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Some Unusual Reactions of Weinreb Amides

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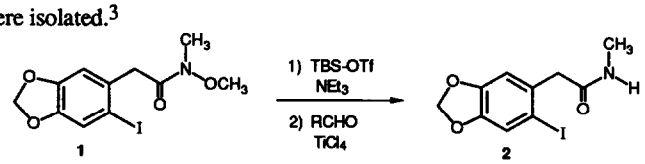
Abstract: Certain N-methoxy-N-methyl amides yield products of formal reduction and/or rearrangement upon exposure to *tert*-butyldimethylsilyl triflate and collidine or triethylamine.

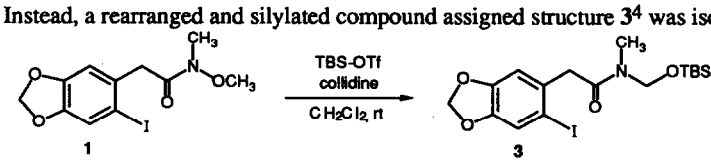
"Weinreb amides" (N-methoxy-N-methyl amides) are now well known as useful intermediates for a variety of synthetic transformations.[1] Recently, we had need of a β-hydroxy Weinreb amide and considered its preparation *via* a Lewis acid promoted condensation of a silyloxy enamine derived from a Weinreb amide with an aldehyde. Although there did not appear to be any direct precedent for such a transformation, other amides, including activated materials such as those derived from Oppolzer's sultams[2] have been successfully employed in such reactions.

Amide **1** was prepared from the corresponding carboxylic acid using a standard protocol ($SOCl_2$, followed by $H_2N^+(OCH_3)CH_3Cl^-$ in pyridine) and its condensation with an aldehyde was attempted using the general procedure of Oppolzer.[2] However, none of the desired material was obtained; only the reduced amide **2** and unreacted aldehyde were isolated.[3]



1 2

Since **2** corresponds to a reduction product of **1**, we considered the possibility that triethylamine might be functioning as a reducing agent in this system, a process which could be thwarted by simply employing an amine base structurally incapable of serving as a hydride donor. To this end, the reaction was repeated using collidine rather than triethylamine, and none of the reduced product **2** was obtained; neither, however, was the desired silyloxyenamine. Instead, a rearranged and silylated compound assigned structure **3**[4] was isolated.



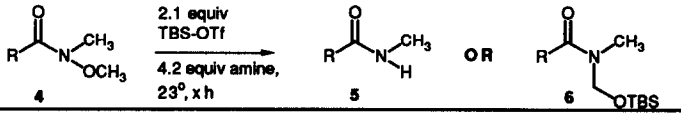
1 3

When the Weinreb amide derived from phenyl acetic acid (entry f, Table I) was subjected to TBS-OTf/collidine conditions the product **6** was obtained, along with an unusual dimer in low (14%) yield.[6]

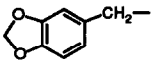
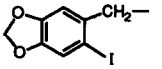
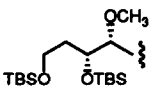
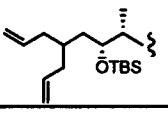
Control experiments revealed that neither TBS-OTf alone, triethylamine alone, or collidine alone would effect these reactions; both the silyl triflate and the amine were necessary. Other examples were investigated to determine whether such reactions were general or were restricted to the substituted aryl case **1**. As can be seen by an examination of the entries in Table I, both reactions appear to be general for Weinreb amides possessing a

CH_2 group adjacent to the carbonyl moiety of the amide; the presence of an alpha substituent either greatly slows the reaction (entry g) or completely precludes it (entries l and m). Substrates lacking alpha hydrogens also fail to react (entry k).

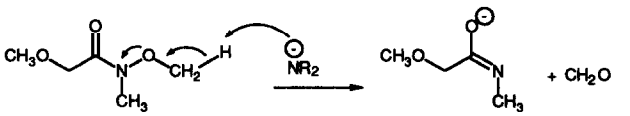
Table I[5]



4 5 6

Entry	(R)	Amine	Time (h)	Product	Yield
a		NEt_3	1.75 h	**5**	84%
b		collidine	2.0 h	**6**	57%
c		NEt_3	3.0 h	**5**	83%
d		collidine	2.0 h	**6**	43%
e	$PhCH_2$-	NEt_3	1.75 h	**5**	73%
f		collidine	2.0 h	**6**	49%
g	$(Ph)_2CH$-	NEt_3	61.0 h	**5**	41%
h		collidine	80.0 h	--	no reaction
i	$CH_3(CH_2)_{14}$	NEt_3	1.75h	**5**	92%
j		collidine	3.0 h	**6**	61%
k	Ph	NEt_3	>100.0 h	--	no reaction
l		NEt_3	48.0 h	--	no reaction
m		NEt_3	48.0 h	--	no reaction

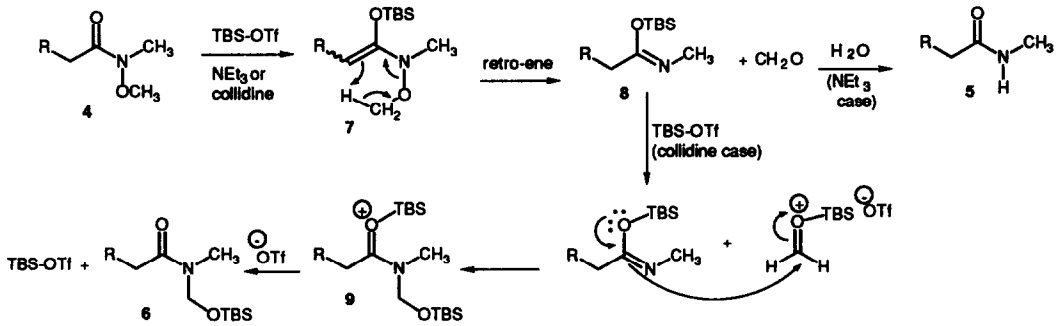
Although such reactions appear to be lacking specific precedent, Graham has reported that related reactions occur when certain Weinreb amides are treated with lithium diisopropylamide (LDA).[7] Apparently only the Weinreb amide derived from acetic acid can be successfully converted to the corresponding enolate under these conditions, as substituted derivatives suffer loss of formaldehyde to afford products similar to those described herein. A simple E_2 mechanism for the loss of formaldehyde was suggested. A mechanism involving initial formation of an enolate was considered but dismissed as inconsistent with the experimental evidence.



In contrast, such a mechanism (not involving an enol derivative) is inconsistent with the experimental data for the reactions reported herein with combinations of TBS-OTf and triethylamine or collidine. Weinreb amides

lacking alpha hydrogens are recovered unchanged in these reactions; amides with alpha substituents either react very slowly or not at all. These observations both suggest that formation of an enol derivative is a necessary step in the reaction mechanism leading to **5** or **6**; the most reasonable candidate for the structure of this enol derivative would be the TBS enol derivative **7**--the desired product when these reactions were initially undertaken. Retro-ene fragmentation, with cleavage of the weak N-O bond, would then yield **8** and monomeric formaldehyde; aqueous workup would afford **5**--the product obtained in all cases (Table I) using triethylamine as the base. Further reaction of **8** with formaldehyde, perhaps involving initial coordination of formaldehyde with *tert*-butyldimethylsilyl triflate as indicated, would lead to **6**--the product obtained in all cases using collidine as the base. Note Scheme I.

Scheme I: Proposed mechanism for the formation of products **5** and **6**



It remains to explain the dependence of product structure (**5** vs **6**) upon the base employed (triethylamine or collidine). In this regard, it is important to note that the experiments with triethylamine tabulated in Table I all reflect the outcome of optimized, standardized reaction conditions (2.1 equiv TBS-OTf, 4.2 equiv NEt_3) chosen to maximize the conversion of starting materials to products with relatively brief reaction times. Experiments with **4c** and triethylamine in which the stoichiometry of reagents was varied provide a clue as to the difference between the triethylamine and collidine reactions. Note Table II below.

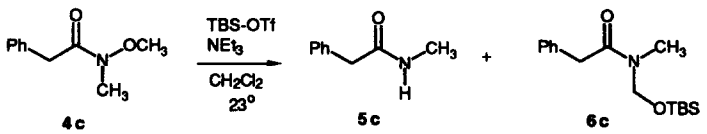


Table II. Product Ratios as a Function of Stoichiometry

Entry	TBS-OTf (equiv)	NEt_3 (equiv)	Ratio (**4c** : **5c** : **6c**)	Ratio **5c** : **6c**
1	1.2	3.0	56 : 23 : 21	1.1
2	2.1	2.1	36 : 48 : 16	3.0
3	2.1	2.4	13 : 75 : 12	6.0
4	2.1	2.7	15 : 80 : 5	16.0
5	2.1	3.0	1.5 : 98.5 : 0	--
6	2.1	3.5	0 : 100 : 0	--

In these experiments (entries 1-4) carried out to investigate stoichiometry, it can be seen that the rearranged silyloxymethyl derivative **6c** is in fact a product of the triethylamine reaction in the experiments represented by entries 1 and 2, when less TBS-OTf (entry 1) or less triethylamine (entry 2) is used than the 2.1 equiv and 3.5 equiv shown in entry 6, where the reduced amide is formed exclusively. More careful bracketing of triethylamine stoichiometry, holding TBS-OTf constant at 2.1 equiv (entries 3-5) shows that increasing the amount of triethylamine present suppressed the formation of **6c**, until at 3.5 equivalents, this product is not detected.

These results, along with those of the optimized and standardized experiments shown in Table I, suggest that the differences between the triethylamine reactions and those employing collidine may reflect the availability of monomeric formaldehyde. The simplest and most appealing explanation is that excess triethylamine reacts rapidly with monomeric formaldehyde (or it's complex with TBS-OTf) while collidine does not. Thus, in the collidine case, reaction between **8** (Scheme I) and formaldehyde leads to **9**. In the triethylamine case, both triethylamine and **8** compete for the formaldehyde formed. At lower triethylamine concentrations, **8** competes successfully. As the concentration of triethylamine increases, no monomeric formaldehyde is available for reaction with **8** and the isolated product is simply the reduced amide **5**.

In summary, two new reaction pathways for Weinreb amides have been uncovered. The triethylamine reaction represents a new method for the reductive cleavage of N-O bonds[8] in certain circumstances. Our main intent, however, is to relay our results to others who may consider employing Weinreb amides along the lines which led us to this investigation.

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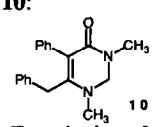
References:

1. (a) Sibi, M.P. *Organic Preparations and Procedures Int.* **1993**, *25*, 15. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Comm.* **1982**, *12*, 989. (c) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (d) Aidhen, I. S.; Ahuja, J. *Tetrahedron Lett.* **1992**, *33*, 5431. (e) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
2. Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61.
3. At this point, a control experiment using the N,N-dimethylamide corresponding to **1** was carried out, which gave the desired coupling product in high (83%) yield under exactly the same reaction conditions [illegible] set of protons corresponding to two different rotamers (~1:1). A variable temperature ^{1}H NMR experiment revealed that the rotamers undergo coalescence at ≈70 °C. (b) Product **6** (entry c) was treated with tetrabutylammonium fluoride and the reduced amide (product **5**) was isolated.
4. [illegible]
5. General procedure for reaction of Weinreb amides with TBS-OTf/base: To a stirring solution of the Weinreb amide in methylene chloride (0.1 M) was added either Et_3N or collidine (4.2 equiv) followed by TBS-OTf (2.1 equiv) at rt. The solution was stirred at rt for 1-3 h, monitoring disappearance of starting material by TLC. The mixture was quenched with saturated $NaHCO_3$ solution, the layers separated, and the aqueous layer extracted with methylene chloride. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude reaction mixtures were purified by flash chromatography and the products fully characterized.
6. The dimeric product was characterized by ^{1}H and ^{13}C NMR, IR, mass spectroscopy, and X-ray analysis and shown to have structure **10**:



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7. Graham S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269.
8. Keck, G. E.; Fleming, S. A.; Nickell, D.; Weider, P. *Synth. Comm.* **1979**, *9*(4), 281.

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