzenes **3** was fast and did not require the presence of $TiCl_4$. It was also verified that even in very long times (24 h) the obtained azobenzenes **3d** and **3g–h** are not converted into the corresponding amines by treatment at room temperature with just $LiAlH_4$ in the molar ratio 1:5.

However, when the azobenzenes **3d**, **3g–h** (1 mmol) were treated with the different reducing system prepared by adding $LiAlH_4$ (10 mmol) to a stirred suspension of $TiCl_4$ (1 mmol) in diethyl ether, they were converted rapidly and in high yields (87–98%) into the corresponding amines **2d** and **2g–h** (Scheme 5, Table 4).

These results indicated that nitrobenzene and nitrobenzenes with electron-donor substituents in the 4-position, only in the presence of a large excess of lithium aluminum hydride and equimolar amounts of titanium tetrachloride can be converted rapidly, through the formation of azobenzenes **3**, into the corresponding anilines **2**. Therefore, in all the cases we examined the azobenzenes are reaction intermediates for the formation of anilines from the corresponding nitrobenzenes.

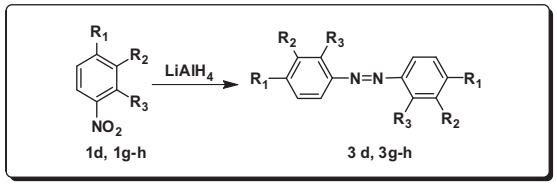
In conclusion, a rapid and practical method employing $LiAlH_4$ and $TiCl_4$ as the reacting system to reduce aromatic nitro compounds into their corresponding substituted anilines is reported.

Efficient reducing systems are generated by treating $LiAlH_4$ with a suspension of $TiCl_4$ in diethyl ether in different molar ratios.

In a 'one-pot' reaction, $LiAlH_4$ achieves the conversion of the nitro compound into symmetrical azobenzene derivative. The azobenzene intermediate is rapidly converted into the corresponding amine by using reducing species of titanium and aluminum generated by the action of $LiAlH_4$ on $TiCl_4$.

The conversion with $LiAlH_4$ of azobenzenes into aniline derivatives is achieved only in the presence of $TiCl_4$. The proposed procedure works well with both 'electron poor' and 'electron rich' substrates.

Substrates with electron donor substituents however, require a larger excess of lithium aluminum hydride. The reducing power of the different prepared reagent systems for reducing substituted nitrobenzenes depends on the respective molar ratio of $LiAlH_4$ and $TiCl_4$.

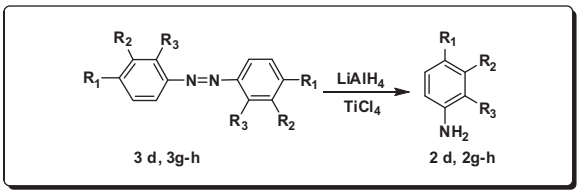


Scheme 4. Reduction of substituted nitrobenzenes with $LiAlH_4$.

Table 3
Results of reduction of substituted nitrobenzenes with $LiAlH_4$

Entry	R_1	R_2	R_3	Yield[a] **3** (%)	Reaction time (min)
d	F	H	H	88	10
g	H	H	H	89	15
h	CH_3	H	H	92	15

[a] Isolated yield.



Scheme 5. Reduction of substituted azobenzenes with the reducing system $LiAlH_4/TiCl_4$ in molar ratio 10:1.

Table 4
Results of reduction of substituted azobenzenes with the reducing system $LiAlH_4/TiCl_4$ in molar ratio 10:1

Entry	R_1	R_2	R_3	Yield[a] **2** (%)	Reaction time
d	F	H	H	98	5
g	H	H	H	87	10
h	CH_3	H	H	92	10

[a] Isolated yield.

Supplementary data

Supplementary data (general experimental details, lists of spectral data, copies of ^1H and ^{13}C NMR spectra for compounds **2a–i**, **3d**, **3g–i**, **5–6**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.089.

References and notes

1. (a) Chandrappa, S.; Vinaya, T.; Ramakrishnappa, T.; Rangappa, K. S. *Synlett* **2010**, 3019–3022; (b) Wienhöfer, G.; Sorribes, I.; Boddien, A.; Westerhaus, F.; Junge, K.; Junge, H.; Llusar, R.; Beller, M. *J. Am. Chem. Soc.* **2011**, *133*, 12875–12879; (c) Kelly, S. M.; Lipshutz, B. H. *Org. Lett.* **2014**, *16*, 98–101.
2. (a) Yuste, F.; Saldana, M.; Walls, F. *Tetrahedron Lett.* **1982**, *23*, 147–148; (b) Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415–3418; (c) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Perri, F.; Siciliano, C. *J. Chromatogr., A* **2005**, *1066*, 143–148.
3. (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989. pp. 411–415; (b) Kabalka, G. W.; Varma, R. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 363–379; (c) Sauvé, G.; Rao, V. S. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 2, pp 737–817.
4. (a) Gowda, S.; Abiraj, K.; Gowda, D. C. *Tetrahedron Lett.* **2002**, *43*, 1329–1331; (b) Sharma, U.; Kumar, P.; Kumar, N.; Kumar, V.; Singh, B. *Adv. Synth. Catal.* **2010**, *354*, 1834–1840; (c) Junge, K.; Wendt, B.; Shaikh, N.; Beller, M. *Chem. Commun.* **2010**, 1769–1771; (d) Sharma, U.; Kumar, N.; Verma, P. K.; Kumar, V.; Singh, B. *Green Chem.* **2012**, *14*, 2289–2293.
5. (a) Stiles, M.; Finkbeiner, H. L. *J. Am. Chem. Soc.* **1959**, *81*, 505–506; (b) Suchy, M.; Winternitz, P.; Zeller, M. World (WO) Patent, 91/00278, 1991; (c) Dowing, R. S.; Kunkeler, P. J.; Van Bekkum, H. *Catal. Today* **1997**, *37*, 121–130; (d) Corma, A.; Serna, P.; Concepcion, P.; Calvino, J. *J. Am. Chem. Soc.* **2008**, *130*, 8748–8753; (e) Blaser, H.-U.; Steine, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210–221.
6. Burk, S. D.; Danheiser, R. L. *Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents*; Wiley-VCH: New York, 1999.
7. Satoh, T.; Suzuki, S.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555–4558.
8. Ono, A.; Sasaki, H.; Yaginuma, F. *Chem. Ind. (London)* **1983**, 480.
9. Yoo, S.; Lee, S. *Synlett* **1990**, 419–420.
10. (a) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413–6416; (b) Guo, F.; Ni, Y.; Ma, Y.; Xiang, N.; Liu, C. *New J. Chem.* **2014**, *38*, 5324–5330; (c) Wu, F.; Qiu, L.-G.; Ke, F.; Jiang, X. *Inorg. Chem. Commun.* **2013**, *32*, 5–8.
11. (a) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738–3740; (b) Joseph, M. M.; Jacob, D. E. *Indian J. Chem., Sect. B* **2004**, *43*, 432–436.
12. Gelder, E. A.; Jackson, S. D.; Lok, C. M. *Chem. Commun.* **2005**, 522–524.

13. Balema, V. P.; Dennis, K. W.; Pecharsky, V. K. *Chem. Commun.* **2000**, 1665–1666.

14. $LiAlH_4$ (5 mmol) was added to a stirred suspension of $TiCl_4$ (1 mmol) in diethyl ether. The resulting suspension was stirred at room temperature for 15 min. Then a solution in diethyl ether of the corresponding nitro compound (**1a**, 1 mmol) was added slowly to the obtained black reducing suspension under inert nitrogen atmosphere. The reaction was kept stirring at room temperature and monitored by TLC (diethyl ether/petroleum ether 60:40 v/v). After complete conversion of the starting material, the reaction mixture was paper filtered, washed with 1 N aqueous NaOH (3×5 mL) and once with brine (5 mL). The ethereal layers were dried (Na_2SO_4) and evaporated to dryness under reduced pressure conditions to give the corresponding amine **2a** in 92% yield. *4-Amino-N,N-diethylbenzenesulfonamide* (**2a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, J = 9.0 Hz, 2H, Ha, Ha′), 6.66 (d, J = 9.0 Hz, 2H, Hb, Hb′), 4.15 (s_{broad}, 2H, NH_2), 3.18 (q, J = 6.6 Hz, 4H, NCH_2), 1.11 (t, J = 6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.2, 129.0, 128.5, 114.0, 42.0, 14.6; GC/MS m/z (% rel.): 228 [M+] (33), 213(40), 156(100), 108(33), 92(35), 65(18); Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06; N, 12.27; S, 14.04; Found: C, 52.70; H, 7.04; N, 11.35; S, 14.05.