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The reduction of aromatic nitro groups on solid supports using sodium hydrosulfite ($Na_2S_2O_4$)

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Abstract

An improved method for reducing aromatic nitro compounds on solid-phase supports using sodium hydrosulfite is presented. Conditions have been optimized to enable the use of this reagent for reductions on both polyethyleneglycol-polystyrene (PEG) resins and traditional polystyrene (PS) resins. © 2000 Published by Elsevier Science Ltd.

In solution-phase chemistry, the reduction of aromatic nitro groups is readily accomplished with a wide variety of reagents. Many of these methods, however, require either heavy metal catalysts, acidic conditions, high temperatures or pressure, which renders most of them unsuitable for use in solid-phase organic chemistry. The most common method currently in use for reduction of solid-phase bound nitro groups utilizes tin(II) chloride.[1] This reagent works well under a variety of conditions and generally provides reliable and clean conversion to the corresponding aniline. Several reports have also appeared, which use other transition metal-containing compounds, such as chromium.[2]

Despite the advantages of tin reduction, we have found that substantial quantities of tin by-products remain bound within the resin matrix and are liberated upon acid cleavage of the desired product. Several cell lines useful in biological compound screening have proven intolerant to tin at these levels.[3] Although attempts to rigorously wash away any tin species remaining within the resin by employing a variety of methods (e.g. chelating agents, solvents, crown ethers, mild acids and bases) were partially successful, we were prompted to investigate alternative reducing agents. In searching for a solid-phase compatible method, which would be reliable, inexpensive, non-toxic, non-nucleophilic, neutral, and specific to the reduction of nitro compounds in the presence of other functionalities, we carried out a rigorous examination of sodium hydrosulfite.[4]

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Initial experiments on a variety of resins quickly demonstrated the advantages and disadvantages of this reagent. Use of the reagent had been previously reported to effect reduction on polystyrene resin by refluxing in ethanol.[5] However, on further investigation, it quickly became apparent that these were not the conditions of choice. While sodium hydrosulfite is stable at temperatures below 50°C, it rapidly disproportionates at higher temperatures, decreasing the effectiveness of the reagent. Owing to the poor solubility of sodium hydrosulfite in organic solvents, we employed water as the solvent of choice. Indeed, sodium hydrosulfite is readily soluble in water, and a 1 M concentration can be readily obtained at ambient temperature. An aqueous 1 M solution of sodium hydrosulfite efficiently reduces aromatic nitro groups on PEG-PS resins such as Argogel® and Tentagel®. It also works efficiently on some of the newer modified resins, such as Argopore®, although here the addition of limited amounts up to 20% (v/v) of organic modifiers (such as EtOH, NMP or DMF) was useful (Fig. 1).

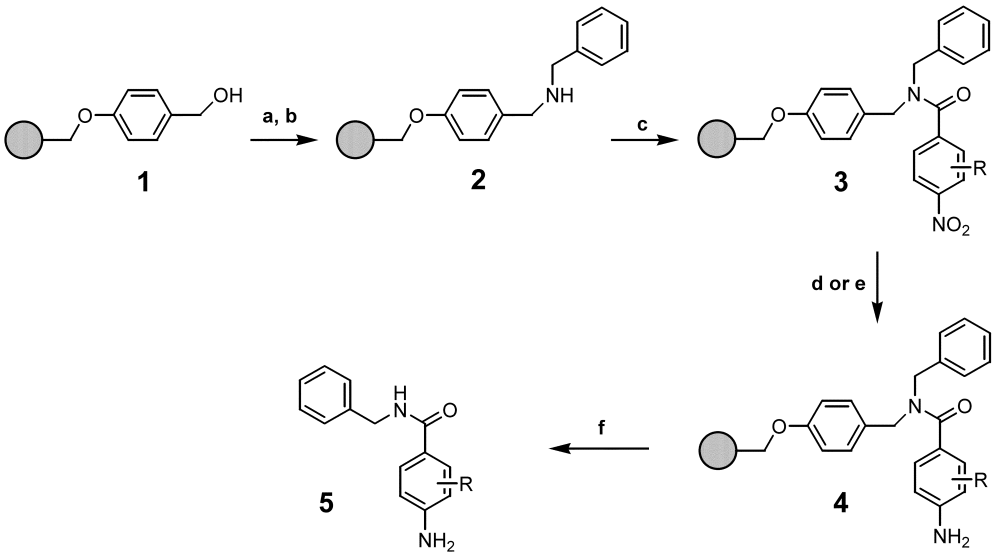

Figure 1. Model system for testing reduction methods. (a) PPh_3Br_2, DCM; (b) benzylamine, DMF; (c) nitroarene carboxylic acid, DIC, NMP; (d) aq. $Na_2S_2O_4$, K_2CO_3; (e) $SnCl_2{\cdot}2H_2O$, DMF; (f) TFA

A more extensive survey of the reduction of various nitroarenes was conducted on Tentagel® resin. Tentagel® MB PHB (10 g, 0.4 mmol/g loading, resin **1**) was treated with 200 mL of 0.25 M PPh_3Br_2 in DCM for 16 h at rt. The corresponding bromide was displaced with 100 mL of 1 M benzylamine in DMF at 70°C for 1 h to afford resin **2**. The resin was divided into 100 mg aliquots, and treated with a mixture of various nitroarene carboxylic acids (100 equiv.) and DIC (50 equiv.) in 1 mL NMP for 16 h at rt. The resulting nitroarene benzamides **3** were split into equal portions of 50 mg each, and treated with either 2 mL of 0.5 M aqueous sodium hydrosulfite/0.5 M potassium carbonate for 16 h at rt, or 2 mL of 1 M tin(II)chloride dihydrate in DMF at 50°C for 16 h to give the resin-bound reduced products **4**. The final products **5** were obtained by cleavage with TFA for 1 h. The results of the two different reduction procedures are summarized in Table 1. Both reaction conditions were quite effective in cleanly reducing the nitro functionality, with the sodium hydrosulfite reagent giving improved results in the more difficult reductions of heteroaromatic nitro compounds.

Table 1
Results of nitro reduction using sodium hydrosulfite and tin(II) chloride[a]

Nitroarene Acid	$SnCl_2$	$Na_2S_2O_4$	Nitroarene Acid	$SnCl_2$	$Na_2S_2O_4$
2-Nitrobenzoic acid	100	100	4,5-Dimethoxy-2-nitrophenylacetic acid	100	100
3-Nitrobenzoic acid	100	100	2-Bromo-5-nitrobenzoic acid	100	100
4-Nitrobenzoic acid	100	100	4,5-Dimethoxy-2-nitrocinnamic acid	100	100
2-Nitrocinnamic acid	100	100	3-Chloro-2,6-dimethoxy-5-nitrobenzoic acid	100	100
3-Nitrocinnamic acid	100	100	5-Nitrothiophene-2-carboxylic acid	100	100
4-Nitrocinnamic acid	100	100	3-Nitrophenylacetic acid	100	100
5-Nitro-2-furoic acid	100	100	3-(3-Nitrophenyl)propionic acid	100	100
2-Nitrophenylacetic acid	75	100	α-Ethyl-3-nitrocinnamic acid	100	100
2-Methyl-3-nitrobenzoic acid	100	100	4-Nitrohippuric acid	100	100
2-Methyl-5-nitrobenzoic acid	100	100	trans-4-Chloro-3-nitrocinnamic acid	100	100
3-Methyl-4-nitrobenzoic acid	100	100	3-Hydroxy-2-nitrobenzoic acid	100	100
3-Methyl-2-nitrobenzoic acid	100	100	2-Chloro-6-nitrobenzoic acid	100	100
4-Methyl-3-nitrobenzoic acid	100	100	2-Nitro-4-(trifluoromethyl)benzoic acid	95	100
3-(5-Nitro-2-furyl)acrylic acid	100	100	2-Chloro-5-nitrocinnamic acid	100	100
2-Hydroxy-5-nitrobenzoic acid	100	100	3(2-Methyl-4-nitroimidazol-1-yl)propionic acid	75	80
3-Hydroxy-4-nitrobenzoic acid	100	100	(3-Nitropyrid-2-yl)thioacetic acid	100	100
4-Hydroxy-3-nitrobenzoic acid	100	100	N-(3-Nitrophenyl)maleamic acid	100	100
2-Fluoro-5-nitrobenzoic acid	98	100	3-(3-Nitro-4-pyrrolidinophenyl)acrylic acid	100	100
4-Fluoro-3-nitrobenzoic acid	100	100	5-Nitro-3-phenylindole-2-carboxylic acid	100	100
5-Fluoro-2-nitrobenzoic acid	100	100	2-(4-Methoxyphenoxy)-5-nitrobenzoic acid	100	100
2-(4-Nitrophenyl)propionic acid	100	100	3-Hydroxy-4-methyl-2-nitrobenzoic acid	100	100
2-Nitrophenoxyacetic acid	100	100	3-Nitro-5-(trifluoromethyl)benzoic acid	100	100
3-Nitrophenoxyacetic acid	100	100	4-Nitrophenylacetic acid	100	100
4-Nitrophenoxyacetic acid	100	100	4-(4-Nitrophenyl)butyric acid	100	100
3-Methoxy-2-nitrobenzoic acid	100	100	4-Acetamido-3-nitrobenzoic acid	100	100
3-Methoxy-4-nitrobenzoic acid	100	100	mono-Methyl 5-nitroisophthalate	100	100
4-Methoxy-3-nitrobenzoic acid	100	100	2,6-Dimethoxy-3-nitrobenzoic acid	100	100
5-Methoxy-2-nitrobenzoic acid	93	97	5-(4-Methyl-2-nitrophenyl)-2-furoic acid	100	100
2-Chloro-3-nitrobenzoic acid	100	100	5-Hydroxy-2-nitrobenzoic acid	100	100
2-Chloro-4-nitrobenzoic acid	100	100	4,5-Methylenedioxy-2-nitrocinnamic acid	100	100
2-Chloro-5-nitrobenzoic acid	100	100	5-Nitrobenzofuran-2-carboxylic acid	100	100
4-Chloro-3-nitrobenzoic acid	100	100	2-Nitrothiophene-4-carboxylic acid	100	100
7-Nitroindole-2-carboxylic acid	100	100	2,5-Dichloro-3-nitrobenzoic acid	100	100
5-(2-Nitrophenyl)-2-furoic acid	100	100	4,5-Dimethoxy-2-nitrobenzoic acid	100	100
5-(3-Nitrophenyl)-2-furoic acid	100	100	5-Nitro-3-pyrazolecarboxylic acid	100	100
5-(4-Nitrophenyl)-2-furoic acid	100	100	Malonic acid Mono-4-nitrobenzyl ester	100	100
N-(4-Nitrobenzoyl)-β-alanine	100	100	4-Nitropyrrole-2-carboxylic acid	40	100

[a]Numbers refer to percentage of target reduced compound **5** obtained on acidolysis compared to unreduced nitro starting material (derived from resin **3**). Percentages determined by HPLC peak integrals at 220 nm and correlation with LC-MS.

As expected, however, the hydrosulfite reagent in aqueous solution was unable to reduce aromatic nitro groups on regular polystyrene resin due to the known hydrophobicity of the solid support, and its inability to swell in an aqueous environment. Attempts were made with the introduction of co-solvents such as NMP, DMF, MeOH, THF, dioxane, and EtOH in concentrations up to 50%, with little beneficial results observed. The use of viologen dibromide as an electron phase-transfer catalyst for similar reductions in solution has been reported.[6] This prompted an investigation into such a system for the reduction of aromatic nitro groups on polystyrene. 4-Nitrobenzoic acid was coupled to PS-Rink resin to give **6** (Fig. 2). This resin was treated with a mixture of 0.5 M sodium hydrosulfite and 0.5 M potassium carbonate in DCM:water (9:1), employing a variety of dialkylbipyridinium dihalides as electron phase-transfer catalysts to give the reduced resin-bound intermediate **7**. The extent of the reduction reaction was assessed by acidolysis to release the product **8**. In all cases, the quantitative reduction of the nitro group on polystyrene resin was observed, independent of the catalyst employed.[7]

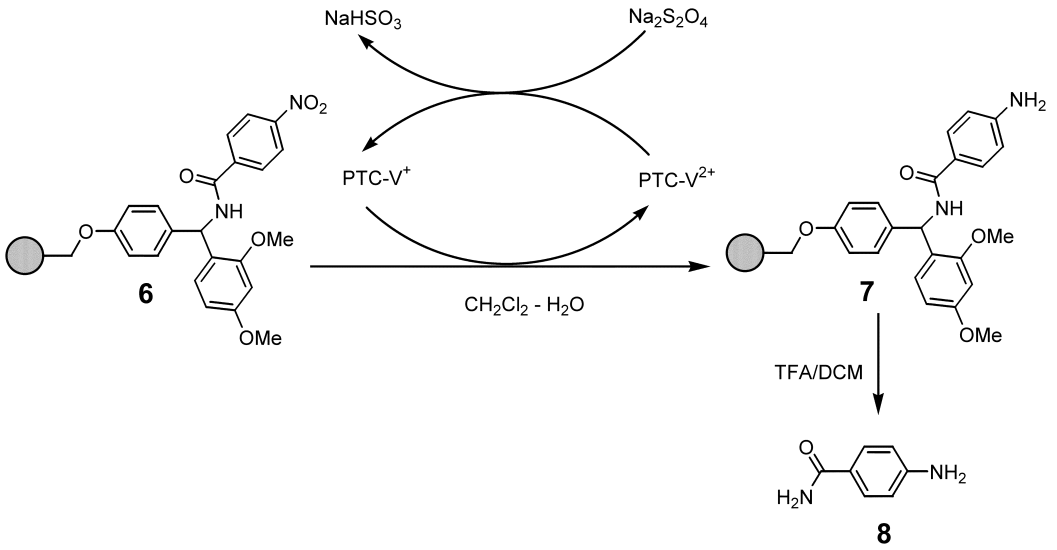

Figure 2. Cyclic pathway for the viologen-mediated reduction of nitroarenes with sodium hydrosulfite

Overall, we have demonstrated that sodium hydrosulfite is a useful alternative to metal-based reducing agents and may be superior in some cases. The use of this reagent in the preparation of combinatorial chemical libraries will be reported in due course.

Acknowledgements

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7. In a typical reaction: To 50 mg of resin-bound nitrobenzamide **6** was added 0.2 mL of 0.5 M sodium hydrosulfite/0.5 M potassium carbonate and 1.8 mL of DCM, followed by the addition of 2 mg of the phase-transfer catalyst (PTC-V^{2+}). The reaction was shaken for 16 h at rt to afford **7**. The final product **8** was obtained by cleavage with 50% TFA in DCM for 1 h. Six different 1,1′-diX-4,4′-bipyridinium dibromide or dichloride reagents were used, where X = ethyl, phenyl, benzyl, heptyl, octyl and octadecyl. Each was equally effective under the described conditions.