Alkali Metals in Silica Gel (M-SG): A New Reagent for Desulfonation of Amines
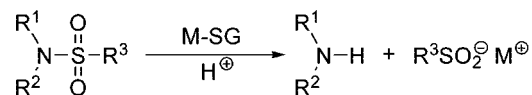
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ABSTRACT

A novel method for the desulfonation of secondary amines is described. Alkali metals absorbed into nanostructured silica (M-SG) were found to be useful solid-state reagents for the desulfonation of a range of N,N-disubstituted sulfonamides. M-SG reagents are room-temperature-stable free-flowing powders that retain the chemical reactivity of the parent metal, decreasing the danger and associated cost of using reactive metals.

In organic synthesis, many protecting groups have been developed for the amine functionality.[1] In pharmaceutical chemistry, amine protections are often accomplished with groups such as Cbz (carbobenzyloxy), Boc (*tert*-butoxycarbonyl), and Fmoc (9-fluorenylmethyloxycarbonyl).[2] But for some uses, these protecting groups are too labile. Sulfonamides, formed by reaction of amines with sulfonyl chlorides, are more robust and have the advantage of being easy to isolate and purify by recrystallization. But practical desulfonation of sulfonamides, *p*-toluenesulfonamides specifi-

cally, can be difficult. This problem has arisen in our own ongoing work on functionalized polyamine cages for construction of organic alkalides and electrides.[3]

Existing methods for sulfonamide cleavage fall into broad categories as follows: (a) strong acid treatment,[4−11] sometimes accelerated with microwaves,[12] (b) cleavage by strong bases or nucleophiles,[13−16] (c) photoreduction[17,18] with

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various reagents, (d) electrochemical reduction,[19,20] and (f) metal-based reductive cleavages.[21–39] Acidic deprotections of tosylated amines use severe conditions such as H_2SO_4,[4,5] 48% HBr,[6] AcOH−HClO₄,[7] HBr with PhOH,[8] and HF−pyridine with anisole.[9] Of recent interest is a "green" phase-transfer-catalyzed cleavage by NaOH and KOH that deprotects tosylated aromatic and heteroaromatic amines.[16] But for secondary amine detosylation, many of these procedures are too harsh and/or reagent-intensive, or lack generality due to limited substrate scope, functional group intolerance, or demanding separations on workup.

The last and most general group, metal-based reductions, use powerful reagents such as sodium naphthalenide,[34–36] Ni(acac)₂ with Grignard reagent,[23] Li/NH₃,[30] Na/NH₃,[31,32] Al−Hg,[25] Na−Hg,[26] Red-Al,[29] Na/2-propanol,[21] Mg/MeOH,[36] low-valent titanium reagents,[26] mischmetal with TiCl₄,[27] and SmI₂ with Bu₃SnH.[24] Although they generally produce the desired amines in good yield, these approaches can be difficult to scale[40] and suffer from issues such as (a) reagent instability, (b) moisture sensitivity, (c) reagent pyrophoricity, (d) difficult removal of the reagent byproduct, (e) the need for cryogenic reaction conditions, (f) reagent toxicity, (g) waste handling, and (h) high cost. There remains a need for a simple general desulfonation which harnesses the reductive power of alkali metals without the associated safety and cost issues.

Recently, solid alkali metal-based reductions in organic solvents became easier with the finding that these metals can be made significantly less pyrophoric by thermal absorption into nanostructured silica to form the metal-silica gel (M-SG) reagents.[41–43] Herein, we report a novel method to cleave toluenesulfonamides to amines by using M-SG. Specifically, we have used M-SG (Stage I) where M is Na or Na₂K. The overall general transformation is analogous to sulfonamide cleavage by alkali metal arenides and is thought to proceed via two single-electron transfers with subsequent cleavage to form the alkali metal amide and sulfinate salt (Scheme 1).[44–46] As described below, treatment with M-SG

Scheme 1. M-SG-Mediated Desulfonation of Protected Secondary Amines (Ar = *p*-Tolyl)
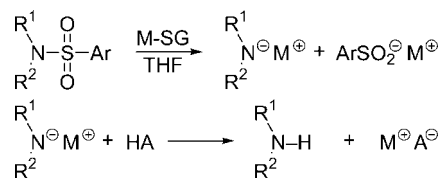
is a mild and general procedure to desulfonate protected amines.

Various sulfonamide substrates were investigated to explore the scope of M-SG desulfonations (Table 1). The reactions were conducted in ethereal solvents, typically in THF with 2.5−5 equiv of Na₂K-SG(I) at room temperature over 8 h, and subsequently quenched with water, except where noted.[47,52] Detosylation with Na₂K-SG (I) tolerates phenyl (entries 1, 2, 4, 9, 11) and ether moieties and is successful for both primary (entry 9) and secondary amines (entries 1−8 and 11). The reaction's success with the bulky aza-cryptand (entry **8**), where both HBr/AcOH and Na/NH₃ methods failed, promises to be useful in our ongoing synthetic studies of azacryptands directed to preparation of alkalides and electrides.[3] Perhaps most interesting, however, is the (modified) reaction's success in detosylating aziridine, a special class of secondary amine (vide infra).

Modifications and Extensions. For reactions in 1,2-dimethoxyethane (entries 7 and 9), the addition of a catalytic amount (20 mol % relative to the sulfonamide starting material) of ethylenediamine (EDA) accelerates N−S bond cleavage, bringing reactions to completion in 3−4 h instead of the 8−10 h seen without EDA.

The mesyl moiety is cleanly cleaved from 4-benzylpiperidine, a simple secondary amine (entry 10), suggesting that the tosyl group's aryl ring is not critical to the electron capture and reductive cleavage process. Similarly, in a preliminary study, the benzenesulfonyl group was removed from bis(2-methoxyethyl)amine with essentially the same efficiency as tosyl group cleavage.

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(43) SiGNa Chemistry has developed three categories of alkali metal-nanostructured silica materials (M-SG): Stage 0 materials are strongly reducing pyrophoric powders. Stage I materials are nonpyrophoric, free-flowing black powders with reactivity equivalent to neat alkali metals. Stage II is less reducing but reacts with water to produce hydrogen at pressures from ambient to several thousand psi. All three categories of M-SG, with different metals and metal alloys absorbed, are available commercially. CAUTION: *With all M-SG materials, strong exothermic reactions may occur with liquid water or sufficiently moist air.*

Table 1. Evaluation of Substrate Scope

entry	substrate	product	yield
1	Ph–N(Ts)–Ph	Ph–N(H)–Ph	93[a]
2	Ph–N(Ts)– (isopropyl)	Ph–N(H)– (isopropyl)	81[b]
3	Cy–N(Ts)–Cy	Cy–N(H)–Cy	81[c,g]
4	Ts–N (piperidine CH2Ph)	H–N (piperidine CH2Ph)	96[a]
5	Ts–N O (morpholine)	H–N O (morpholine)	75[c]
6	(O)2 N–Ts	(O)2 N–H	85[a]
7	Ts–N N–Ts (piperazine)	H–N N–H (piperazine)	76[a,d]
8	macrocyclic tetraamine N–Ts	macrocyclic tetraamine N–H	68[a]
9	Ph NHTs	Ph NH2	76[a,d,f]
10	Ms–N (piperidine CH2Ph)	H–N (piperidine CH2Ph)	89[a]
11	aziridine N–Ts CH2Ph	aziridine N–H CH2Ph	61[a,e]

[a] Isolated yield. [b] Percent conversion as determined by ^{1}H NMR. [c] Isolated as HCl salt. [d] DME used as solvent at 60 °C (in all other cases THF was used as reaction solvent at room temperature). [e] 3 equiv of Na-SG(I) was used at −60 °C in THF (in all other cases, Na$_2$K-SG was used). [f] 5 equiv of Na$_2$K-SG was used (in all other cases, 3−4 equiv of Na$_2$K-SG was used). [g] Similar yields were seen in runs with 4−6 equiv of Na$_2$K-SG(I) and solid acidic salts such as (NH$_4$)$_2$HPO$_4$, NH$_4$Cl, or HCO$_2$NH$_4$ included in situ.

As entries to the strained aziridine (azacyclopropane) framework, the *N*-tosyl-protected aziridines are relatively easily synthesized.[48] Their desulfonations, however, are synthetically challenging.[49] For example, 2-benzyl-*N*-tosylaziridine gives substantial ring opening products on treatment with Na/NH$_3$, SmI$_2$, or phenyldimethylsilyllithium.[49,50]

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At ambient temperatures, Mg/MeOH,[24] activated by sonication, does give modest aziridine yields,[49] and Li/arene (arene = naphthalene or 4,4′-di-*tert*-butylbiphenyl [DBB]) or Na/naphthalene deprotections are also effective at low, but not at ambient, temperatures.[51]

Attempts at M-SG detosylation under our usual conditions (Na$_2$K-SG in THF, room or low temperature; H$_2$O quench) of 2-benzyl-*N*-tosylaziridine led to both desulfonation and ring opening. However, the milder Na-SG reagent in THF cleanly detosylates 2-benzyl-1-tosylaziridine at −60 to −78 °C without any electron-transporting species (Table 1, entry 11). Not surprisingly Na-naphthalide generated from Na-SG at −50 °C also gave 67% yield of the desired product.

In the general M-SG desulfonation procedure, as an alternative to a postreduction aqueous quench, the quenching proton source can be included with the M-SG reductant. Organic-soluble proton sources such as acetic acid or alcohols reacted directly with the M-SG, evolving hydrogen and diminishing reducing capacity. However, relatively insoluble solid proton sources in intimate contact with M-SG can neutralize the soluble amide shortly after its formation without direct rapid reaction of the proton source with the M-SG. In the detosylation of Cy$_2$NTs, solid inorganic acid salts, such as (NH$_4$)$_2$HPO$_4$, NaH$_2$PO$_4$, NH$_4$Cl, and potassium hydrogen phthalate, were found to react with the metal amides, affording clean dicyclohexylamine product in THF at room temperature.

To demonstrate one-pot detosylation and trapping with a nonproton electrophile, the M-SG(I) deprotection was applied to *N*-tosylpyrrole, with benzoyl chloride serving as the electrophile in the final quench (Scheme 2). This reaction was complete in 6 h with an 85% yield of *N*-benzoylpyrrole.

Scheme 2. Generation of Alkali Metal Amide and Electrophilic Quenching In Situ
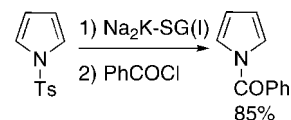
As a first probe of selectivity, detosylations of Ph$_2$NTs and Cy$_2$NTs were run separately with the individual substrates and with a 1:1 mixture of the two substrates. The time evolution of each reaction was monitored by ^{1}H NMR. For these rate studies, solvents freshly distilled from NaK alloy were used, and 1.5 equiv of M-SG(I) was found to be sufficient to drive the reactions to completion.[52] As expected, Ph$_2$NTs was cleaved faster than Cy$_2$NTs by Na$_2$K-SG(I), but only by a factor of 2. No evidence of competitive inhibition was seen, i.e., the rate of detosylation of Cy$_2$NTs did not slow down to any significant extent in the presence of an equal amount of Ph$_2$NTs, and the 2:1 rate ratio was observed in the mixture as well, suggesting (a) independent reactions and (b) little difference in electron-accepting ability or access

to the metal sites between these two substrates, despite the very large difference between the pK_a values of the Ph$_2$NH and Cy$_2$NH product amines.

In summary, M-SG materials (Na or Na−K alloys absorbed in silica gel) can act as efficient reagents for removing sulfonyl protecting groups from primary and secondary amines. These M-SG reagents offer simple alternatives to the other alkali-metal based reagents such as Na-NH$_3$ or Na-arenides often used for sulfonamide deprotections in total syntheses. Further investigations of related deprotection processes are currently underway.

Supporting Information Available: Experimental procedures and NMR data from these studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(52) Because a two-electron S−N bond cleavage is this paper's focus, the molar equivalency of the M-SG reactants is reckoned in terms of pairs of electrons, i.e., as 1/2 the total number of moles of alkali metal present. Thus, if reaction efficiency were perfect, 1 equiv of M-SG, so termed, would cleave 1 mol of tosyl amides; its reaction with ethanol (2 mol) forms 1 mol of H$_2$ gas. This choice of terminology places the M-SG reagents on the same equivalence-counting scale as, for instance, lithium triethylborohydride or other single hydride donor reducing agents.