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Synthesis of *N*-Acyl-*N*,*O*-Acetals from *N*-Aryl Amides and Acetals in the Presence of TMSOTf

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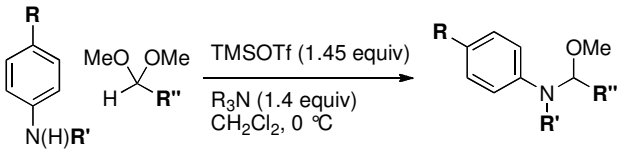

Abstract Secondary amides undergo in situ silyl imidate formation mediated by TMSOTf and an amine base, followed by addition to acetal acceptors to provide *N*-acyl-*N*,*O*-acetals in good yields. An analogous, high-yielding reaction is observed with 2-mercaptothiazoline as the silyl imidate precursor. Competing reduction of the acetal to the corresponding methyl ether via transfer hydrogenation can be circumvented by the replacement of *i*-Pr_2NEt with 2,6-lutidine under otherwise identical reaction conditions.

Keywords: *N*,*O*-acetal; silyl triflate; silyl trifluoromethanesulfonate; silyl imidate.
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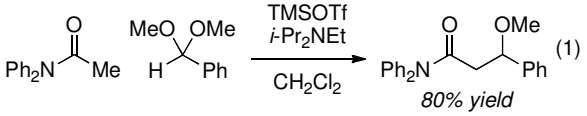
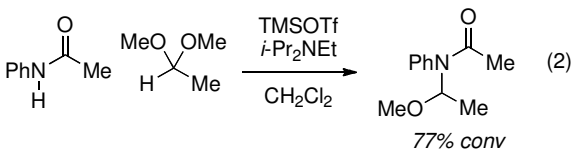
Addition of nucleophiles to *N*-acyliminium ions is a proven method for the construction of substituted amines.[1] Iminium ions derived in situ from *N*,*O*-acetals are popular electrophiles, and are often used in conjunction with Mannich reactions to yield β-amino carbonyl compounds[2] and organometallic additions to yield substituted alkyl amines,[3] among other reactions.[4] The *N*-acyl-*N*,*O*-acetal functionality is also a key component of important natural products like zampanolide[5] and psymberin.[6] Accordingly, a convenient synthesis of *N*-acyl-*N*,*O*-acetals from readily available starting materials would provide access to a class of compounds that may easily act as acyliminium ion precursors.[7] We now report that *N*-aryl amides can be *N*-alkoxyalkylated with acetals in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and a trialkylamine base, providing *N*-acyl-*N*,*O*-acetals in good yield.

In the course of our study of the Mukaiyama aldol reaction,[8] we examined the addition of in situ-generated silyl ketene acetals to dimethyl acetals, including nucleophiles derived from tertiary amides (eq 1).[9] When the tertiary amide was replaced with a secondary amide, however, methoxyalkylation was observed at the amide nitrogen rather than at the α carbon (eq 2). High conversion to the *N*,*O*-acetal occurred with only a trace of aldol-type adduct formation.





Given the importance of *N*-acyliminium ions, we chose to pursue optimization of this *N*,*O*-acetal formation reaction. Replacement of *i*-Pr_2NEt with Cy_2NMe provided improved and more reproducible product yields. A slight excess of TMSOTf (1.45 equiv) relative to acetal (1.4 equiv) was used to ensure that a catalytic amount of silylating agent remained in solution even after full conversion of the acetal to the oxocarbenium ion. After conversion to products was complete, the unpurified reaction mixture was quenched with pyridine in order to sequester any remaining TMSOTf, which otherwise facilitated product decomposition during purification on silica gel.

A reasonable mechanism for this one-pot silyl imidate formation-*N*,*O*-acetal formation reaction appears in Figure 1. Deprotonation of the TMSOTf-activated secondary amide with a trialkylamine rapidly generates a silyl imidate, a process that appears to be rapid and quantitative by ^{1}H NMR spectroscopy. Reaction of the acetal substrate with TMSOTf provides the oxocarbenium electrophile, which is attacked by the silyl imidate through a Mukaiyama aldol-like addition. Silyl transfer to another acetal provides the final product and generates another oxocarbenium ion, completing the reaction cycle.

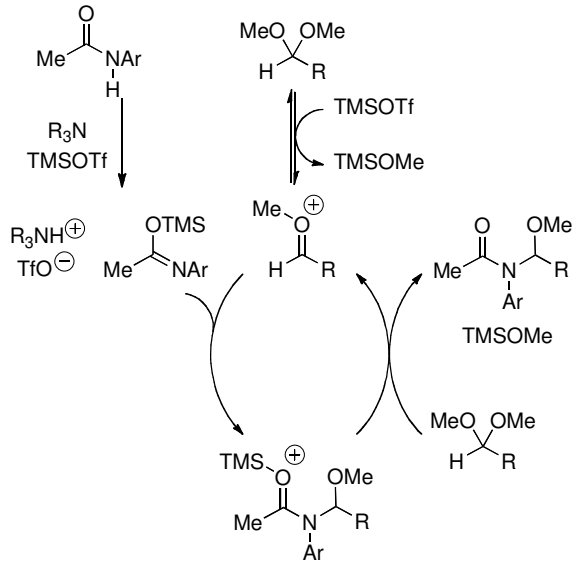
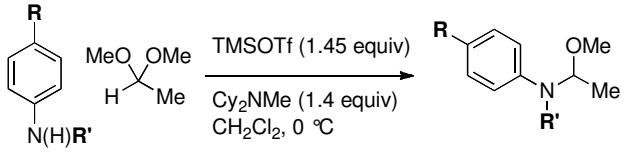
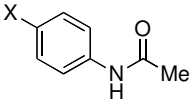
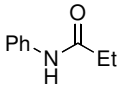
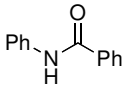
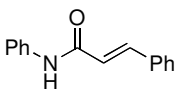


Figure 1. Proposed Mechanistic Scheme

The scope of the secondary amide reaction partner was determined through reaction with two representative acetals. A survey of condensations with acetaldehyde dimethyl acetal is summarized in Table 1. Various anilides performed well, including both electron-rich and electron-poor secondary amides. The poor reactivity displayed by acetanilide itself (entry 1) remains unexplained, but replacement of the acetyl group with other acyl groups (propionyl, benzoyl, cinnamoyl) provided good yields of the *N*,*O*-acetal. To date, amide nucleophiles appear to be limited to *N*-aryl secondary amides. Other silyl imidate precursors displayed no reactivity (*N*-alkyl) or provided complex mixtures of unidentified products (*N*-allyl, *N*-benzyl).

Table 1. Condensation of various anilides with acetaldehyde dimethyl acetal[a]

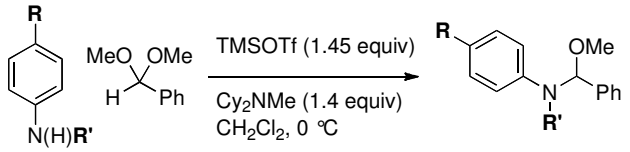


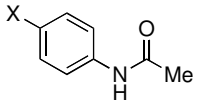
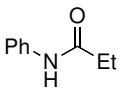
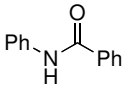
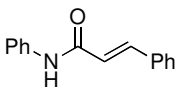
entry	amide		product	yield (%)[b]
1		X = H	**1**	41
2		X = OMe	**2**	68
3		X = NO_2	**3**	65
4			**4**	65
5			**5**	88
6			**6**	93

[a]Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0 °C, 2 h. [b]Isolated yield after chromatography.

Similar or better reactivity was observed when benzaldehyde dimethyl acetal was employed as the electrophile (Table 2). Whereas the oxocarbenium ion derived in situ from acetaldehyde dimethyl acetal was potentially susceptible to deprotonation to yield an enol ether, potentially instigating byproduct formation and loss in yield, the benzaldehyde derivative is not acidic. This observation may explain why acetaldehyde dimethyl acetal was an inferior reaction partner with acetanilide (Table 1, entry 1), but benzaldehyde dimethyl acetal reacted quite efficiently, providing an isolated yield of 74% (Table 2, entry 1). Propionanilide displayed a similar increase in yield with benzaldehyde dimethyl acetal (89% vs. 65%, entry 2). The other anilides investigated reacted similarly well (entries 3-6).

Table 2. Addition of various anilides to benzaldehyde dimethyl acetal[a]

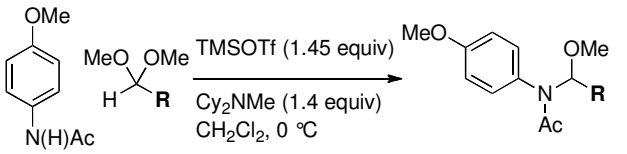


entry	amide		product	yield (%)[b]
1		X = H	**7**	74
2		X = OMe	**8**	73
3		X = NO_2	**9**	69
4			**10**	89
5			**11**	76
6			**12**	93

[a]Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0 °C, 2 h. [b]Isolated yield after chromatography.

The representative *N*-aryl amide *p*-methoxyacetanilide was chosen for a survey of various acetals under our optimized reaction conditions (Table 3). For some substrates, the use of Cy_2NMe resulted in the competitive reduction of the acetals to the corresponding aryl methyl ethers (vide infra), so 2,6-lutidine was employed as a surrogate. Under the appropriate reaction conditions, acetals derived from aromatic or heteroaromatic aldehydes generally performed well (entries 3-7). Yields were lower for aliphatic acceptors (entries 1-2), presumably because of competing enol ether formation via deprotonation of the oxocarbenium ion.

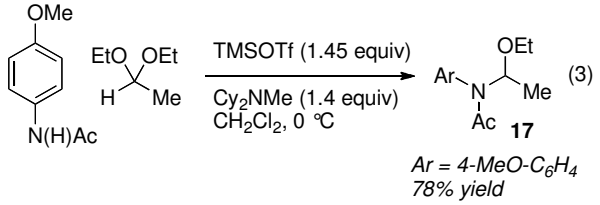
Table 3. Condensation of *p*-methoxyacetanilide with various dimethyl acetals[a]



entry	R	product	yield (%)[b]
1	Me	**2**	68
2	Et	**13**	52
3	X = H	**8**	73
4	X = Br	**14**	99[c]
5	X = MeO	**15**	77[c]
6		**16**	61

[a]Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0 °C, 2 h. [b]Isolated yield after chromatography. [c]2,6-lutidine was used instead of Cy_2NMe.

Despite attempts at re-optimization, however, for some other acetals were inferior substrates. For example, 2-thiophene carboxaldehyde dimethyl acetal appeared to react cleanly but the product was unstable to chromatography. Initial conversion for formaldehyde dimethyl acetal (dimethoxymethane) appeared to be 80-90%, but the preliminary product quickly decomposed under the reaction conditions. Glycosidation-like reactions with 2-methoxytetrahydropyran provided intractable mixtures. The reaction was effective, however, for the diethyl acetal of acetaldehyde, which reacted to afford desired product **17** in 78% yield (eq 3).



As mentioned above, formation of aryl methyl ethers occurred as a major side reaction during the attempted condensation reactions with some aryl acetals. A number of further observations led us to hypothesize that ether formation occurs via transfer of a hydride from the trialkylamine base to the oxocarbenium ion, as illustrated in Figure 2. First, the ether byproduct was observed in some reactions when Cy_2NMe or *i*-Pr_2NEt was used as base, but never when 2,6-lutidine was employed as base, presumably because 2,6-lutidine bears no α hydrogens that may be transferred to the oxocarbenium ion. Second, no reaction was observed when the dimethyl acetal was stirred with TMSOTf in the absence of amine. Third, when the amine base was replaced with cyclohexadiene, a known hydride donor, similar reduction to the methyl ether was observed.

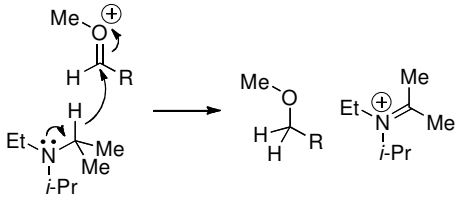
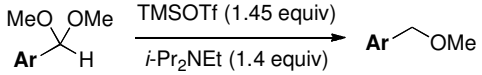


Figure 2. Reduction of oxocarbenium ion by *i*-Pr_2NEt

Noyori has reported that TMSOTf catalyzes the reduction of dimethyl acetals with silanes.[10] We attempted to optimize a similar reaction with *i*-Pr_2NEt as the hydride source, as summarized in Table 4. In general, conversion for the electron-rich *p*-anisaldehyde (entry 2) was consistently higher than for other aromatic dimethyl acetals (entries 3-5). More discouragingly, isolated yields for these reactions did not approach the conversions observed by ^{1}H NMR spectroscopy. Overreduction of the acetal carbon to the corresponding methyl group was observed, but only in trace amounts that did not account for the loss of yield. In order to rule out volatility of the product as a problem, 2-naphthaldehyde dimethyl acetal was subjected to the reaction conditions. Despite a 95% conversion to the methyl ether, only 32% yield was isolated after chromatography. Further attempts at optimization of the reduction were abandoned.

Table 4. Reduction of dimethyl acetals to methyl ethers[a]



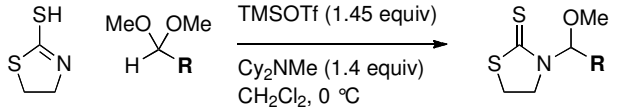
entry	solvent	Ar		conv (%)[b]	yield (%)[c]
1	CH_2Cl_2		X = OMe	67	20
2	Et_2O		X = OMe	94	23
3	Et_2O		X = H	69	ND[d]
4	Et_2O		X = Br	65	27
5	Et_2O		X = Cl	57	ND[d]
6	Et_2O			95	32

[a]Standard reaction conditions: acetal (2.00 mmol), TMSOTf (2.90 mmol), *i*-Pr_2NEt (2.80 mmol), solvent (10 mL), rt, 2 h. [b]Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [c]Isolated yield after chromatography. [d]ND = Not Determined

Upon completion of the anilide study, we expanded the *N*,*O*-acetal formation reaction to include the thioamide equivalent 2-mercaptothiazoline. The products of these reactions are *N*-(1-alkoxy)alkylated thiazolidinethiones, compounds that hold promise as precursors to *N*-acyliminium ions equivalents.[11] The results of this survey are summarized in Table 5. The identity of the products was confirmed by X-ray crystallographic analysis of a single crystal of product **21**.[12] Yields were consistently

high, although replacement of Cy_2NMe with 2,6-lutidine was necessary in some cases. Even formaldehyde dimethyl acetal, an inferior acetal when reacted with *p*-methoxyacetanilide, provided a good yield of the methoxymethylated thiazolidinethione. Interestingly, the formaldehyde dimethyl acetal reaction suffered slightly from byproduct formation even when 2,6-lutidine was employed as the base. In this instance, however, the observed byproduct was not the reduced acetal, but rather appeared to be a methylene-bridged bis-thiazolidinethione. Future efforts will be directed toward the synthesis and applications of chiral versions of these thiazolidinethione species because of their prevalent position as chiral auxiliaries in organic synthesis.[13]

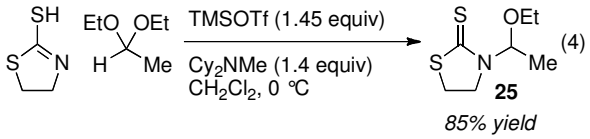
Table 5. Condensation of 2-mercaptothiazoline with dimethyl acetals[a]



entry	R	product	yield (%)[b]
1	Me	**18**	97
2	Et	**19**	85
3	X = H	**20**	88
4	X = Br	**21**	98
5	X = MeO	**22**	89[c]
6		**23**	83
7	H	**24**	68[c,d]

[a]Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0 °C, 2 h. [b]Isolated yield after chromatography. [c]2,6-lutidine was used instead of Cy_2NMe. [d]Product was contaminated with approximately 5 mol% side product (see text).

Condensation of 2-mercaptothiazoline with the diethyl acetal of acetaldehyde under typical reaction conditions was plagued by competing enol ether formation. Substitution of Cy_2NMe with the less basic 2,6-lutidine alleviated this issue, allowing *N*,*O*-acetal **25** to be isolated in 85% yield (eq 4).



In conclusion, TMSOTf mediates the one-pot silyl imidate formation-*N*,*O*-acetal formation reactions of secondary amides and thioamide equivalents. The reaction is general to *N*-aryl amides, and performs competently with acetals derived from both aryl and aliphatic aldehydes. It appears that TMSOTf plays two roles in this reaction, silylating an alkoxy group on the acetal and activating the amide toward deprotonation. Further investigations of these *N*-acyliminium ion precursors will be reported in due course.

Acknowledgment We gratefully acknowledge Research Corporation and the American Chemical Society-Petroleum Research Fund for funding. A.S.F. acknowledges the University of Richmond Department of Chemistry for a Puryear-Topham fellowship. We thank Dr. Diane Kellogg for assistance with mass spectral data. We are indebted to NSF (CHE-0443345) and the College of William and Mary for the purchase of the X-ray equipment, and to NSF (CHE-0541848) and the University of California-Riverside for mass spectral data.

Supplementary Data Experimental procedures and spectral data. Tables of crystal data, atomic coordinates, bond lengths and angles, and anisotropic displacement parameters.

1. For reviews, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817-3856; (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339-368; (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513-541.

2. For recent examples, see (a) Kamogawa, S.; Ikeda, T.; Kuriyama, M.; Matsumura, Y.; Onomura, O. *Heterocycles* **2010**, *82*, 325-332; (b) Sakai, N.; Sato, A.; Konakahara, T. *Synlett* **2009**, 1449-1452.

3. For recent examples, see (a) Hirner, S.; Somfai, P. *J. Org. Chem.* **2009**, *74*, 7798-7803; (b) Sakai, N.; Asano, J.; Kawada, Y.; Konkahara, T. *Eur. J. Org. Chem.* **2009**, 917-922.

4. For recent examples, see: (a) Yamaguchi, Y.; Hashimoto, M.; Tohyama, K.; Kimura, M. *Tetrahedron Lett.* **2011**, *52*, 913-915; (b) Kim, C.; Bae, J. J.; Lee, J. H.; Jeong, W.; Kim, H.; Sampath, V.; Rhee, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14660-14661; (c) Yian, Y.-G.; Wang, X.-W.; Zheng, X.; Ruan, Y.-P.; Huang, P.-Q. *Chem. Commun.* **2009**, 7045-7047.

5. Konishi, M.; Saito, K.; Numata, K.; Tsuno, T.; Asama, K.; Tsukiura, H.; Naito, T.; Kawaguchi, H. *J. Antibiot.* **1977**, *30*, 789-805.

6. (a) Pettit, G. R.; Xu, J.; Chapuis, J.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149-1152; (b) Cichewicz, R. J.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951-1954.

7. For previous syntheses of *N*-acyl-*N*,*O*-acetals, see (a) Wan, S.; Green, M. E.; Park, J.-H.; Floreancig, P. E. *Org. Lett.* **2007**, 5385-5388; (b) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216-12217; (c) Kiren, S.; Shangguan, N.; Williams, L. J. *Tetrahedron Lett.* **2007**, *47*, 7456-7459; (d) Venkov, A. P.; Minkov, M. M.; Lukanov, L. K. *Synth. Commun.* **1989**, *19*, 2133-2139. For a synthesis of related *N*,*O*-acetals, see (e) Fujioka, H.; Kubo, O.; Senami, K.; Okamoto, K.; Okitsu, T.; Kita, Y. *Heterocycles* **2009**, *79*, 1113-1120.

8. (a) Downey, C. W.; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559-3562; (b) Downey, C. W.; Johnson, M. W.; Lawrence, D. H.; Fleisher, A. S.; Tracy, K. J. *J. Org. Chem.* **2010**, *75*, 5351-5354.

9. Downey, C. W.; Johnson, M. W.; Tracy, K. J. *J. Org. Chem.* **2008**, *73*, 3299-3302.

10. Silyl trifluoromethanesulfonate-catalyzed reductions of acetals with silanes: (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, *20*, 4679-4680.

11. For recent examples of related oxazolidinones as acyliminium ion precursors, see: a) Le Corre, L.; Kizirian, J.–C.; Levraud, C.; Boucher, J.–L.; Bonnet, V.; Dhimane, H. *Org. Biomol. Chem.* **2008**, *6*, 3388-3398. b) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608-1617. c) David, M.; Dhimane, H.; Vanucci-Bacque, C.; Lhommet, G. *Synlett* **1998**, 206-208.

12. Coordinates have been deposited at the CCDC, deposition number CCDC 824052. See supplementary data for cif file and ORTEP diagram.

13. For recent examples, see: (a) Galvez, E.; Larrosa, I.; Romea, P.; Urpí, F. *Synlett* **2009**, 2982-2986. (b) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061-15074. (c) Crimmins, M. T.; Stevens, J. M.; Schaaf, G. M. *Org. Lett.* **2009**, *11*, 3990-3993.