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ABSTRACT

The use of sodium in alumina and silica gels for the reductive cleavage of the N–O bond of *N*-methoxy-*N*-methylamides, commonly referred to as Weinreb amides, has been investigated. This method reduces a diverse set of Weinreb amides with different functional groups to give modest to excellent yields. In the course of the studies to explore mechanisms and functional group tolerance, an apparently novel group transfer emerged, implying base-promoted cleavage of the Weinreb amide to form formaldehyde, followed by aldol condensation.

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Weinreb amides (WAs) have played key roles in many organic syntheses.¹ Their main value is as acylating agents for various organometallic reagents, giving direct access to useful ketones and aldehydes without overalkylation.² Complementing this functionality, their stability makes Weinreb amides especially useful as intermediates in exploration and scale-up for pharmaceutical production.^{3–5}

A less-exploited use of WAs is as N-protected species which can undergo N–O cleavage and functionalization leading to secondary and tertiary amides and amines.⁶ Weinreb amides, after N–O bond cleavage, have been catalytically derivatized with alkynes⁷ and with olefins⁸ in both intermolecular and intramolecular annulative processes.⁹

Weinreb amides are easily synthesized from the corresponding carboxylic acid or acid chloride forms.^{2d,10} A generic example of a WA synthesis is shown in Scheme 1.

Various reagents have been used to effect reductive cleavage of the N–O bonds in Weinreb amides. These include samarium diiodide,^{11–13} sodium amalgam,¹⁴ lithium powder,¹⁵ organic 'super electron donors',¹⁶ and RuCl₃/Zn-Cu/alcohols.¹⁷ Although these methods are effective, the reagents involved can be expensive, difficult to make and/or handle, or such powerful reducing agents that they reduce other groups in the compound of interest.

http://dx.doi.org/10.1016/j.tetlet.2015.09.099 0040-4039/© 2015 Elsevier Ltd. All rights reserved. Here we report the use of sodium metal trapped in the nanoscale pores of alumina gel (Na-AG) or silica gel (Na-SG)¹⁸ to reduce a range of Weinreb amides, chosen to explore the chemoselectivity of the method. Alkali metals, usually employed as finely divided dispersions in an inert hydrocarbon, are simple and potent reducing agents, but their use is often limited due to their pyrophoricity and the need to remove the dispersant before or after the reaction. Na-AG and Na-SG are commercially available free-flowing powders that are powerful reductants and are non-pyrophoric in dry air.^{19–21} Other advantages are that many of their reductions can be run under ambient conditions and that the environmentally benign spent reducing agent can be removed by simple filtration. In this Letter, we explore both the modest range of applicability of such reagents for WA reduction, and some mechanistic issues raised by these studies.

Table 1 lists reductions effected by Na-AG and Na-SG on a group of aromatic and aliphatic Weinreb amides. All WAs used were synthesized from their acid chloride counterparts as in Scheme 2 above, with purity and structures confirmed by¹H NMR and in most cases, GC-MS.^{2d} Reaction times and conditions listed were optimized by TLC monitoring. For example, two and three equivalents (counted as electron pairs—i.e. 4 and 6 mol of Na/mol substrate) did not fully convert all of **1** to product within a reasonable time (4 h) so the number of Na-AG equivalents was increased to speed the reaction to completion. Isolated yields were determined by the mass of the purified product. For the

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Scheme 1. Representative synthesis of a Weinreb amide.

isolated yields shown, Na-AG was used as the reducing agent since it proved more difficult to quantitatively recover the products from silica gel. However, ¹H NMR spectra showed that both reagents achieved similar extents of reaction and product purities under similar conditions.

Besides the substrates and products, Table 1 also lists the WAs' frontier orbital energies, calculated via ab initio theory at the HF/6-31G*//HF/6-31G* level using Spartan 14.²² These values (in eV) are presented for comparison with results reported by Murphy et al.,¹⁶ who correlated low-lying LUMO energies and reaction yields in their studies of tetraaminoalkene electron donors. This overall trend was also roughly seen in the data of Table 1, but when a competition was set up between 1 and 4, species that differ by roughly 2 eV in their LUMO energies, the two compounds were reduced unselectively and at essentially the same rates as when each was the sole reactant. This finding suggests that unlike reductions with the soluble reagents studied by Murphy et al.,¹³ the present heterogeneous reagents yield prompt N-O reduction (and in some cases, further reaction) upon adsorption of either molecule at the nanoscale sodium cluster in the Na-SG or Na-AG particle, making the LUMO energies irrelevant to the process of WA cleavage by these reagents. Instead, extent and rate of reduction may reflect the potent but finite reaction capacity of a given nanoparticle surface region, prior to its occlusion with ionic products of low solubility.

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N-O	bond	cleavage	by	Na-SG	and	Na-AG ^a
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Reactant	Na-SG		Na-AG		Isolated
LUMO (L), HOMO (H) energies ^b (eV)	Equiv	v Time (h)	Equi	v Time (h)	yield (%)
N-O-	4	2	5	2	91
(1) $L = 3.13, H = -9.16$	4	2	5	2	96
(2) $L = 3.38$, $H = -8.52$	3.5	2	4	2	75
(4) $L = 5.21$, $H = -10.42$	5	3	4	2	68
(5) L = 3.11, H = -8.95	6	4 ^c	6	4 ^c	78
O_{2N} O	5	2	5	4	57

^a Reactions were run in THF under nitrogen at room temperature, unless otherwise indicated.

^b Frontier orbital energies from ab initio calculations at the HF/6-31G*//HF/6-31G* level of theory for each compound's lowest energy conformation. ^c Reaction run in refluxing THF. Along these lines, and in view of the facile reduction of aromatic nitro groups by powerful soluble reducing agents such as Sml_2 , it was noteworthy that compound **6**, with its low-lying LUMO, gave only a modest yield of desired product. Especially surprising was the lack of nitro group reduction products, but in fact a control study of nitrobenzene also showed no reduction.

To explore reactions of higher functionality WA substrates, we examined the *t*BOC-protected WA of glycine, *t*-butyl(2-(methoxy (methyl)amino)-2-oxoethyl)carbamate. This WA was cleanly reduced with 2 equiv of Na-AG in two hours (80% crude yield by ¹H NMR). However, product purification was stymied by degradation during chromatographic workup.

Overall, the simplicity of these reactions, run under ambient conditions, are comparable with the procedures used for comparable reactions using reagents such as SmI₂/THF (typically -78 °C, or Li/di-*t*-Butylbiphenyl (-78 °C or ambient). More recent exciting developments with SmI₂/H₂O²³ do not appear to have been applied to WA reductions, to our knowledge.

Mechanistic studies and over-reduction

A possible mechanism for *homogeneous* reduction of WAs by 'super electron donors' as suggested by Murphy et al. consists of two single-electron transfers followed by proton addition.¹⁶ The present *heterogeneous* reductions, however, are different.

Since Na-AG and Na-SG are such powerful reducing agents, the selectivity between *N*-methoxy cleavage and the reduction of other groups is of particular interest, as are strategies to modulate such selectivities. Schemes 2 and 3 show two reactions chosen to probe for reduction selectivity and control. In addition to N–O cleavage, **7** (4-chloro-*N*-methoxy-*N*-methylbenzamide) can lose chlorine to form *N*-methylbenzamide, the compound formed upon N–O cleavage of **1**. Similarly, compound **8** (*N*-methoxy-*N*-methylcinnamide) gives a mix of the expected *N*-methoxy cleavage product and over-reduced (hydrogenated) compound, the same product as that from **3**. To our surprise, in addition, **8** yields varying amounts of a third product, as shown in Scheme 3; formation of this compound, in which the elements of the WA's methoxy group are retained, is further discussed below.

Over-reduction is not surprising; alkali metals in silica gel can effect Birch reductions under similar conditions.²¹ The relative yields of products and over-reduced compounds vary somewhat from run-to-run, apparently due to batch-to-batch differences in the Na-AG reagent, rather than variations in the methodology used. For example, three reductions run side-by-side with the same reagents and concentrations gave essentially the same product





Scheme 3.

yields. Variations in yield may in part reflect numbers and distribution of the residual Al-OH groups that surprisingly remain in the material (see below) and serve as proton sources.

Though competing reductions of functional groups within a compound do occur, the absence of products in which only the C-Cl bond is cleaved (7) or only the pi bond is reduced (8) suggests preferential N-OCH₃ cleavage in advance of, or to initiate further reduction. Thus, when both reductions occur, it is likely that a single encounter of the Weinreb amide with the reducing site is involved. Reaction does not appear to depend on special sites; explicit attempts to quench the most reactive sites of Na-AG by pre-treatment with ethanol at 10-30% of the Na content do not alter selectivity. Since each of the reactive sites on a nanoparticle of sodium has many adjacent sodium atoms that can exchange rapidly with a reducing site,¹⁸ multiple reduction steps are possible. If a molecule with two reducible sites stavs adsorbed long enough, a second reduction could occur. The resulting reduced but unprotonated products would remain bound to the alumina gel until protonation released them.

Since protonation of intermediates seems required to release products, a number of runs were made with H₂O or D₂O or alcohols added to the THF as possible protonating agents or used to quench reactions which had been run in dry THF. The percentage of desired product increased slightly, but no conditions completely prevented over-reduction. When 5-10% H₂O or D₂O and 2 equiv of Na-AG were used at 25 °C, five reductions of compound 8 yielded $37 \pm 9\%$ desired product, compared with $19 \pm 3\%$ for six runs in dry THF.

Although the formation of over-reduced compounds could not be eliminated, the percent desired reduction at the N-O site alone is influenced by several factors. Complete over-reduction of 8 occurs in 2 h at 25 °C when 4 equiv of Na-AG are used, but about 25% simple N-O cleavage product is produced with 2 equiv. Lowering the temperature also yields more of the desired product although higher reagent amounts and/or longer reaction times are required.

Consistent with the idea that both N-O reduction and over-reduction processes happen in one encounter, sampling at time intervals through the reaction showed essentially no selectivity variation; except for a slight preference for N–O reduction early in the reaction, the relative ratios of reduced to over-reduced products were essentially independent of reaction progress. If protonation of the amide's N(-) site and release to solution occurred before reduction at the secondary site, the proportion of over-reduced intermediates formed in a second reduction step should vary, and reduced products should undergo further reduction; neither of these outcomes are seen.

The over-reduced product of the 4-chloro WA (compound 7), has the Cl replaced by H. Similarly, the reduction of the double bond in compound **8** requires the addition of two hydrogen atoms. In an attempt to determine the source of this hydrogen, the normal reduction in dry THF, followed by quenching with saturated NH₄Cl was modified (in separate experimental studies) by (1) reduction in deuterated THF, (2) quenching with D_2O and (3) reaction in THF containing small amounts of H₂O, D₂O, or deuterated alcohols. Product analyses (¹H NMR and GC-MS) in all cases showed at most small amounts of deuterium in the over-reduced products from either of these experiments (see Supporting information). The absence of deuterated over-reduced products suggests that the strongly basic amide anion and carbanion intermediates formed are bound to the alumina gel until protonation, which must occur at or near the site of reduction before the products migrate into the solution. Thus, proton donor sites must remain in the AG. Indeed, even after alumina calcination at 600 °C, -OH bands could be seen in FT-IR spectra of the AG, and the formation of hydrogen upon reaction with liquid Na₂K alloy verified the presence of at least

0.9 mmol of reducible Al-OH groups per gram of Al₂O₃, enough to protonate all reduced intermediates. Thus, the residual Al-OH groups on the surface of the alumina nanocrystals, and therefore near the encapsulated sodium, could provide the proton source. The variable density of such sites from sample to sample could also be responsible for the variations of desired versus overreduced product ratios from run to run. It had been thought that Al-OH groups would be eliminated by hydrogen production during normal preparation (by molten Na treatment at 160 °C) of Na-AG from alumina that had been calcined at 600 °C. However, careful monitoring of the gas phase during Na-AG preparation revealed that hydrogen is not formed during this incorporation of sodium.

The above findings prompted several attempts in D₂O under hydrothermal conditions to pre-deuterate the alumina used for preparation of the Na-AG. Despite the use of rigorous glassware drving and drvbox techniques, no replacement of H by D was seen. either by FT-IR of the dried, calcined AG, nor in either of the overreduction products from Na-AG treatment of 7 or 8.

The rearranged byproduct from compound **8** (Scheme 3) can most simply be understood in terms of base- or radical promoted elimination across the HCH₂-ON bond of the Weinreb amide to form formaldehyde. This electrophile, trapped in the pore in proximity to the reduced cinnamate anion evidently undergoes aldol condensation with the amide enolate, forming a hydroxymethyl group vicinal to the amide. Such base-promoted cleavage of Weinreb amides has been observed previously under treatment with strong bases such as LDA.²⁴ N-Hydroxymethylated amides have been produced in one case,²⁵ albeit in a Lewis acid context, but formaldehyde adducts directly analogous to the present case have not been reported from such reductions, even under conditions where enolate formation was verified via H/D exchange. Interestingly, in the present case, only the cinnamide 8 yields this product; its saturated analogue 3 yields no hydroxymethylation. We speculate in analogy to previous suggestions^{24,25} (Scheme 4) that the radical anion formed upon addition of an electron to the cinnamide pi system serves as a base to abstract one of the methoxy –OCH₂-H hydrogen atoms, forming the formaldehyde in close proximity to the enolate anion and leaving an unpaired electron on the amide N, which then rapidly accepts an additional electron.

In summary, this work shows that Na-AG and Na-SG easily and cleanly effect WA reduction in simple, batch reactions under ambient conditions and in modest reaction times. These reactions are not highly selective, but in situations with simple substrates or where global reduction is desired, they are quite effective. Cases where over-reduction occurs show how powerful the reducing agents Na-AG and Na-SG are, and demonstrate unambiguously that even after 600° calcination and treatment with molten sodium, the alumina in Na-AG retains a nontrivial load of -OH sites. In the absence of secondary reducible sites, this method can be usefully applied to WAs to form secondary amines under



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simple conditions and in reasonable yields. Though these reagents are not as selective as SmI_2 or Murphy's super electron donors, their simplicity, potent reducing power, and benign byproducts nonetheless make them a useful addition to the synthesis chemist's toolbox.

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Supplementary data

Supplementary data (experimental procedures and characterization of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09. 099. These data include MOL files and InChiKeys of the most important compounds described in this article.

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