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A reversible safety-catch method for the hydrogenolysis of *N*-benzyl moieties

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Abstract—The benzyl groups of β-hydroxy-*N*-benzyl sulfonamides are labile toward hydrogenolysis-unlike *N*-benzyl sulfonamides lacking the β-hydroxy moiety. We find that *N*-acyl-*N*-benzyl sulfonamides undergo hydrogenolysis under very mild conditions. Based upon these observations, we developed a reversible safety-catch method using *tert*-butoxycarbonyl moieties to activate *N*-benzyl sulfonamides toward hydrogenolysis. We also explored the utility of the safety-catch activation method for other nitrogen-based functionality such as *N*-benzyl carboxamides, imides, and related functionality.

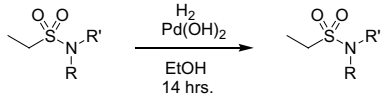
1. Introduction

There are an abundant number of molecules that contain the sulfonamide moiety. Chiral auxiliaries,[1] peptidomimetics,[2] modified oligonucleotides,[3] amine synthons,[4] and therapeutics[5] illustrate diverse applications for the sulfonamide group. Although many methods exist for the synthesis and manipulation of the sulfonamide functional group, there is a general dearth of protecting groups[6] for this functionality. In principle, the benzyl group could serve as a useful protecting group for sulfonamides, its deprotection could be effected by hydrogenolysis—a process orthogonal to conditions used for the removal of many other protecting groups. Unfortunately, hydrogenolysis of *N*-benzyl moieties—particularly *N*-benzyl sulfonamides—can be quite problematic.[7,8] We now present a general method to facilitate hydrogenolysis of *N*-benzyl sulfonamides using a reversible safety-catch modification. Further, we explore the utility of the reversible safety-catch strategy toward the hydrogenolysis of *N*-benzyl protecting groups from sulfonamides and other similar nitrogen-based functional groups.

2. Results and discussion

N-Benzyl-ethanesulfonamide (**1**) undergoes no appreciable hydrogenolysis under atmospheric pressures of hydrogen in the presence of Pearlman's catalyst.[9] Such stability might be attenuated through modification of the sulfonamide nitrogen—similar to the safety-catch strategies used in solid-phase peptide synthesis. Ellman and co-workers[10] and others[11] have shown that alkylation of *N*-acyl sulfonamides increases the lability of the acyl-functionality. However, alkylation of sulfonamide **1** does not activate the *N*-benzyl group toward hydrogenolysis. Acylation of sulfonamide **1**, however, is an effective way to activate the benzyl group to affect hydrogenolysis in good yield (83%) (Table 1). Although, acylation is not the most useful activation strategy, as *N*-acyl sulfonamides are very resistant to hydrolysis.[12]

Table 1. Hydrogenolysis of *N*-substituted-*N*-benzyl sulfonamides conducted under an atmosphere of hydrogen



	R	R′		R	R′	
(**1**)	Bn	H	(**1**)	Bn	H	(95%)
(**2**)	Bn	CH_3	(**2**)	Bn	CH_3	(94%)
(**3**)	Bn	Ac	(**4**)	H	Ac	(83%)[a]

[a] No evidence was observed by NMR for reduction of the phenyl ring in the recovered starting material.

Keywords: Sulfonamide; Amide; Protecting group; Benzyl; Safety catch; Hydrogenolysis.
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Table 2. Reversible 'safety-catch' deprotection of *N*-benzyl sulfonamides

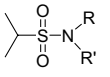
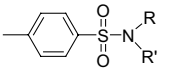
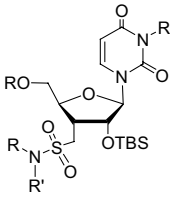
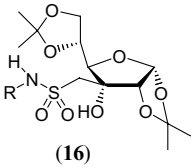
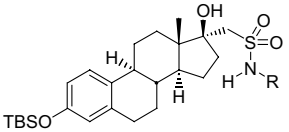
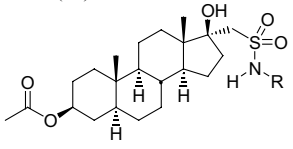
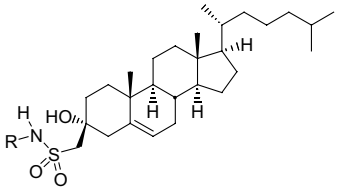
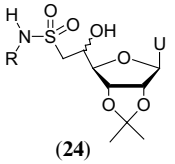
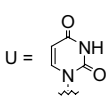
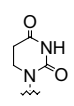
	R = H R'= Bn	Boc_2O DMAP	R = Boc R'= Bn	$Pd(OH)_2$ H_2	R = Boc R'= H	TFA 0 °C	R = H R'= H
	(**5**)	(97%)	(**6**)	(98%)	(**7**)	(96%)	(**8**)
	(**9**)	(99%)	(**10**)	(96%)	(**11**)	(97%)	(**12**)
	(**13**)	(86%)	(**14**)	(95%) for two steps			(**15**)

Table 3. Yield for the deprotection of structurally diverse *N*-benzyl protected sulfonamides using $Pd(OH)_2$ in ethanol under an atmosphere of hydrogen gas (22 psi)

Starting material (R = Bn)	% Yield
 (**16**)	94 (**17**), R = H
 (**18**)	92 (**19**), R = H
 (**20**)	94 (**21**), R = H
 (**22**)	87[a] (**23**), R = H
 (**24**)	 49 (**25**), R = H
	 48 (**26**), R = Bn

[a] The alkene is reduced in the product.

Therefore, we explored a means to reversibly activate *N*-benzyl sulfonamides through carbamoylation.

The *tert*-butoxycarbonyl (Boc) moiety effectively activates alkyl and aromatic *N*-benzyl sulfonamides toward hydrogenolysis (Table 2). The resultant Boc-protected sulfonamides are easily deprotected using acid to reveal free sulfonamides. The three-step process (activation, hydrogenolysis, and cleavage of the Boc group) can be conducted in very high yield; the isolation of all intermediates being unnecessary. Unfortunately, the benzyloxycarbonyl (Cbz) moiety cannot be used as an activating group, as it undergoes hydrogenolysis preferentially with respect to the *N*-benzyl moiety.[†]

The safety-catch activation strategy is not the only means to hydrogenolyze *N*-benzyl sulfonamides. Indeed, in a recent study[13] we hydrogenolyzed a *N*-benzyl sulfonamide (Table 3, sugar **16**) without activation; although, the reaction conditions differed from those used with the safety-catch method. However, our result seemed atypical because hydrogenolysis of the *N*-benzyl sulfonamide was effected in ethanol (rather than acetic acid) at much lower pressures (22 psi as opposed to >700 psi) than previously reported for the hydrogenolysis of other *N*-benzyl sulfonamides.[7] Nonetheless, this result was generally applicable to various sugars and steroids. Thus, deprotection of several *N*-benzyl sulfonamide-containing sugars and steroids was effected in high yield using the aforementioned conditions (Table 3).

Many common functional groups are compatible with the high pressure hydrogenolysis protocol. For example, isopropylidene groups, aryl-silyl ethers, carboxylicesters, *tert*-butyl carbonates[‡] as well as *tert*-butyl carbamates[‡]

[†] Under the same conditions used for the safety-catch method: *N*-benzyl-*N*-Cbz isopropylsulfonamide gives *N*-benzyl isopropylsulfonamide in 97% yield and *N*-benzyl-*N*-Cbz toluylsulfonamide gives *N*-benzyl toluylsulfonamide in 93% yield.

[‡] Data not shown.

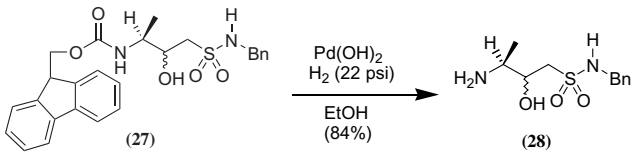
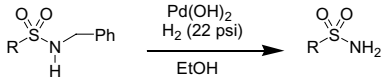


Figure 1. Fmoc-protected amines are preferentially cleaved under the reaction conditions. The resultant amine presumably deactivates the catalyst; thereby, leaving the *N*-benzyl sulfonamide intact.

Table 4. *N*-Benzyl sulfonamides lacking a β-hydroxy moiety hydrogenolyze in poor yield



	R	% Recovered		R	% Product
(**1**)	Et	82[a]	(**29**)	Et	16
(**5**)	*i*-Pr	87[a]	(**30**)	*i*-Pr	7
(**9**)	Tol	79	(**31**)	Tol	9

[a] Recovered starting materials contained a mixture of the phenyl-form and the reduced cyclohexyl-form of the benzyl protecting group.

are stable to the deprotection conditions. Though many functional groups are stable, alkenes are reduced (Table 3, steroid **22** and nucleoside **24**). Interestingly, in the presence of an Fmoc-protected amine, hydrogenolysis of the *N*-benzyl sulfonamide moiety does not occur; instead, preferential deprotection of the Fmoc group occurs (Fig. 1). Amines inhibit the hydrogenolysis of the benzyl moiety from heteroatoms (e.g., oxygen)[14] presumably by formation of a complex[15] between the amine and the palladium catalyst, thereby deactivating the catalyst. Thus, facile hydrogenolysis of the Fmoc-amine subsequently inhibits hydrogenolysis of the *N*-benzyl sulfonamide.

To test the generality of the reaction conditions associated with hydrogenolysis of β-hydroxy-containing sulfonamides, we subjected several simple *N*-benzyl sulfonamides lacking the β-hydroxy-group to the deprotection conditions. As expected, hydrogenolysis of simple *N*-benzyl sulfonamides proceeds in poor yield (Table 4). This result suggests that hydrogenolysis of *N*-benzyl sulfonamides, without use of the safety-catch protocol, seems dependent upon the presence of the β-hydroxy moiety.

Van Bekkum and co-workers,[16] as well as McQuillin and co-workers,[17] have reported kinetic data that is consistent with an anionic transition state for hydrogenolysis. An increase in anionic character in the transition state is also supported by competition experiments reported by Baltzly and Buck.[§,18] The β-hydroxy moiety may form an intramolecular H-bond to stabilize such an anionic transition state, thus promoting hydrogenolysis.

To test the possible involvement of an intramolecular H-bond, β-hydroxy sulfonamide **32**, and β-methoxy sulfonamide **34** were subjected to identical reaction conditions. Hydrogenolysis of the benzyl group occurs for both the hydroxy-containing (86%) and methoxy-containing (61%) molecules (Table 5). These data negate the involvement of an internal H-bond. However, H-bonding could still be involved, as the reactions were conducted in protic solvent. Therefore, to test the possibility of intermolecular H-bonding, hydrogenolysis was conducted in ethyl acetate—an aprotic solvent. Again, hydrogenolysis of the benzyl group occurs for both the hydroxy-containing (89%) and methoxy-containing (99%) molecules. Collectively, these data mitigate against the involvement of H-bonding as the determining factor responsible for the hydrogenolysis of β-hydroxy-*N*-benzyl sulfonamides. Another possibility for the facility of hydrogeno- lysis of β-hydroxy-containing sulfonamides is that the hydroxyl group assists in chelation between reactive species. The same possibility may occur for the *N*-acylated sulfonamides, as the carbonyl oxygen may participate in chelation between reactive species.

N-Benzyl sulfonamides are not the only *N*-benzyl functionality that is very difficult to hydrogenolyze; *N*-Benzyl carboxamides are also notoriously difficult to hydrogenolyze.[6] Indeed, attempted hydrogenolysis of *N*-benzyl-propanamide and *N*-benzyl-benzamide failed using Pearlman's catalyst under atmospheric pressures of hydrogen gas.[¶] Similarly, use of the Boc-safety-catch activation method also failed to effect appreciable hydrogenolysis of the *N*-benzyl moiety, even after prolonged reaction times.[‖] However, use of the safety-catch method at elevated temperature (55 °C) led to the reaction of *N*-benzyl-*N*-Boc-benzamide (**36**); giving both *N*-Boc-benzylamine (**37**) and *N*-Boc-cyclohexylmethylamine in 81% total yield.[**] Similarly, the aromatic imide *N*-acetyl-*N*-benzyl-benzamide gives a mixture of *N*-benzyl-acetamide and *N*-cyclohexylmethyl acetamide in 80% total yield. These products could arise by two different pathways, as illustrated in Figure 2.

To test the operative pathway, *N*-benzyl-*N*-Boc-*m*-methyl benzamide (**40**) was subjected to the reaction conditions. Quenching the hydrogenolysis early leads to exclusive formation of *N*-Boc-benzylamine (**37**) (47%) with recovery of unreacted starting material (39%) possible (Fig. 3). Additionally, hydrogenolysis of *N*-Boc-benzamide (**38**) under the same reaction conditions gives benzamide (36%) and starting material (35%). These data support regioselective acyl-cleavage of the aromatic amide bond and support pathway *a* of

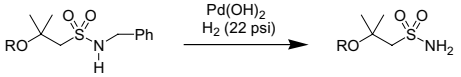
[§] Baltzly and Buck report a competition experiment where bis-benzyl diamines are hydrogenolyzed in acidic medium. Benzyl groups are found to hydrogenolyze in preference to ρ-substituted benzyl groups bearing electron-donating substituents.

[¶] *N*-Benzyl-propanamide was recovered in 97% yield and *N*-benzyl benzamide was quantitatively recovered.

[‖] After 4 days, *N*-benzyl-*N*-Boc-propanamide was recovered in 81% yield, and *N*-benzyl-*N*-Boc-benzamide was recovered in 68% yield.

[**] *N*-Benzyl-*N*-Boc-propanamide (and the reduced cyclohexyl-form) was recovered in 95% combined yield from the same reaction conditions used with the benzamide species.

Table 5. Hydrogenolysis of *N*-benzyl sulfonamides containing β-oxy functionality occurs in both protic and aprotic solvents



	R	% Recovered	Solvent		R	% Product
(**32**)	H	13[a]	EtOH	(**33**)	H	86
(**34**)	Me	36[a]		(**35**)	Me	61
(**32**)	H	9[a]	EtOAc	(**33**)	H	89
(**34**)	Me	—		(**35**)	Me	99

[a] Recovered starting materials contained a mixture of the phenyl-form and the reduced cyclohexyl-form of the benzyl protecting group.

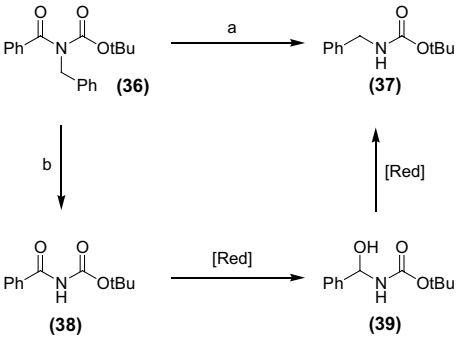


Figure 2. Two possible pathways to form *N*-Boc-benzylamine from *N*-benzyl-*N*-Boc-benzamide in the presence of $Pd(OH)_2$ in ethanol at 55 °C under an atmosphere of hydrogen.

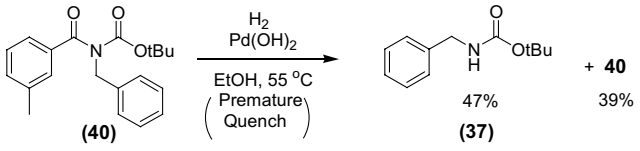


Figure 3. Regioselective reduction of aromatic amide bonds occurs for aryl-*N*-carboxyl-carboxamides.

Figure 2. Furthermore, these results are in agreement with a report by Ragnarsson et al.[19] who observe a decrease in the reduction potential (i.e., increase in lability) of aromatic amide bonds when incorporated into carboxamide functionality—such as *N*-carboxyl-carboxamide **36**.

3. Conclusions

N-Benzyl sulfonamides are resistant to hydrogenolysis. Yet, acylation or carbamoylation of *N*-benzyl sulfonamides facilitates hydrogenolysis of the benzyl moiety. Based upon these observations, we have introduced the *tert*-butoxycarbonyl (Boc) moiety as a reversible activation (i.e., safety-catch) method to facilitate hydrogenolysis of both alkyl and aryl-*N*-benzyl sulfonamides. Through reversible carbamoylation of *N*-benzyl protected sulfonamides using the *tert*-butoxycarbonyl (Boc) moiety, we have introduced a new protecting strategy for the sulfonamide functionality. Unfortunately, this activation strategy cannot be extended to similar functionality such as alkylcarboxamides, arylcarboxamides, or arylimide functionality. The *N*-benzyl moiety of an alkylcarboxamide does not undergo hydrogenolysis under the reaction conditions tested and arylcarboxamides and alkylcarboxamides decompose in an undesirable fashion.

4. Experimental procedures

4.1. General procedure for the synthesis of Boc-activated *N*-benzyl sulfonamides

Di-*tert*-butyl dicarbonate (1.5 equiv) was slowly added to an ice-cold 0.45 M THF solution of *N*-benzyl sulfonamide (1 equiv). DMAP (0.1 equiv) was then added and the reaction stirred overnight at rt. All volatiles were removed with a rotary evaporator and the desired compound isolated by silica gel chromatography using the solvent system indicated.

4.1.1. *N*-Benzyl *N*-(*tert*-butoxycarbonyl) *iso*-propylsulfonamide (6). Quantities: sulfonamide **5** (500 mg, 2.344 mmol), Boc_2O (0.81 mL, 3.516 mmol), DMAP (28 mg, 0.2344 mmol). Eluent = 2:1 hexanes:Et_2O gives **6** (712 mg, 2.272 mmol) as a solid. Yield = 97%.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 7.4$ Hz, 2H), 7.34–7.24 (m, 3H), 4.82 (s, 2H), 4.01 (sept, $J = 6.9$ Hz, 1H), 1.47 (s, 9H), 1.31 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 152.00$, 137.65, 128.55, 128.16, 127.70, 84.69, 54.54, 50.02, 28.14, 16.25; IR (film): $\nu = 3089$, 3070, 3031, 2981, 2938, 2879, 1726, 1497, 1456, 1371, 1349, 1254, 1136, 1058 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{15}H_{24}NO_4S$ (MH^+): 314.14206, found 314.14215.

4.2. General procedure for the hydrogenolysis of *N*-activated *N*-benzyl sulfonamides

Pearlman's catalyst (10 mg/100 mg sulfonamide) was suspended in a 0.35 M EtOH solution of the appropriate *N*-activated sulfonamide. The heterogeneous mixture was stirred overnight under an atmosphere of hydrogen gas (balloon). The mixture was then filtered through a 1 in. cake of Celite 545 with EtOH. All volatiles were removed with a rotary evaporator and the desired compound isolated by silica gel chromatography using the solvent system indicated.

4.2.1. *N*-(*tert*-Butoxycarbonyl) *iso*-propylsulfonamide (7). Quantities: sulfonamide **6** (160 mg, 0.5105 mmol), Pearlman's (16 mg). Eluent = 1:1 Et_2O:hexanes gives **7** (112 mg, 0.5016 mmol) as a solid. Yield = 98%.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.72$ (sept, $J = 7.0$ Hz, 1H), 1.47 (s, 9H), 1.40 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.17$, 84.24, 53.68, 28.08, 16.19; IR (film): $\nu = 3590$, 3241, 2983, 2940, 2880, 1742, 1435, 1371, 1340, 1243, 1163, 1135, 1061 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_8H_{18}NO_4S$ (MH^+): 224.09511, found 224.09584.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.118. Experimental procedures and spectral data (^{1}H, ^{13}C, MS, IR) for all compounds synthesized in this study. The supplementary data is available online with the paper in ScienceDirect.

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