Reductive amine deallyl- and debenzylation with alkali metal in Silica Gel (M-SG)

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ABSTRACT

Alkali metals in silica gel (the M-SG materials) are effective reagents for reductive deallylation, debenzylation, debenzhydrylation, and detritylation of amines. As such, these reagents provide a convenient alternative to traditional metal ammonia solutions for this class of deprotections.

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Cleavage of the C–N bond is important in functional group inter-conversions and in deprotection reactions such as deallylation and debenzylation.[1,2] Reductive methods using metal ammonia solutions,[3,4] Pd-reagents,[5–9] low valent Ti,[10] or Ni-based reagents[11,12] have conventionally been used for these transformations.[13] Mild oxidative methods, such as the aziridine debenzhydrylation with O_3 followed by excess $NaBH_4$[14] and the recently reported debenzhydrylation of azetidinone with NBS and catalytic Br_2 in the presence of light[15] offer useful strained ring deprotections. A particularly selective example is the amine N-debenzylation with diisopropyl azodicarboxylate (DIAD)[16,17] in a sugar also protected with O-benzyl and N-tosyl groups. Though much more common for alcohols, amine detritylation under acidic condition is known.[18] Grubbs's catalyst[19] and other Ru- and Rh(III)-based reagents[20–22] have proven useful for efficient deallylation of amines. However, these agents initiate reaction by isomerization of the double bond[23,24] which can be problematic for certain substrates.[25] Thiol-mediated radical cleavage of allylic amines has been used to deprotect secondary amines.[26,27]
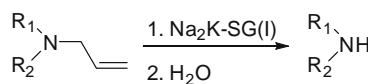
The above deprotections represent elegant and selective tools for organic synthesis. However, a single reagent able to generally cleave N-allylic and -benzylic amines would enhance the toolbox. For example, sodium in ammonia was used in the final step for global deprotection in the total synthesis of an oligosaccharide natural product.[28] Similarly, Li in isoprene was shown to be capable of cleaving a variety of protecting groups bound to imidazole.[29]

Alkali metals absorbed in porous silica gel (or the M-SG reagents) are free-flowing dry powders that are free of contamination by oily hydrocarbons and are non-pyrophoric upon brief exposure to dry air.[30–32] Our interest in exploring the usefulness of these materials in amine deprotections such as amine desulfonations[33] prompted us to investigate reductive C–N cleavages in the context of deallylation, debenzylation, debenzhydrylation, and

detritylation. Although the focus of this Letter is on deallylation (Scheme 1), a few examples of the other deprotections are also described herein.

Several allyl amine substrates were cleaved by treatment with Na_2K-SG(I) at ambient temperature in ethereal (e.g., THF and 1,2-DME) solution under an inert atmosphere. These experiments are summarized in Table 1. We found that a sub-stoichiometric amount (20 mol %) of ethylenediamine (EDA) was necessary to promote reaction of the aliphatic substrates, which were then cleanly deprotected in 16–24 h. Examples include N-allylpiperazine (entry 1), N-allyl-hexamethyl-disilazane (entry 2), N-allylpiperidine (entry 3), and a hindered substrate, N-allyl-dicyclohexylamine (entry 4). Aromatic substrates (entries 5–7) reacted relatively faster, affording the corresponding amines in 8–10 h without the need of EDA. Over-reduction of the aromatic rings was not observed in these cases. Reaction of N-allyl-3,5-dimethylpyrazone (entry 6) gave a high yield; in this reaction, replacing Na_2K-SG(I) with the more air stable Na-SG(I) gave a lower yield, and no product was obtained when THF was replaced with toluene. However, successful, selective allyl cleavage in the presence of a ^{t}Boc group was achieved in modest yield (entry 8).[34]

The expected propene byproduct of deallylation was observed by analysis of the gas phase via GC–MS. No 1,5-hexadiene, the allyl radical homodimerization product, was seen in the reaction mixture. This finding suggests that an allyl metal intermediate likely formed during the cleavage reaction. However, attempts to trap the allyl metal reagent with electrophiles such as benzophenone at −78 °C did not give any substantial nucleophilic adduct. Appar-

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Scheme 1. Deallylation of allyl-protected amines.

Table 1
Deallylation of tertiary amines

Entry	Reactant	Product	Yield
1			56[a,d,f]
2			90[c]
3			88[b]
4			69[b]
5			71[a]
6			91[a],65[e]
7			65[a]
8			60[g,a]

[a] Isolated yield.
[b] Isolated as HCl salt.
[c] Conversion by NMR.
[d] Performed in 1,2-dimethoxyethane (DME).
[e] Yield obtained with Na-SG.
[f] 5 equiv of metal was used in this case.
[g] Reaction was run at 0 °C with Na-SG(I) in presence of EDA.

Table 2
Other amine deprotections

Entry	Reactant	Product	Yield
1			96[a,d]
2			82[b]
3			75[a]
4			90[a]
5			95[a]
6			100[c]

[a] Isolated yield.
[b] Isolated as HCl salts.
[c] Conversion by GC.
[d] 1,2-DME was used as solvent.

ently, the allylmetal species, if formed, does not survive for long in ethereal solvent. Alkyllithiums in the presence of lithium alkoxide can readily abstract protons from ethereal solvent above −60 °C.[35] In a similar way, in the presence of dialkylamide salts, allyl metal species could be highly aggressive in proton abstraction reactions with ethereal solvents (typical procedures for preparation of allyl-sodium are carried out in hydrocarbon solvents). In the case of N-allyl-benzotriazole, besides the intended allyl group removal, loss of N_2 was observed, yielding aniline. Secondary N-allyl-amines, such as N-allyl-cyclohexyl amine, also encountered diffi-culties in these deprotections. Although some cyclohexylamine product was observable, a complex mixture of other products was obtained.

Exploratory work on reductive cleavages of other related pro-tecting groups of amines are summarized in Table 2. Effective re-moval of benzyl (entries 1 and 2), benzhydryl (entry 3), and trityl (entries 4 and 5) groups was demonstrated. For debenzylations (entries 1 and 2), the expected toluene byproduct was detected, while debenzhydrylation and detritylation gave the corresponding diphenylmethane and triphenylmethane products. It is noteworthy that the debenzylation of the aliphatic amine piperidine (entry 2) proceeded to completion without the need for activation by ethyl-ene diamine. From a brief exploration in oxygen deprotection we also found that benzyl nopyl ether (entry 6) cleanly yielded the bicyclic alcohol nopol in less than 3 h. A more detailed study on debenzylation reactions is underway and will be reported elsewhere.

An additional extension of this deprotection method was the successful one-pot reduction/deprotection of benzophenone hydrazone (Scheme 2), enabling reduction to amine via N–N bond cleavage, or full reduction to the diphenylmethane. In the above-mentioned reaction, the use of 2.5 equiv of metal yielded benzhy-dryl amine as the predominant product (NMR detection). However, with 5 equiv of metal, diphenylmethane was the major product.

To summarize, alkali metals in silica gel (M-SG) are capable of reductive cleavage of the C–N bonds in tertiary allyl, benzyl, benz-hydryl, and trityl amines. The simplicity of the reaction, ease of
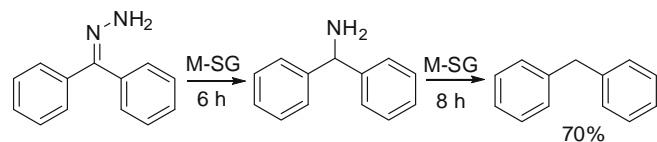
Scheme 2. One-pot reduction and debenzhydrylation of benzophenone hydrazone.

work-up and isolation, low cost of the reagent precursors, and low toxicity make this method a useful addition to chemists' toolbox.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.058.

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33. For detailed procedure refer to the **Supplementary data**.
34. Under similar conditions, ether, aziridine,[32] and ketal groups tolerated exposure to M-SG reagents. As expected, however, both 2-phenyl-1,3-dithiane and 1-(trimethylsilyl)-1*H*-imidazole formed the reduction products toluene and imidazole (after quenching).
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