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A New Method for the Mild and Selective Reduction of Aryl Nitro Groups on Solid Support

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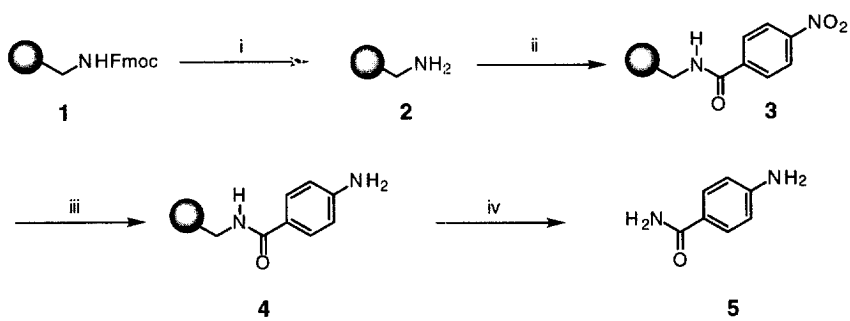
Abstract: An efficient method for the solid-phase reduction of aryl nitro groups to anilines is described. Among the several reagents tried, chromium chloride was found to be most effective for this reaction. For the substrates examined, reduction occurs in high yield regardless of the substitution pattern on the aromatic ring, and without affecting other reducible functionality.

Combinatorial methods for the generation of compound libraries have recently received tremendous attention, particularly as a means of accelerating the drug discovery process.[1] Since many combinatorial libraries are generated on solid support, adapting standard synthetic transformations to the solid phase is an essential part of increasing the range of compounds which are accessible by this technique. In this connection, significant progress has been made in the development of solid phase methodologies.

The reduction of nitro compounds to amines is a very useful synthetic transformation, for which a vast array of reagents are known in the solution phase. However, relatively few reagents are known for this synthetically and industrially important reaction on a solid support. This is primarily due to the fact that the majority of solution-phase methods for the conversion of nitroaromatic compounds to anilines require heterogeneous conditions. Nonetheless, several reports of solid-phase reduction of nitroarenes have appeared, including the use of stannous chloride,[2-7] sodium dithionite in ethanol under refluxing conditions,[8] and, under certain conditions, $NaBH_4$-$Cu(acac)_2$.[9] In our own hands, we found sodium dithionite and $NaBH_4$-$Cu(acac)_2$ to have a limited range of substrate suitability, and yields for the stannous chloride procedure to be moderate (70%-79%). Therefore, we set out to identify other reagents that might be widely useful for this transformation. After examining a wide range of reagents and conditions, we found chromium chloride ($CrCl_2$) in dimethylformamide (DMF) to be the most efficient reduction system.



Conditions: i) 20% piperidine – DMF; ii) 4-nitrobenzoic acid (2 eq.), DCC (2 eq.), HOBt (2 eq.) Et_3N (2.2 eq.); iii) $CrCl_2$ (16 eq.) in DMF, 12 hours, r.t.; iv) TFA:CH_2Cl_2 (95:5)

Scheme 1

PII: S0040-4039(98)02330-2

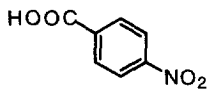
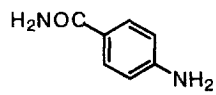
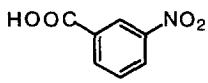
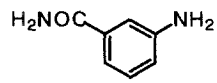
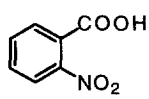
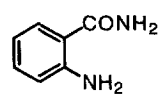
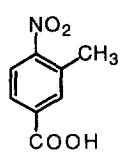
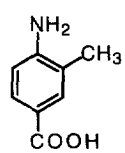
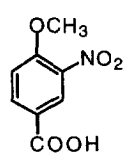
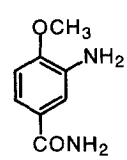
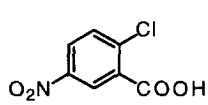
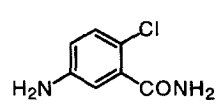
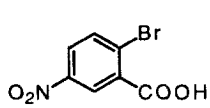
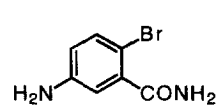
A typical procedure is outlined in Scheme I. Treatment of Rink amide resin (Nova Biochem) with 20% piperidine in dimethylformamide (DMF) solution allowed for removal of the 9-fluorenylmethyloxycarbonyl (Fmoc) group. Coupling of the nitrobenzoic acid was carried out under standard conditions (2 eq. of the acid in the presence of DCC, HOBt, Et_3N in DMF). Reaction completion was monitored by ninhydrin test. The reduction of the nitro group was successfully achieved by treating the resin with $CrCl_2$ in DMF. The product was cleaved from the solid support using TFA - methylene chloride (95:5) to afford 4-amino benzamide **5** as its trifluoroacetate salt. Confirmation of the success of the reaction was obtained by analysis of the product by IR, NMR, and comparison with an authentic sample. While a number of reduction conditions were evaluated, optimal results were obtained by treating the resin with 16 eq. of $CrCl_2$ in DMF with mechanical agitation at room temperature overnight. This provided **5** in an overall isolated yield of 97%, based on the original loading of the Rink amide resin.

Reduction conditions developed for 4-nitrobenzoic acid on resin were found to be suitable for a wide range of substituted nitrobenzoic acids (Table 1). All reductions were carried out under analogous conditions to those described in the experimental section, and gave products which exhibited satisfactory spectroscopic data. Under the conditions used, other potentially reducible groups such as halides are unaffected (entries 6 and 7). Furthermore, we found that the yields of the substituted anilines are not affected by the nature or the position of the aromatic substituents on corresponding nitrobenzoic acids. An additional advantage of this reagent over stannous chloride as a reducing agent is that the reaction proceeds at room temperature; literature reports suggest that $SnCl_2$-mediated reduction only occurs at elevated temperatures.[3] This suggests that the $CrCl_2$-DMF system is optimal for the solid-phase reduction of aromatic nitro groups. Of course, the requirement for such a large excess of chromium chloride is less than ideal, both from a reagent cost and environmental standpoint; therefore, we are currently exploring the potential for carrying out this reaction in a *catalytic* manner, by analogy to other chromium-mediated reactions that have been rendered catalytic.[10, 11]

EXPERIMENTAL

The preparation of *p*-amino benzamide (Table 1, entry 1) is illustrative. Rink amide resin (50 mg, 0.033 mmol), previously swollen in DMF for 15 minutes, was deprotected by two successive 1h treatments with 20% piperidine in DMF solution. After draining the solvent, the resin was thoroughly washed with DMF, followed by CH_2Cl_2, and followed again by DMF. To the deprotected resin, DCC (13.6 mg, 2 eq.) HOBt (8.9 mg, 2 eq.), and Et_3N (9.2 µl, 2.2 eq.) were added in DMF and shaken (Burrell wrist-action shaker) for 15 min. Next, *p*-nitrobenzoic acid (11 mg, 2 eq.) was added and shaken overnight to afford resin **3**. After washing the resin as descibed above, chromium chloride (65 mg, 16 eq.) was added to resin **3** suspended in DMF. The reaction mixture was shaken overnight. The resin was then successively washed with DMF, MeOH, and CH_2Cl_2 in order to remove residual chromium chloride. Cleavage of the support-bound amine **4** from the resin was accomplished by treatment with TFA / CH_2Cl_2 (95:5) for 1h. The solvent was collected, and the resin was washed with CH_2Cl_2. The combined organic layers were then collected and evaporated to give the desired compound **5** as its trifluoroacetate salt (8.0 mg, 97%).

Table 1: Reduction of Nitroarenes to Anilines on Rink Amide Resin

Entry	Substrate	Product	Yield [a]
1.			97%
2.			90%
3.			92%
4.			96%
5.			93%
6.			91%
7.			90%

[a] Yields based on the original loading of the Rink Amide resin, and reflect isolation of the product as a trifluoroacetate salt.

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