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## Fast and effective reduction of nitroarenes by sodium dithionite under PTC conditions: Application in solid-phase synthesis

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### Abstract

Herein, conditions for the fast and effective reduction of aromatic nitro groups bound to hydrophobic polystyrene-based Wang and Ring resins utilizing sodium dithionite in dichloromethane–water under PTC conditions is reported. Tetrabutylammonium hydrogen sulfate (TBAHS) was found to be an effective phase-transfer catalyst for this reaction. This method allows for the reduction of nitro groups to amino groups under mild conditions with complete conversion and is tolerant of other functional groups. This method is a superior alternative to tin(II) chloride-based reduction, which is known for its shortcomings.

### Keywords

Solid-phase synthesis; Sodium dithionite; Reduction; Phase-transfer catalysis; Resin-bound nitroarene

Aromatic amines play a key role in the synthesis of heterocyclic compounds, particularly in solid-phase synthesis. They are usually prepared by the reduction of polymer-supported nitro derivatives. In solution-phase chemistry, many reduction methods are commonly used; unfortunately, many of these methods are not applicable to solid-phase chemistry, including methods that involve heterogeneous catalysts or acidic conditions (in the case of typically used acid-labile linkers). The most common method for the reduction of solid-phase-bound aromatic nitro groups involves the use of tin(II) chloride in the presence of a base.<sup>1-6</sup> The main disadvantages of this method are the formation of insoluble tin salts that are practically impossible to wash from the resin matrix and the possible coordination of tin salts to organic substances on the resin. Tin salts are liberated during the final acidic cleavage step, resulting in contamination of the product and complicating purification. In addition, tin(II) chloride reductions are occasionally very sluggish and require the use of a 2 M solution of tin(II) chloride in DMF at an elevated temperature (80 °C) under argon.<sup>7</sup>

We have synthesized and purified several hundred heterocyclic compounds using solid-phase syntheses that involve the reduction of nitro groups.<sup>8-10</sup> In a model synthesis of a benzimidazolinopiperazinone,<sup>6</sup> we reduced a resin-bound nitroarene with a 1 M solution of tin(II) chloride in DMF overnight. After we thoroughly washed the resin beads with DMF, MeOH and dichloromethane (DCM), we released the products using 50% TFA in DCM for 1 h, evaporated the solvent and precipitated the product with ether. The crude yield was greater than 400%, which indicated substantial contamination. This material was dissolved in deuterated DMSO, and the product quantity was estimated using <sup>1</sup>H NMR spectroscopy. The results indicated that the crude product contained less than 25% of the target compound. Such crude preparations were typically

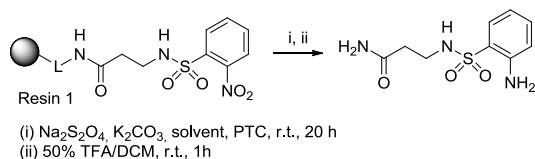
purified by reverse-phase HPLC. This purification removed any inorganic components from the crude reaction mixture. However, the tin salts precipitated at the head of the column, which caused an increase in the column back-pressure and led to irreversible deterioration of the column performance. Therefore, we included a pre-purification step that involved passing a solution of the crude material through a column that contained a plug of octadecyl-functionalized silica gel to reduce the risk of damage to the columns.<sup>6</sup>

For these reasons, the search for alternative reduction methods that do not use metal salts is still required. One promising reducing agent is sodium dithionite (sodium hydrosulfite; sodium hypodisulfite;  $\text{Na}_2\text{S}_2\text{O}_4$ ).

Only a few examples of the use of sodium dithionite as a reducing agent for nitro derivatives on a solid support have been reported. In 1996, Hughes<sup>11</sup> reported using sodium dithionite in refluxing ethanol for the reduction of a nitrobenzyl group bound to a phosphonium-type polystyrene resin. Unfortunately, the author did not provide any experimental details, such as the ratio of nitro group: $\text{Na}_2\text{S}_2\text{O}_4$ , the conversion or the yield. In 2000, Scheuerman and Tumelty<sup>12</sup> published an account of the reduction of nitroarene acids immobilized on hydrophilic polyethylene glycol-based resins with an aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_4/\text{K}_2\text{CO}_3$ . Hydrophobic polystyrene resins do not swell in water, and the use of various organic co-solvents was also not successful. Thus, Rink resin-bound 4-nitrobenzoic acid was reduced using  $\text{Na}_2\text{S}_2\text{O}_4/\text{K}_2\text{CO}_3$  in a 9:1 mixture of DCM and water with an alkyl viologen (*N,N'*-dialkyl-4,4'-bipyridinium dihalogenide) as a single-electron phase-transfer catalyst (SET catalyst, ETC). In 2007, Zimmermann, Avemaria and Bräse<sup>13</sup> reported the reduction of nitroarenes linked via a triazine spacer to a resin using  $\text{Na}_2\text{S}_2\text{O}_4/\text{K}_2\text{CO}_3$  in a DMF–water (9:1) or THF–MeOH–water (5:1:1) mixture at 40°C for 2–5 days without any catalyst, which showed 29–87% conversion.

As previously mentioned, viologens were used as single-electron phase-transfer catalysts in this work.<sup>12,14</sup> We hypothesize that their catalytic effect is due to their phase-transfer ability. Thus, we focused on the examination of sodium dithionite as a mild and selective reducing agent for nitroarenes bound to hydrophobic polystyrene resins (Wang and Rink resins) under PTC conditions.

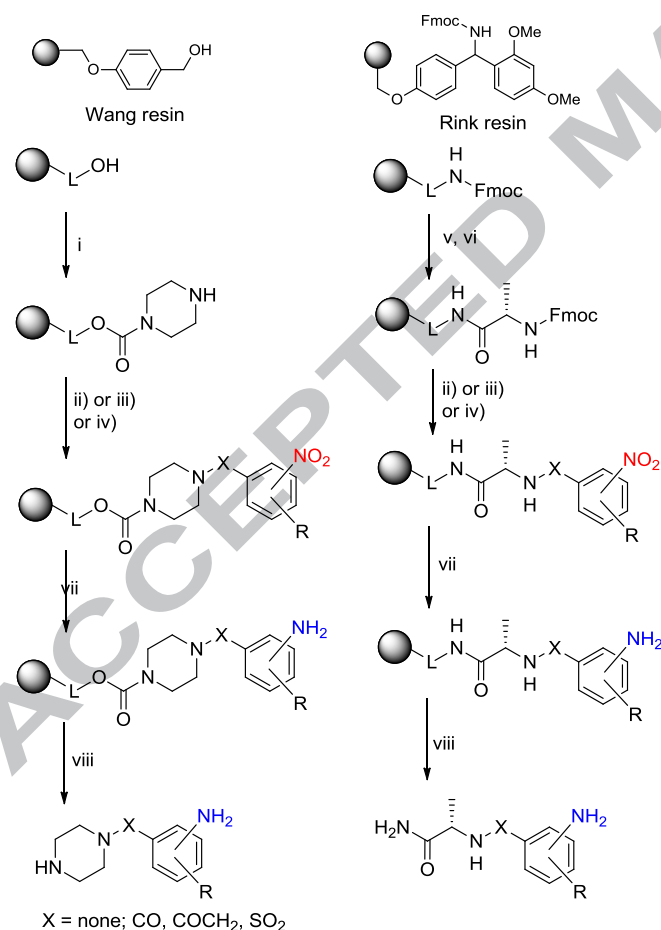
To find a suitable phase-transfer catalyst and solvent system, we first prepared a model nitroarene compound on Rink resin (Resin 1 in Scheme 1). In the initial screening, three commonly utilized phase-transfer catalysts were tested: tetrabutylammonium hydrogen sulfate (TBAHS), hexadecylpyridinium chloride (CPC) and hexadecyltrimethylammonium chloride (HTAC) in two solvent systems: DCM–water (1:1, v/v) and DMF–water (1:1, v/v) (Scheme 1). These solvent systems were chosen because hydrophobic polystyrene resins swell well in both DCM and DMF and because water is the best solvent for inorganic salts. Common phase-transfer catalysts are soluble in both water and organic solvents. The concentration of the phase-transfer catalyst was 10 mol% in all of the experiments. Our results demonstrated that only TBAHS was able to catalyze reductions in both solvent systems (reduction with complete conversion of the nitro group to an amino group as determined by LC-MS analysis of the reaction mixture after cleavage with 50% TFA in DCM). The reduction reaction failed if either CPC or HTAC was used.



Scheme 1. Optimization of the phase-transfer catalyst and solvent system

In the next phase of screening, the tolerance for several different functional groups and types of spacers between the resin and nitroarene in the developed reduction conditions, which involved  $\text{Na}_2\text{S}_2\text{O}_4/\text{K}_2\text{CO}_3/\text{TBAHS}$  in DCM–water, were investigated. Thus, we prepared a set of nitroarenes linked via piperazine spacers to Wang resin or via alanine spacers to Rink resin (Scheme 2). We used standard synthetic procedures, including the nucleophilic substitution of fluorine in fluoro-nitroarenes, acylation by substituted benzoic and phenylacetic acids and reaction with arylsulfonyl chlorides, to prepare these substrates (Scheme 2). The nitroarenes used as substrates contained both electron-donating and electron-withdrawing substituents (Table 1).

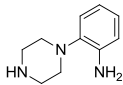
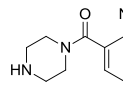
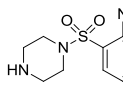
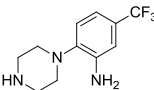
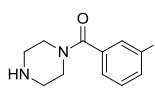
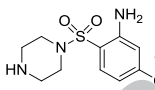
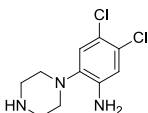
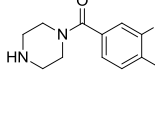
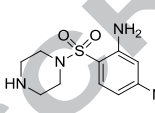
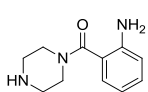
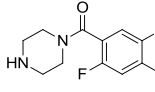
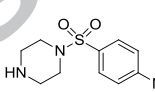
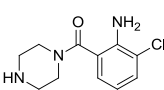
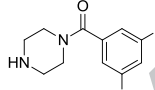
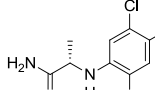
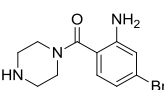
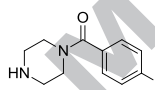
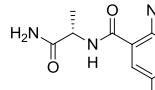
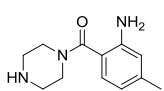
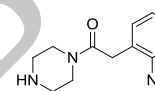
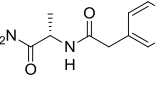
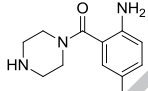
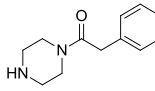
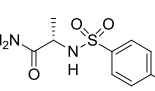
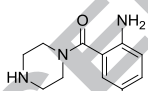
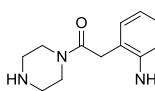
Reduction with sodium dithionite under phase-transfer catalysis conditions in DCM–water occurred with complete conversion of the nitro group to an amino group (Scheme 2). The structures of the amino products and their yields are summarized in Table 1. Calculated yields and structures consistent with the LC/MS and  $^1\text{H}$  NMR data obtained for the final amino derivatives in the unpurified product were determined via  $^1\text{H}$  NMR<sup>15</sup> after acidic cleavage and were typically 64–98%. In the case of dinitro derivatives (entries 14 and 18 in Table 1), no product was isolated after TFA cleavage, probably due to premature cyclative cleavage during reduction.<sup>5</sup> A typical procedure for the reduction is described in the Notes section.<sup>16</sup>



(i) 1. CDI, Py, r.t., 3 h; 2. Piperazine, DCM, r.t., on; (ii) Ar-F, DIEA, DMSO, 50°C, on; (iii) ArCOOH, HOBT, DIC, DCM-DMF, r.t., on; (iv) ArSO<sub>2</sub>Cl, Lutidine, DCM, r.t., 4 h; (v) Piperidine, DMF, r.t., 30 min; (vi) Fmoc-Ala-OH, HOBT, DIC, DCM-DMF, r.t., on; (vii)  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{K}_2\text{CO}_3$ , TBAHS,  $\text{H}_2\text{O}$ -DCM, r.t., 2 h; (viii) TFA-DCM (1:1), r.t., 1 h

Scheme 2. Synthesis of nitro derivatives bound to Wang resin (left) and Rink resin (right)

Table 1. Structures of amino derivatives<sup>a</sup> and yields<sup>b</sup> of reduction by Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> under PTC conditions

Entry	Amino derivative	Yield	Entry	Amino derivative	Yield	Entry	Amino derivative	Yield
1		87%	10		84%	19		70%
2		86%	11		79%	20		92%
3		75%	12		79%	21		68%
4		93%	13		94%	22		64%
5		81%	14		0%	23		91%
6		82%	15		84%	24		84%
7		98%	16		66%	25		92%
8		87%	17		89%	26		92%
9		75%	18		0%			

<sup>a</sup> Structure of the amino derivative after acidic cleavage from the resin<sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product after cleavage from the resin

In the last phase of screening, the reaction time was optimized. The reduction was stopped after 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h and 20 h. The results indicated that the reduction of nitroarenes is fast for nitroarenes that possess both electron-donating and electron-withdrawing groups. In Figure 1, the <sup>1</sup>H NMR spectra of the aromatic region of three differently substituted substrates after reduction for different times are shown (i.e., after subsequent cleavage with 50% TFA in DCM for 1 h; the spectra and structure of the corresponding nitro compounds are shown at the bottom). These spectra clearly demonstrate that the reduction is complete within 30 minutes and that a prolonged reaction time did not result in deterioration of the products.

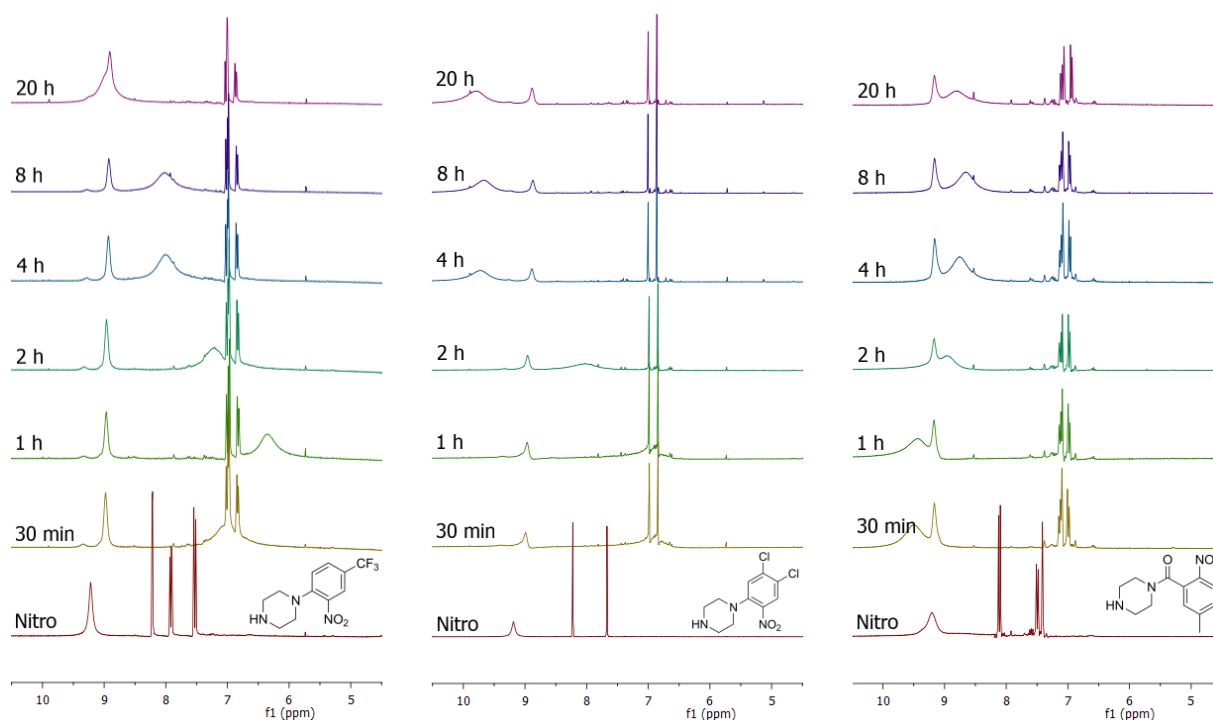


Figure 1. Optimization of reaction time (NMR of the aromatic moiety after reduction)

In summary, we have demonstrated that  $\text{Na}_2\text{S}_2\text{O}_4/\text{K}_2\text{CO}_3/\text{TBAHS}$  in DCM–water is an efficient system for the reduction of nitroarenes bound to hydrophobic polystyrene resins. This method allows for the fast reduction of nitro groups to amino groups with complete conversion under mild conditions and tolerates other functional groups and spacers.

### Acknowledgements

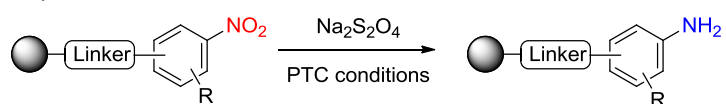
This research was supported by the Department of Chemistry and Biochemistry, University of Notre Dame, by projects P207/12/0473 from GACR and CZ.1.07/2.3.00/20.0009 from the European Social Fund.

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16. Typical procedure for reduction: Resin-bound nitroarene (500 mg; loading  $\approx$  0.5 mmol/g) was swollen in DCM. Then, a solution of sodium dithionite (1050 mg, 5 mmol), potassium carbonate (968 mg, 7 mmol) and TBAHS (170 mg, 0.5 mmol) in water (5 mL) and DCM (5 mL) was added, and the reaction slurry was shaken at room temperature for 2 h. Then, the resin was washed three times with each solvent: DCM-water (1:1, v/v), DMF, MeOH and DCM.

## Graphical abstract



Hydrophobic polystyrene-based resin