Molybdenum Hexacarbonyl and DBU Reduction of Nitro Compounds under Microwave Irradiation

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Received 5 July 2007

Abstract: An ethanolic mixture of molybdenum hexacarbonyl and DBU mediates the reduction of nitroarenes to the corresponding anilines in excellent yields in 15–30 minutes under microwave irradiation.

Key words: amines, microwave, molybdenum, nitroarenes, reductions

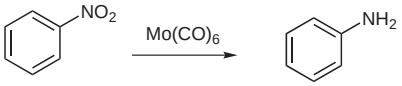
The high cost of drug development and the capabilities of high throughput screening (HTS) dictate the need for a medicinal chemist to synthesise libraries of molecules in high yields and purities, with minimal bottlenecks. In this respect, microwave-assisted organic synthesis (MAOS) is a particularly useful tool since many thermal processes can be accelerated and performed in minutes.[1]

The aniline motif is ubiquitous in medicinal chemistry as both a side chain in bioactive molecules or as a precursor to other functional groups including amides, sulfonamides, substituted amines and heterocycles. Anilines can be prepared by the reduction of nitro compounds using catalytic or transfer-hydrogenation routes or stoichiometric reducing agents.[2] Many of these processes employ microwave reactors,[3] although the use of a monomodal system is preferable for safety and reproducibility.[4]

The molybdenum hexacarbonyl mediated reduction of nitro compounds to anilines, via thermal energy, is limited to a handful of substrates and requires long reaction times (24 h).[5] We were interested in preparing a library of anilines from their corresponding nitroarenes via MAOS inspired by reports that demonstrated the use of $Mo(CO)_6$ as a convenient source of CO in aminocarbonylation processes.[1a,6] Our brief initial optimisation studies focused on the reduction of nitrobenzene **1a** to aniline **2a** with $Mo(CO)_6$ by varying the following parameters: temperature, solvent, reaction time, metal carbonyl stoichiometry, and the use of additives {1,8-diazabicyclo[5.4.0]undec-7-ene, (DBU)}.[6]

Given that the original thermal process used EtOH as solvent, we examined the effect of temperature on the reduction process. From Table 1, 150°C appears to be the optimal temperature since higher temperatures (200 °C) often led to cracking of the microwave tube and at 125 °C lower conversions were observed (entries 1–3).

Table 1 Reduction of Nitrobenzene **1a** to Aniline **2a**



1a **2a**

Entry[a]	Solvent	Reagent equiv $Mo(CO)_6$	**1a**	DBU	Conversion (%)[b]
1	EtOH	1	1	0	33
2	EtOH	1	1	0	20[c]
3	EtOH	1	1	0	0[d]
4	EtOH	0	1	0	0
5	EtOH	2	1	0	50
6	EtOH	3	1	0	60
7	H_2O	1	1	0	<10
8	THF	1	1	0	[e]
9	EtOH	1	1	3	93
10	DMF	1	1	3	0
11	diglyme–H_2O (1:1)	1	1	3	75

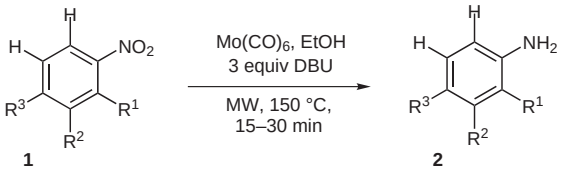
[a] General conditions: 150 °C, 30 min, 5 mL solvent, CEM Discover Unit (P = 300 W).
[b] By ^1H NMR.
[c] At 125 °C.
[d] At 200 °C; tube cracks.
[e] Reproducibility problems.

N,*N*-Dimethylformamide (DMF), tetrahydrofuran (THF), diglyme/water, used for aminocarbonylations,[6] and neat water were found to be inferior to EtOH as solvent (entries 7–11). In terms of stoichiometry, when zero equivalents of $Mo(CO)_6$ were used, in EtOH (control, entry 4), there was no reaction. Increasing the number of equivalents of $Mo(CO)_6$ led to an increase in the conversion of nitrobenzene into aniline at the given temperature (150 °C, 33%, 1 equiv; 50%, 2 equiv, 60%, 3 equiv; entries 5 and 6) although the use of excess reducing agent is undesirable. The benefit of adding DBU, known to facilitate CO liberation from $Mo(CO)_6$, is evident from entry 9.[6b]

We employed the latter conditions to prepare a library of anilines from nitroarenes (Table 2).[7]

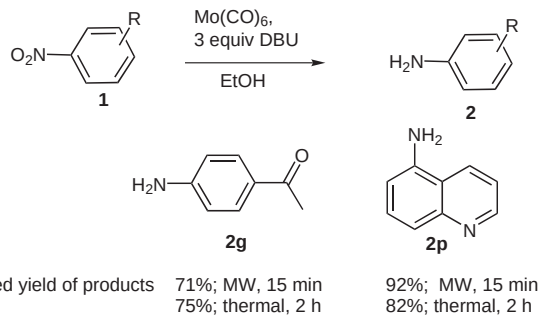
SYNLETT 2007, No. 16, pp 2557–2558
Advanced online publication: 23.08.2007
DOI: 10.1055/s-2007-986628; Art ID: D19807ST

Table 2 Reduction of Nitrobenzene Derivatives



Product	R^1	R^2	R^3	Yield of **2** (%)[a]
2b	H	H	OMe	85
2c	H	H	Me	89,[b,c] 50[d]
2d	F	H	Me	66[b]
2e	C(O)Me	H	H	50[b]
2f	H	C(O)Me	H	77[b]
2g	H	H	C(O)Me	71[b]
2h	H	I	H	89[b]
2i	H	H	CN	71[b]
2j	H	H	$C(O)NH_2$	81[b]
2k	H	$CH=CH_2$	H	81[b]
2l	Br	H	H	89,[a] 52[b]
2m	H	Br	H	93
2n	H	H	Br	79
2o	Cl	H	CH_2OH	90

[a] Isolated yield after column chromatography. General conditions: 150 °C, 300 W (power), 30 min, EtOH (solvent), 1 equiv $Mo(CO)_6$, 3 equiv DBU.
[b] Reaction time = 15 min.
[c] Quantitative conversion by ^1H NMR.
[d] 0.5 Equiv $Mo(CO)_6$, 1.5 equiv DBU; conversion determined by ^1H NMR; 15 min reaction time.



Scheme 1 Microwave-mediated vs. thermal-mediated reductions

The reduction process is rather general, rapid and gives a high yield of product. It operates for electron-rich and electron-poor nitroarenes and tolerates *ortho* substituents, halides, and other functional groups such as ketones, alcohols, vinyl, nitrile, and benzamides. We have also been able to reduce the reaction times to 15 minutes (e.g., Table 2, **2c**–**l**). This reaction can also be carried out thermally with yields comparable to those observed for the microwave-mediated route. The reduction of nitroheteroaromatics[8] proceeds smoothly under microwave or thermal conditions; 5-aminoquinoline could be synthesised in excellent yields (5 mmol scale, unoptimised) within two hours in refluxing EtOH (Scheme 1).

In summary, we have developed a general, convenient, expedited microwave-mediated method for the synthesis of a series of anilines from their corresponding nitro precursors, which displays excellent chemoselectivity.[9] Current work in our group is exploring the generalization of this reduction process towards the synthesis of polysubstituted aniline intermediates found in bioactive molecules.[10]

References and Notes

(1) Reviews: (a) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406. (b) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. (c) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 1141. (e) Mavandadi, F.; Lidstrom, P. *Curr. Top. Med. Chem.* **2004**, *4*, 773. (f) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66. (g) Mavandadi, F.; Pilotti, A. *Drug Discovery Today* **2006**, *11*, 165.

(2) (a) Larock, R. C. *Comprehensive Organic Transformations*; VHC Publishers: New York, **1987**. (b) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, **2006**.

(3) (a) Chapman, N.; Conway, B.; O'Grady, F.; Wall, M. D. *Synlett* **2006**, 1043. (b) Meshram, H. M.; Ganesh, Y. S. S.; Sekhar, K. C.; Yadav, J. S. *Synlett* **2000**, 993. (c) Vass, A.; Dudas, J.; Toth, J.; Varma, R. S. *Tetrahedron Lett.* **2001**, *42*, 5347.

(4) Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473.

(5) Suresh, I.; Kulkarni, G. M. *Synth. Comm.* **2004**, *34*, 721.

(6) (a) Wannberg, J.; Larhed, M. J. *Org. Chem.* **2003**, *68*, 5750. (b) Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4; and references cited therein.

(7) (a) **Typical Work-up**
After solvent concentration, the resulting crude product is passed over a short SiO_2 plug (6 cm × 3 cm). Typical eluent: neat CH_2Cl_2 to 5:1 CH_2Cl_2–acetone gradient. All products were characterised by ^1H NMR, ^{13}C NMR, GC-MS, or MS and correspond to commercial samples or literature values (see ref. 7b and also ref. 9). Compound **2o**: ^1H NMR (270 MHz): δ = 3.67 (2 H, br s), 4.67 (2 H, s), 6.54 (1 H, d, *J* = 8.4 Hz), 6.78 (1 H,s), 7.07 (1 H, s), 7.11 (1 H, s). ^{13}C NMR (67 MHz): δ = 62.9, 115.1, 121.1, 129.8, 138.7, 145.4. (b) *The Aldrich Library of ^{13}C and ^1H FT NMR Spectra*, 1st ed.; Pouchert, C. J.; Behnke, J., Eds.; Aldrich Chemical Company: USA, **1993**.

(8) Spencer, J.; Rathnam, R. P.; Patel, H.; Anjum, N., *manuscript in preparation.*

(9) Similar 'multifunctional' nitro analogues were selectively reduced with H_2 in the presence of catalytic gold nanoparticles: (a) Corma, A.; Serna, P. *Science* **2006**, *313*, 332. (b) See also: Blaser, H. U. *Science* **2006**, *313*, 312; and references cited therein.

(10) For example; kinase inhibitors: (a) Knesl, P.; Roseling, D.; Jordis, U. *Molecules* **2006**, *11*, 286; and references cited therein. (b) CNS active molecules: Adams, D. R.; Duncton, M. A. J.; Roffey, J. R. A.; Spencer, J. *Tetrahedron Lett.* **2002**, *43*, 7581.