2-Nitro- and 2,4-Dinitrobenzenesulfonamides as Protecting Groups for Primary Amines

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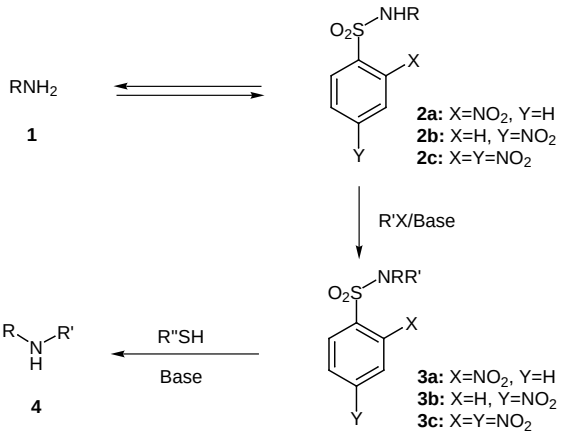
Abstract: Procedures for the deprotection of the 2-nitro- and 2,4-dinitrobenzenesulfonamides to give the corresponding primary amines were developed. The 2-Nitrobenzenesulfonyl group was effectively removed by $HSCH_2CH_2OH$/DBU or PhSH/Cs_2CO_3 in DMF under mild conditions to give the corresponding primary amines in high to excellent yield. For removal of the 2,4-dinitrobenzenesulfonyl group, the use of thiol alone ($HSCH_2CH_2OH$ or PhSH) was quite effective. Selective deprotection of 2,4-dinitrobenzenesulfonamide in the presence of 2-nitrobenzenesulfonamide has also been achieved.

Key words: 2-nitrobenzenesulfonamide, 2,4-dinitrobenzenesulfonamide, protecting groups, deprotection, primary amines

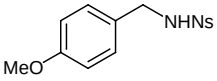
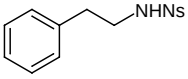
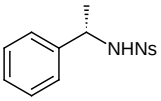
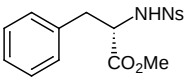
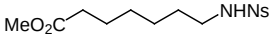
2- and 4-Nitrobenzenesulfonamides, **2a** and **2b**, are unique among the amino protective groups. They are readily prepared from primary amines **1**, then easily *N*-alkylated to give *N*,*N*-disubstituted sulfonamides **3a**,**b**, with subsequent removal of the arylsulfonyl groups to afford secondary amines **4**. Accordingly, since introduced by Fukuyama et al.,[1] these protecting/activating groups have been widely used for the preparation of secondary amines both in solution- and solid-phase syntheses.[2,3] 2,4-Dinitrobenzenesulfonamides **3c** can be utilized in the same manner and, in addition, it is selectively deprotected in the presence of 2-nitrobenzenesulfonamides **3a**, leading to a wide variety of diamines with the combined use of these groups.[4] Direct transformation of **2c** to amides, ureas, thioamides, and thioureas through a deprotection/functionalization sequence has also been reported.[5] However, simple deprotection of **2** to reproduce the corresponding primary amines **1** has not been fully investigated; thus, deprotection of 2-nitrobenzenesulfonamide **2a** resulted in low yield[6] or should be carried out indirectly through further protection with urethane groups.[7] Only a few such successful results have been reported.[8] In fact, we have encountered difficulty during our studies on the synthesis of acylpolyamine spider toxins, which prompted us to investigate the deprotection of **2** to **1**. We report herein the procedures for the deprotection of 2-nitro- and 2,4-dinitrobenzenesulfonamides, **2a** and **2c**, to directly give the corresponding primary amines **1**. Selective deprotection of 2,4-dinitrobenzeneulfonamide in the presence of 2-nitrobenzenesulfonamide on diamine is also described.



Scheme 1

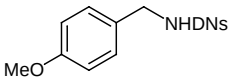
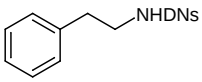
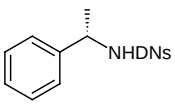
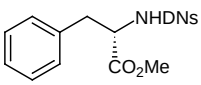
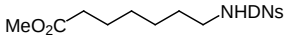
A variety of conditions for removing the 2-nitrobenzenesulfonyl (Ns) group from 2-nitrobenzenesulfonamide **2a** were examined using 4-methoxybenzylamine as a model substrate (Entry 1 in Table 1). Consequently, we found that the use of $HSCH_2CH_2OH$/DBU (Method A) and PhSH/Cs_2CO_3 (Method B) in DMF were the most effective, giving the primary amine in 86% and 88% yield, respectively, at 0 °C-room temperature for 30 min. Table 1 summarizes the results of a variety of substrates. In Method A, DBU can be replaced by Cs_2CO_3 and, in Method B, Cs_2CO_3 can be replaced by DBU; thus, any combination of $HSCH_2CH_2OH$ or PhSH as a thiol with DBU or Cs_2CO_3 as a base may essentially give the same results. Furthermore, when using PhSH/DBU, acetonitrile (MeCN) can be used as the solvent instead of DMF. Under the conditions of Methods A and B, no racemization took place when applied to the optically active α-branched amines (Entries 3 and 4). Fukuyama's standard procedures using PhSH/K_2CO_3/DMF and $HSCH_2CO_2H$/LiOH for secondary sulfonamides were sluggish and did not go to completion. The conditions similar to Method A have been successfully used for the deprotection of secondary 2-nitrobenzensulfonamides in the solid-phase.[2c,h] Accordingly, the conditions employing $HSCH_2CH_2OH$/DBU/DMF may be the most widely used and the method of choice for any situation, primary or secondary sulfonamide and solution- or solid-phase synthesis.

Table 1 Deprotection of the 2-nitirobenzenesulfonamides

Entry	Sulfonamide	Method A[a] (% isolated yield)	Method B[b] (% isolated yield)
1		86	88
2		95	96
3		87[c]	91[c]
4		91[c,d]	81[c,d]
5		85[d]	86[d]

[a] $HSCH_2CH_2OH$ (2.0 eq), DBU (1.5 eq), DMF, 0 ºC - rt, 30 min.
[b] PhSH (2.0 eq), Cs_2CO_3 (1.2 eq), DMF, 0 ºC - rt, 30 min.
[c] The enantiopurity was confirmed by ^1H NMR analysis of its MTPA amide.
[d] Isolated as the HCl salt.

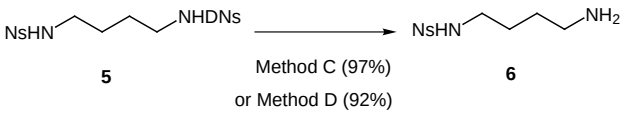
Table 2 Deprotection of the 2,4-dinitirobenzenesulfonamides

Entry	Sulfonamide	Method C[a] (% isolated yield)	Method D[b] (% isolated yield)
1		98	91
2		92	94
3		85[c]	83[c]
4		88[c,d]	96[c,d]
5		83[d]	98[d]

[a] $HSCH_2CH_2OH$ (2.0 eq), DMF, rt, 1 h.
[b] PhSH (2.0 eq), DMF, rt, 15 min.
[c] The enantiopurity was confirmed by ^1H NMR analysis of its MTPA amide.
[d] Isolated as the HCl salt.

For removal of the 2,4-dinitrobenzenesulfonyl (DNs) group from **2c**, the use of the thiol alone ($HSCH_2CH_2OH$ or PhSH) was quite effective. Table 1 summarizes the results of a variety of 2,4-dinitrobenzensulfonamides. The reaction smoothly proceeded with 2 equiv of $HSCH_2CH_2OH$ (Method C) or PhSH (Method D) in DMF and went to completion within 1 h or 15 min, respectively, with excellent yields. For Method C, no other solvent is compatible, but various solvents (CH_2Cl_2, THF, MeCN and MeOH) can be used as well as DMF for Method D. Under these conditions, no racemization occurred as shown in Entries 3 and 4. In all cases, Fukuyama's original procedures for the secondary sulfonamides using *n*-$PrNH_2$ or $HSCH_2CO_2H/Et_3N$ gave only a poor yield or a complex mixture. Employing *i*-$PrNH_2$ or NH_3 aq. instead of *n*-$PrNH_2$ did not improve the results, nor any conditions with the combined use of thiol ($HSCH_2CO_2H$, $HSCH_2CH_2OH$, PhSH) and base ($NaHCO_3$, pyridine, Et_3N, imidazole). Consequently, the procedures for deprotecting primary 2,4-dinitrobenzenesulfonamides are distinct from those of secondary 2,4-dinitrobenzenesulfonamides.

For the secondary sulfonamides, the DNs group is preferentially removed in the presence of the Ns group as Fukuyama et al. reported.[4a] A similar transformation was realized for the primary sulfonamides as well. When the disulfonamide **5**, prepared from mono-nosylated putrescine **6**[2h] in high yield, was subjected to the conditions for deprotecting the DNs group (Methods C and D), the primary amine **5** was obtained in 97% and 92% yields, respectively, without affecting the Ns group at all (Scheme 2).



Scheme 2

In this study, we found the conditions for the deprotection of the 2-nitro- and 2,4-dinitrobenzenesulfonamides to reproduce primary amines, demonstrating that these groups are useful protective groups for primary amines as well as secondary amines and, therefore, the scope of these protective groups will become much wider and more useful. Moreover, the 2,4-dinitrobenzenesulfonyl group is preferentially deprotected in the presence of the 2-nitrobenzenesulfonyl group, which would also be useful for the synthesis of a variety of polyamine compounds.

Representative experimental procedures

Method A: To a stirred solution of *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (258 mg, 0.80 mmol) in DMF (3 mL), $HSCH_2CH_2OH$ (125 mg, 1.60 mmol, 2 equiv) and DBU (182 mg, 1.20 mmol, 1.5 equiv) were slowly added at 0 °C. After stirring 30 min at room temperature, the reaction mixture was directly chromatographed on silica gel (8% MeOH-$CHCl_3$ and then 1: 3: 36 *i*-$PrNH_2$-MeOH-$CHCl_3$) to give 4-methoxybenzylamine (94 mg, 86%) as a colorless oil.

Method B: To a stirred solution *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (258 mg, 0.80 mmol) in DMF (3 mL), PhSH (176 mg, 1.60 mmol, 2 equiv) and Cs_2CO_3 (313 mg, 0.96 mmol, 1.2 equiv) were slowly added at 0 °C. After stirring for 0.5 h at room temperature, the reaction mixture was directly chromatographed on silica gel (8% MeOH-$CHCl_3$ and then 1: 3: 36 *i*-$PrNH_2$-MeOH-$CHCl_3$) to give 4-methoxybenzylamine (96 mg, 88%) as a colorless oil.

Method C: To a stirred solution of *N*-(4-methoxybenzyl)-2,4-dinitrobenzenesulfonamide (294 mg, 0.80 mmol) in DMF (2 mL), $HSCH_2CH_2OH$ (125 mg, 1.60 mmol, 2 equiv) was added. After stirring 1 h at room temperature, the reaction mixture was directly chromatographed on silica gel (8% MeOH-$CHCl_3$ and then 1: 3: 36 *i*-$PrNH_2$-MeOH-$CHCl_3$) to give 4-methoxybenzylamine (107 mg, 98%) as a colorless oil.

Method D: To a stirred solution of *N*-(4-methoxybenzyl)-2,4-dinitrobenzenesulfonamide (294 mg, 0.80 mmol) in DMF (2 mL), PhSH (176 mg, 1.60 mmol, 2 equiv) was added. After stirring 15 min at room temperature, the reaction mixture was directly chromatographed on silica gel (8% MeOH-$CHCl_3$ and then 1: 3: 36 *i*-$PrNH_2$-MeOH-$CHCl_3$) to give 4-methoxybenzylamine (100 mg, 91%) as a colorless oil.

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