Deprotection of *o*-Nitrobenzensulfonyl (Nosyl) Derivatives of Amines Mediated by a Solid-Supported Thiol

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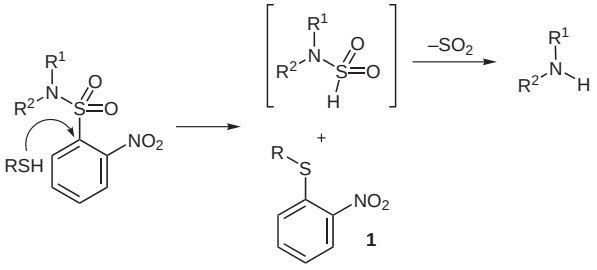
Abstract: A new protocol based on a solid-supported thiol was developed for high yielding deprotection of *o*-nitrobenzensulfonyl amides derived from primary and secondary amines. The reaction can be carried out at room temperature for 24 hours or accelerated by microwave irradiation, going to completion in six minutes.

Key words: solid-supported reagents, amines, protecting groups, microwaves

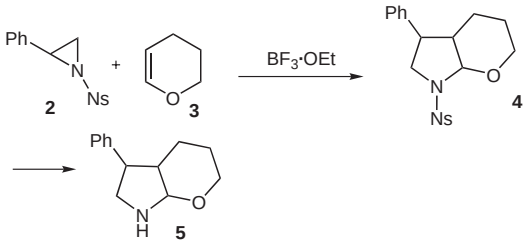
The use of polymer-supported reagents and scavengers is a powerful technique for expedited synthesis and purification.[1] With the use of polymer-supported reagents and scavengers it is possible to selectively carry out organic transformations removing the excess of the reagents and by-products by simple filtration rather than liquid–liquid extraction and chromatographic purification.[2] In addition, polymer-supported reagents offer further advantages that include selectivity, reaction of active intermediates by 'catch-and-release' and immobilization of toxic intermediates. In order to broaden the range of reactions capable of being carried out using such polymer-assisted techniques, new polymer-supported reagents are continually being developed.[3]

On the other hand, there are few examples of the use of solid-supported reagents for deprotection reactions[4] although deprotection is often the last step of a synthesis and the product must be obtained pure in high yields. The nosyl (*o*-nitrobenzensulphonyl) group has been largely employed for the protection of amines as it is orthogonal with respect to popular Boc and Cbz protections.[5] It can be removed in the presence of a strong nucleophilic agent as a nucleophilic aromatic substitution at the aromatic ring occurs with contemporary loss of SO_2 and generation of the free amine (Scheme 1).[6] Thiols are the most largely employed nucleophiles with formation of an aromatic sulfide (**1** in Scheme 1) that must be separated from the amine.[7]

During the development of a project for the preparation of kainic acid analogues, we came across the problem of deprotection of product **4** prepared following a published procedure from nosyl-aziridine **2** and DHP **3** (Scheme 2).[8]



Scheme 1



Scheme 2

With the aim of obtaining **5** under conditions compatible with parallel synthesis, we decided to investigate the possibility to use a thiol linked to an insoluble support to remove the sulphonamide. Thus, we prepared the *o*-nitrobenzensulfonamide of *N*-methylbenzylamine (**7**) as a model compound to find the best reaction conditions. At first, we used the mercaptomethyl-PS-DVB resin (**9**) and the PS-DVB supported thiophenol (**10**) as deprotection agents.[9] The reactions were carried out in DMF in the presence of the resin and a base that would generate the more nucleophilic thiolate ion. As reported in Table 1, Cs_2CO_3 gave better results than stronger bases such as NaH or LiHMDS. Moreover, the thiophenol-based resin resulted much superior to the other as, using **10**, the complete conversion of **7** into **8** was achieved in 24 hours at room temperature.

As the use of DMF as the solvent could be troublesome when volatile or highly polar amines are required, we started to explore different solvents and we were very pleased to find that the reaction worked well in THF and Cs_2CO_3 at room temperature for 24 hours.

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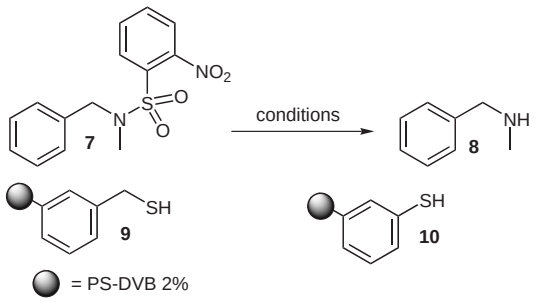
Table 1 Optimization of the Deprotection Procedure



Resin	Conditions	Yield of **8** (%)[a]
9	NaH, DMF, r.t., 24 h	35
9	Cs_2CO_3, DMF, r.t., 24 h	40
9	Cs_2CO_3, THF, r.t., 24 h	38
10	NaH, DMF, r.t., 24 h	49
10	Cs_2CO_3, DMF, r.t., 24 h	96
10	LiHMDS, THF, r.t., 24 h	37
10	Cs_2CO_3, DMF, MW, 120 °C, 250 psi, 6 min	72
10	Cs_2CO_3, THF, r.t., 24 h	96
10	Cs_2CO_3, THF, MW, 80 °C, 250 psi, 6 min	95

[a] Amounts of compound **8** present in the reaction determined by HPLC-MS (total ion current) in the crude reaction mixture.

A second addition of one equivalent of the resin with respect to the substrate was required to obtain a complete conversion of the sulfonamide into the amine. The same result was not achieved using 2 equivalents of resin just from the beginning. Moreover, the high yields reported in Table 1 were obtained treating the commercial resin with a solution of PPh_3 in deoxygenated THF in order to reduce possible disulfides formed by air oxidation of the resin during storage. A possible alternative was to use a supported thiophenol protected as trytil.[10] In this case the resin was deprotected with 1% TFA in CH_2Cl_2 just before the use giving excellent results.

The deprotection process can be accelerated by microwave irradiation. Three cycles of one minute each at 120 °C in a sealed tube (monomode irradiation) in DMF gave complete conversion of **7** into **8**. Unfortunately, the GCMS analysis of the crude showed the presence of a by-product, probably originated from degradation of the resin in DMF at high temperature. However, the use of THF at lower temperature (80 °C for 6 cycles of 1 min each, sealed tube, internal pressure 250 psi) allowed the isolation of compound **8** in high yield and purity without the presence of resin degradation by-products. In order to get complete conversion, a second addition of resin was needed after the first three cycles of microwave irradiation.

This method was successfully applied to deprotection of several primary and secondary nosyl derivatives giving the corresponding amines reported in Figure 1 in very good yields just after filtration and evaporation of the solvent. In most of the cases investigated, the ^1H NMR of the crude showed exclusively the peaks attributed to the desired amine. In the case of compounds **15**, **16** and **20** an additional purification by selective SCX extraction was needed to obtain purity higher than 95%.

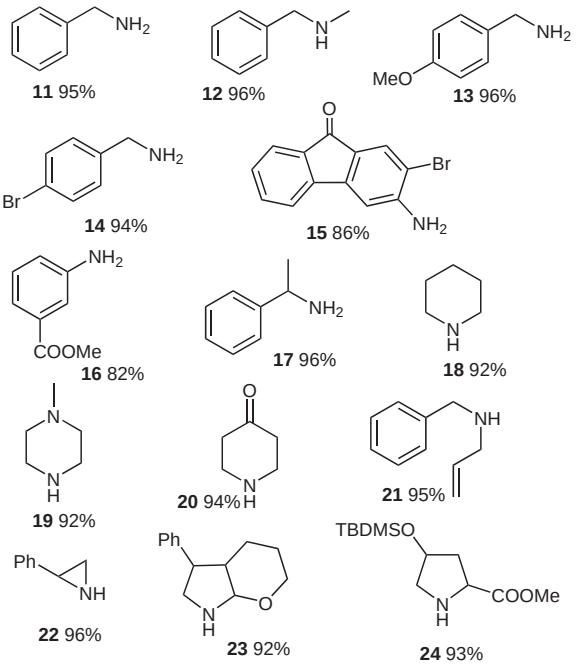


Figure 1 Amines obtained by deprotection of the corresponding nosyl derivatives

In conclusion, we have described a new rapid protocol for deprotection of secondary and tertiary nosylamides using a supported reagent. The reaction can be also accelerated by microwave irradiation. The application of this methodology to the synthesis of arrays of biologically relevent molecules will be reported elsewhere.

Deprotection of *N*-Methyl-*N*-benzyl-*o*-nitrobenzensulfonamide (7) – General Procedure

Sulfonamide **7** (0.306 g, 1 mmol) was dissolved into 2 mL of dry THF and to this solution Cs_2CO_3 (1.025 g, 3.25 mmol) was added followed by PS-thiophenol (0.56 g of a resin with 2 mmol/g of loading, 1.12 mmol). This amount of resin was previously treated by shaking for 30 min in a sealed vial with 2 mL of a 0.7 M solution of PPh_3 in dry deoxygenated THF. The resin was filtered on a sintered glass, washed with dry THF and used immediately without drying. The mixture was shaken in a sealed vial at r.t. for 8 h. Additional PS-thiophenol was added (0.56 g, 1.12 mmol) and the mixture was shaken again for 16 h. The content of the vial was filtered, the solid washed several times with THF and CH_2Cl_2. The solvent was evaporated and product **8** was isolated in 96% yield (0.116 g). The identity and the purity of the product was determined by comparison with an authentic sample.

Microwave-Assisted Procedure

Sulfonamide **7** (0.306 g, 1 mmol) was dissolved into 2 mL of dry THF and to this solution Cs_2CO_3 (1.025 g, 3.25 mmol) was added followed by PS-thiophenol (0.56 g of a resin with 2 mmol/g of loading, 1.12 mmol) treated as reported above. The vial was sealed and inserted in the cavity of a Discover system (from CEM). The mixture was irradiated for 3 cycles of 1 min at 80 °C and 250 psi internal pressure. After cooling, the vial was opened, additional resin was added (0.56 g), the vial was closed and then submitted to 3 additional cycles of 1 min each at 80 °C and 250 psi internal pressure. After cooling, the vial was opened, the contents were filtered, and the solid was washed with THF and CH_2Cl_2. The solvent was collected and evaporated to give compound **8** in 95% yield (0.114 g).

The identity and the purity of all the amines described in Figure 1 were determined by comparison of their ^{1}H NMR and MS spectra with authentic samples.

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