Protecting Groups

ortho-Anisylsulfonyl as a Protecting Group for Secondary Amines: Mild Ni^0-Catalyzed Hydrodesulfonylation

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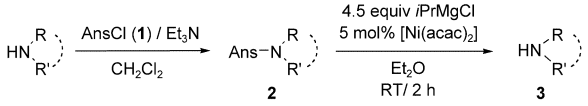
In the current armamentarium of amine-protecting groups,[1] aryl sulfonamides occupy an ambivalent position of facile formation and ease of handling but extreme robust character, undergoing cleavage only under harsh reductive (e.g. sodium naphthalenide)[1a,2] or acidic (e.g. 48% HBr/cat. phenol)[3] conditions.[4] The *p*-toluenesulfonyl (Ts) and, to a lesser extent, the benzenesulfonyl groups are central in synthetic practice, not only as protecting groups for amines, but also as part of reagents and in derivatization procedures.[5] The Achilles heel position of the Ts group can be seen in the difficult deprotection measures in multifunctional organic molecules[6] and/or lack of further manipulation of the obtained NTs derivatives.[7] A second long-standing feature of the NTs function is its enabling use as a method for the synthesis of pure secondary amines,[8] which, although advanced by the development of Mitsunobu alkylation conditions,[9] suffers from the harsh cleavage conditions. Thus, the Fukuyama method[10] has been a welcome addition to the arsenal of amine-deprotection protocols.

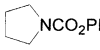
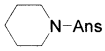
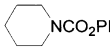
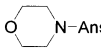
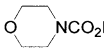
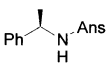
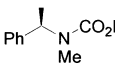
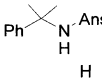
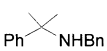
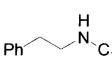
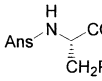
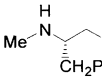
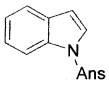
As a logical sequel to the finding of hydrodesulfamoylation and cross-coupling reaction of aromatic sulfonamides,[11] we report herein that the readily appended *ortho*-anisylsulfonyl (Ans = 2-MeO-$C_6H_4SO_2$-) group is cleanly detached from secondary amines by using the β-hydride transfer conditions of the standard Corriu–Kumada–Tamao cross-coupling procedure (Ni^0, *i*PrMgCl, Et_2O, room temperature).[12]

Thus, use of the Ni^0-catalyzed reductive cross-coupling protocol[11] results in the smooth and rapid deprotection of *N*-Ans acyclic and cyclic amines, chiral amines and amino alcohols, anilines, pyrrole, indole, and aziridines (Table 1). Furthermore, stepwise alkylation of *N*-Ans primary amines followed by cleavage allows the synthesis of unsymmetrical secondary amines. Taken together, this new methodology promises generality and provides a significant alternative to the established *N*-Ts and *N*-benzenesulfonamide protection tactics.

An array of diverse amines were derivatized with the readily prepared *ortho*-anisylsulfonyl chloride (AnsCl; **1**) and subjected to deprotection in the presence of excess *i*PrMgCl (commercially available as a solution in Et_2O), [Ni(acac)$_2$] (5 mol%), in diethyl ether at room temperature (Table 1).[13]

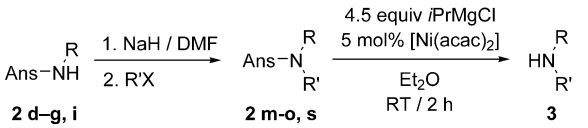
Table 1: Protection and deprotection of *N*-Ans amines



Entry	Protection		Yield [%][a]	Deprotection		Yield [%]
1		**2a**	72		**3a**	68[e]
2		**2b**	82		**3b**	73[e]
3		**2c**	76		**3c**	69[e]
4		**2d**	81		**3d**	92[e,f]
5		**2e**	66		**3e**	78
6		**2f**	87		**3f**	88[e]
7		**2g**	74		**3g**	74[e]
8		**2h**	81[b]		**3h**	89[f]
9		**2i**	97[c]		**3i**	95
10		**2j**	85[c]		**3j**	82
11		**2k**	65[d]		**3k**	82[g]
12		**2l**	77[d]		**3l**	77

[a] Conditions: Et_3N/CH_2Cl_2 unless otherwise indicated. [b] Conditions: **2g**/DIBAL/CH_2Cl_2; TsCl, aq KOH/THF/reflux. [c] Conditions: DMAP/Pyridine. [d] Conditions: 1. *n*BuLi/ −78 °C; 2. AnsCl. [e] Compound isolated as carbamate for ease of purification or due to volatile nature of amine. [f] Amines were converted into their *N*-acetyl derivatives for HPLC analysis (Chiracel OD column (hexane/*i*PrOH). [g] Yield by GC analysis. DIBAL = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine.

Aliphatic and aromatic primary *N*-Ans amines **2d–g,i** were readily alkylated to form **2m–o,qs** (Scheme 1) and cleaved to provide unsymmetrical secondary amines **3d–g,i** (Table 1, entries 4–10). The application of the *N*-cumylsulfonamide[14] allows, after decumylation, the synthesis of primary amines (Table 1, entry 5). No decrease in optical activity was observed for chiral substrates (Table 1, entries 4 and 7). Although α-amino esters, as expected, do not tolerate the reaction conditions, a corresponding reduced and *O*-benzylated amino alcohol is readily deanisylated in high yield (Table 1, entry 7). The cleavage of the *N*-Ans aziridine



Scheme 1. Alkylation and hydrodesulfonylation of *N*-Ans amines. DMF = *N*,*N*-dimethylformamide, acac = acetoacetonate.

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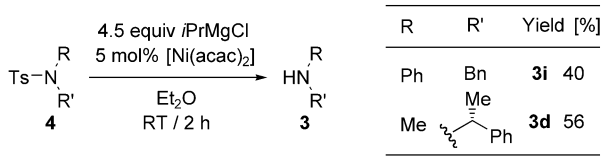
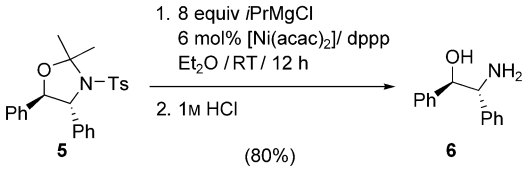
(Table 1, entry 8) also proved unexceptional. *N*-Ans-pyrrole and indole[15] are smoothly deprotected. However, *N*-Ans-allyl amines are not compatible with the hydrodesulfonylation conditions and give products of deallylation.[16]

The poor reaction of *N*-Ts amines **4** has thus far precluded its deprotection under Ni^0-catalyzed conditions (Scheme 2).[17] However, the widespread use of the Ts protecting group makes the development of a Ni^0-catayzed deprotection protocol a priority. To this end, preliminary experiments with oxazolidine **5** indicate that Ni–phosphane catalysts, extended reaction times (12–18 h), and the use of a large excess of the Grignard reagent result in increased yields of the product of *N*-Ts cleavage.[18]





Scheme 2. Ni^0-catalyzed hydrodesulfonylation of *N*-Ts amines. dppp = propane-l,3-diylbis(diphenylphosphane)

To conclude, the *N*-Ans group constitutes a new amine-protecting group that overcomes the necessity for harsh cleavage conditions normally demanded by the *N*-Ts and related sulfonamides.[1] Furthermore, its value for the synthesis of unsymmetrical secondary amines and primary amines has been demonstrated. Although the scope and limitations of the new methodology, and hence its potential complementarity to the Fukuyama[4a,b,10] and Gabriel[19] syntheses of primary amines, remains to be established, it allows a significant departure from the classical *N*-Ts deprotection modes.[20] The combined advantages of convenient derivatization with mild and rapid deprotection bodes well for its broader application in organic synthesis.

Experimental Section

2-Methoxybenzenesulfonyl chloride (**1**):[20] *n*BuLi (35.4 mL, 2.85 M, 101 mmol) was added to a solution of TMEDA (15.2 mL, 101 mmol) in Et_2O (200 mL) at 0 °C, and the reaction mixture was stirred for 5 min. Anisole (10 mL, 92 mmol) was added and the mixture was stirred for 1 h, cooled to −78 °C, treated with SO_2 (g) passed through a syringe for 30 min, and allowed to warm to room temperature over 1 h. SO_2Cl_2 (8.8 mL 110 mmol) was added, and the mixture was stirred at room temperature for 6 h. The mixture was partitioned between Et_2O and H_2O, the organic layer was separated, washed with brine, and dried (Na_2SO_4), and the solvent was removed in vacuo to give AnsCl (10.1 g, 81 %). M.p. 53–54 °C (hexanes) [Lit.[21] m.p. 56 °C]; ^{1}H NMR (300 MHz): $\delta = 7.95$ (dd, 1 H, $J = 8.0$, 1.7 Hz), 7.70(ddd, 1 H, $J = 8.5$, 7.5, 1.7 Hz), 7.13 (t, 1 H, $J = 8.3$ Hz), 7.09 (d, 1 H, $J = 7.5$ Hz), 4.06 ppm (s, 3 H); ^{13}C NMR (75.5 MHz): $\delta = 157.3$, 137.3, 131.7, 129.7, 120.2, 113.2, 56.6 ppm; LRMS (EI): *m*/*z* (%): 205 [M^+] (1), 163 (10), 83 (58), 81 (39), 67 (16), 55 (100).

N-Benzylphenylamine (**3i**): A solution of *i*PrMgCl (6.34 mL, 2.13 M in Et_2O, 13.5 mmol) was added to a solution of **2s** (1.06 g, 3.0 mmol) and [Ni(acac)$_2$] (39.0 mg, 0.15 mmol) in Et_2O (80 mL), and the reaction mixture stirred at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted twice with EtOAc. The organic layer was washed three times with saturated NH_4Cl solution, once with H_2O, and once with brine. The solution was dried (Na_2SO_4), and the solvent was removed in vacuo to give **3i** (395 mg, 95 %) as a colorless solid after chromatography (20:1 hexane/EtOAc). M.p. 35.5–37.8 °C (Lit.[21]); ^{1}H NMR (300 MHz): $\delta = 7.38$–7.13 (m, 7 H), 6.78–6.50 (m, 3 H), 4.87 ppm (br s, 1 H), 4.26 (s, 2 H); ^{13}C NMR (50.3 MHz): $\delta = 148.1$, 139.4, 129.2, 128.5, 127.4, 127.1, 117.5, 112.8, 48.2.

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[17] Considerable effort was expended to use the benzenesulfonyl, Ts and *meta*-toluenesulfonyl derivatives in order to present the most cost-effective new *N*-protecting group. Thus, in a comparison of deprotection ease with the *N*-Ans group, the selected *N*-Ts amines **4** underwent Ni^0-catalyzed hydrodesulfonylation to give **3** only in modest yield. Similarly, although *meta*-toluenesulfonyl amides are conveniently prepared from the commercial *meta*-toluenesulfonyl chloride, their deprotection, while proceeding in high yields, occurs much more slowly (8–12 h) than that of the Ans group (2 h).[11]

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[20] The sluggish reaction of *N*-Ts amines under the Ni^0-catalyzed conditions has, to date, stifled the development of this widely used Ts protective group. However, preliminary experiments on oxazoline **5** with Ni–phosphane catalysts, extended reaction times (12–18 h), and excess Grignard reagent have shown promise in the improved yields of the *N*-detosylation reaction.[18]

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