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C. Wade Downey
University of Richmond, wdowney@richmond.edu

Grace Ann L. Robertson

Jhonmattew Santa

Kari R. Flicker

William M. Stith

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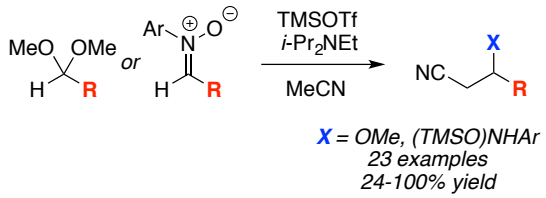
C. Wade Downey, Grace Ann L. Robertson, Jhonmattew Santa, Kari R. Flicker, and William M. Stith*

University of Richmond
Gottwald Center for the Sciences
28 Westhampton Way
Richmond, VA 23173
wdowney@richmond.edu

ABSTRACT

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) and a trialkylamine base promote the conversion of acetonitrile to its silyl ketene imine in situ when acetonitrile is employed as solvent. Residual TMSOTf acts as a Lewis acid catalyst to activate acetals and nitrones in the reaction mixture, yielding β-methoxynitriles and β-(silyloxy)aminonitriles, respectively. Some reaction products undergo elimination under the reaction conditions to provide the α,β-unsaturated nitrile directly.



One-pot silyl ketene imine formation-nucleophilic addition reactions of acetonitrile with acetals and nitrones

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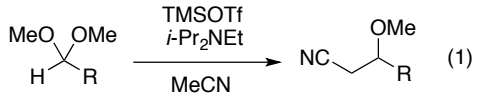
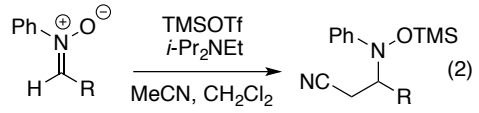
Keywords: acetonitrile; silyl ketene imine; silyl triflate; acetals

The prevalence of the cyano functional group in natural products[1] and pharmaceuticals[2] drives persistent study of the synthesis of elaborated nitriles, and their synthetic versatility and stability makes them convenient building blocks for total synthesis.[3] The α substitution of nitriles under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was first reported by Simchen and Emde, who observed that treatment of acetonitrile with TMSOTf and a trialkylamine produced (trimethylsilyl)acetonitrile.[4] More recently, Yoshimura and Tanino have described one-pot reactions wherein various nitriles were treated with a sterically encumbered silyl triflate (TESOTf or TIPSOTf) and an amine base (Et_3N or 2,2,6,6-tetramethylpiperidine) to generate silyl ketene imine nucleophiles that can be used for the cyanoalkylation of aldehydes and nitrones, among other reactions.[5] These one-pot reactions provide practical and efficient alternatives to traditional, base-mediated syntheses of α-substituted nitriles, especially for aldol and related products that are prone to elimination or retroaddition.[6] We recently reported the TMSOTf-promoted condensation of (trimethylsilyl)acetonitrile with dimethyl acetals to yield β-methoxynitriles under conditions where other Lewis acids appeared to be ineffective.[7] We now disclose TMSOTf-promoted one-pot reactions in which acetonitrile is converted to its silyl ketene imine prior to attack upon acetal and nitrone electrophiles (eq 1, 2).



(1)



(2)

Prior work in our laboratory established that acetonitrile was the most effective solvent for the TMSOTf-promoted condensation of (trimethylsilyl)acetonitrile with dimethyl acetals.[7] Given the high cost and limited availability of commercial (trimethylsilyl)acetonitrile ($18/g), in situ formation of the required nucleophile is a more convenient and economical option. Recent results from our laboratory showed that esters are converted to silyl ketene acetals by TMSOTf and trialkylamines without competing self-condensation, even when the ester is employed as solvent,[8] which suggested that a similar strategy might be employed with acetonitrile.[9] When benzaldehyde dimethyl acetal was treated with TMSOTf (2.1 equiv) and *i*-Pr_2NEt (1.1 equiv) in acetonitrile, conversion to the β-methoxynitrile was observed with minimal formation of the α,β-unsaturated nitrile byproduct. A brief survey of other trialkylamines (Et_3N, Cy_2NMe, 2,6-lutidine) and cosolvents (CH_2Cl_2, toluene, Et_2O, hexane) did not result in an improvement in conversion,

although the inclusion of hexane as a cosolvent appeared to result in lower amounts of byproduct formation in some cases. More significantly, a brief incubation period (1 h), which may allow in situ formation of the silyl ketene imine nucleophile[10,11,12] in equilibrium amounts prior to addition of the acetal, led to generally superior results (eq 3).

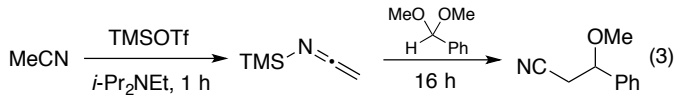
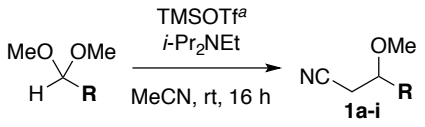


Table 1 illustrates the scope of this one-pot reaction. The optimized reaction conditions were highly effective for reactions of acetals derived from benzaldehyde derivatives, generally providing yields from 80-100%. The electron-poor nitrobenzaldehyde derivative, however, suffered from low conversion and the bulk of the mass balance in the unpurified reaction mixture consisted of the parent aldehyde. Notably, the electron-poor (4-trifluoromethyl)benzaldehyde derivative afforded 87% yield of the desired product, which suggests that the electron deficiency of the 4-nitro derivative may not be responsible for its poor reactivity. Some substrates reacted more efficiently when hexane was added as a cosolvent, including two halogenated derivatives (entries 4,5). The 4-chloro- and 4-bromobenzaldehyde derivatives reacted somewhat sluggishly at room temperature, but smoothly afforded the desired product when heated to 70 °C for 2 h. Attempts to synthesize heteroaryl-substituted nitriles resulted only in decomposition of the electrophile (entry 8), but some reactivity was observed for the purely aliphatic cyclohexyl substrate (entry 9). When the electron-rich dimethyl acetal derived from *p*-anisaldehyde was subjected to the reaction conditions, an intractable reaction mixture dominated by the α,β-unsaturated nitrile product was observed, in analogy to previously reported results.[7]

Table 1. Reaction of acetonitrile with various dimethyl acetals

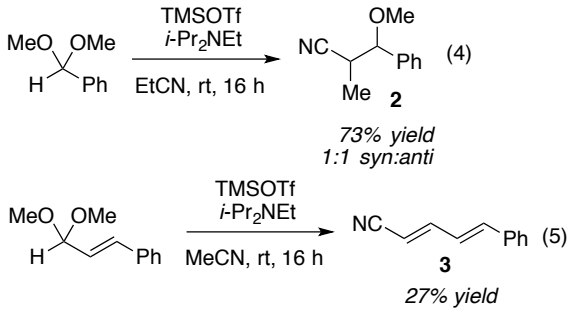


entry	**R**	product	yield (%)[b]
1	Ph	**1a**	100
2	4-(NO_2)Ph	**1b**	36
3	4-(CF_3)Ph	**1c**	87
4	4-ClPh	**1d**	85[c,d]
5	4-BrPh	**1e**	92[c,d]
6	4-MePh	**1f**	86[c]
7	2-naphthyl	**1g**	81[c]
8	2-thienyl	**1h**	0[e]
9	Cy	**1i**	24

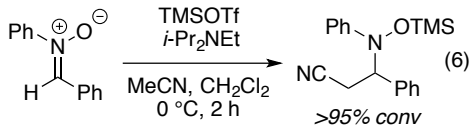
a. Reaction conditions: 1. MeCN (2.5 mL), TMSOTf (2.06 mmol), *i*-Pr_2NEt (1.12 mmol), rt, 1h. 2. Acetal (1.0 mmol), 16 h.
b. Isolated yield after chromatography.

c. Hexane (12.5 mL) was added as a cosolvent.
d. After addition of the acetal, the reaction was heated to reflux (70 °C) for 2 h.
e. Decomposition of the acetal was observed.

The scope of this reaction is not limited to the examples illustrated in Table 1. For example, when benzaldehyde dimethyl acetal was added to a mixture of propionitrile, TMSOTf, and *i*-Pr_2NEt, the β-methoxynitrile was provided as a mixture of diastereomers in 73% yield (eq 4). When the acetal featured alkenyl substitution, a notable change in chemoselectivity occurred. Cinnamaldehyde dimethyl acetal was subjected to the standard reaction conditions, but elimination occurred under the reaction conditions to yield the α,β,γ,δ-unsaturated nitrile (eq 5).



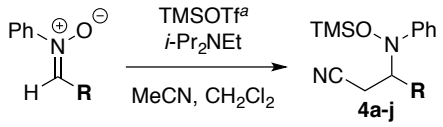
Based on the success of the reactions of acetonitrile with acetals, the application of this method to the cyanomethylation of nitrone electrophiles was targeted in order to provide products that can act as β-amino acid precursors.[13] Yoshimura and Tanino have shown that α-substituted nitriles can be converted to their silyl ketene imines in situ prior to addition to nitrones, but the use of acetonitrile itself has not been addressed in this context. Based upon our previous success with nitrone electrophiles under silylative conditions[14] and the successful development of the dimethyl acetal methodology described above, a standard set of reaction conditions was rapidly established. Acetonitrile again proved viable as both reaction solvent and substrate, but reactivity was somewhat sluggish due to the poor solubility of the nitrone electrophiles. To combat this problem, a small amount of CH_2Cl_2 (~10% by volume) was added to the reaction mixture, and high conversion to the β-(silyloxy)aminonitrile was observed (eq 6).



A variety of nitrones reacted under similar conditions, as illustrated in Table 2. Nitrones derived substituted from benzaldehydes proved to be excellent substrates, providing the conveniently protected products in 65-84% yield (entries 1-6). Even the electron-rich *p*-anisyl nitrone, which is particularly prone to rearrangement to the N-aryl amide at warmer temperatures,[14b] reacted efficiently at room temperature. Heteroaryl substitution, which was incompatible with the acetal reactions described above, provided no obstacle in the nitrone case and both the furyl and thienyl substrates reacted in acceptable yield (entries 7-

8). In further contrast with the acetal electrophiles, a cinnamyl nitrone reacted without elimination to yield the desired β-(silyloxy)aminonitrile when the reaction was conducted at 0 °C (entry 9), and the challenging cyclohexane derivative reacted in good yield (entry 10).

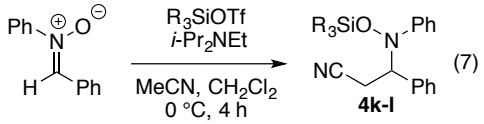
Table 2. Addition of acetonitrile to various nitrones



entry	**R**	T (°C)	*t*	product	yield (%)[b]
1	Ph	0	2 h	**4a**	84
2	4-(NO_2)Ph	23	2 h	**4b**	65
3	4-FPh	0	2 h	**4c**	85
4	4-BrPh	23	2 h	**4d**	66
5	4-MePh	23	16 h	**4e**	78
6	4-MeOPh	23	2 h	**4f**	83
7	2-furyl	0	2 h	**4g**	53
8	2-thienyl	23	16 h	**4h**	80
9	cinnamyl	0	2 h	**4i**	64
10	Cy	23	2 h	**4j**	76

a. Reaction conditions: nitrone (1.00 mmol), MeCN (10 mL), CH_2Cl_2 (1 mL), *i*-Pr_2NEt (1.50 mmol), TMSOTf (1.40 mmol).
b. Isolated yield after chromatography.

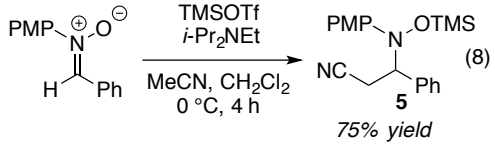
Substitution of TMSOTf with other silylating agents provided very good results, yielding products with more robust protecting groups. For example, the use of triethylsilyl trifluoromethanesulfonate (TESOTf) resulted in the generation of the TES-protected product in 85% yield, and the analogous reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) afforded the desired TBS-protected product in 89% yield.



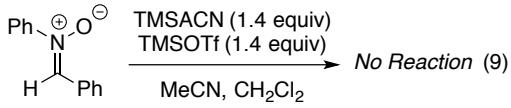
R_3Si = TES: ***4k****, 85% yield*
R_3Si = TBS: ***4l****, 89% yield*

No reactivity was observed when N-phenyl nitrones were replaced with their N-methyl or N-*tert*-butyl analogs. Although N-phenyl nitrones were the reactants of choice for this study because of their reactivity and the ease of their synthesis, the use of a more labile protecting group would greatly increase the applicability of this methodology. Accordingly, the (*p*-methoxyphenyl)nitrone illustrated in eq 8 was subjected to the

standard reaction conditions, and a 75% yield of the PMP-protected β-(silyloxy)amino nitrile was recovered.[15] Product **5** decomposed significantly during standard silica gel chromatography, but high yields were achieved by replacement of silica gel with basic alumina, *or* by the addition of 1% Et_2NH (v/v) to the mobile phase.



Although the lifetime of the putative silyl ketene imine nucleophile is too fleeting for observation,[12] our previous work with acetal electrophiles suggests that it may be accessible through the reaction of (trimethylsilyl)acetonitrile (TMSACN) with TMSOTf, even in the absence of base.[7] Whereas TMSACN reacts smoothly with acetals in the presence of TMSOTf, however, similar attempted reactions with a standard nitrone electrophile failed (eq 9). It appears that, in contrast with the dimethyl acetal substrates, the more Lewis basic nitrone disrupts the TMSOTf-promoted equilibrium between TMSACN and the nucleophilic silyl ketene acetal. Accordingly, the one-pot silyl ketene imine formation-Mannich addition method is superior to the use of TMSACN for practical as well as economic reasons.



In conclusion, a convenient and reliable set of addition reactions has been developed where the nucleophilic silyl ketene imine is generated in situ from acetonitrile, TMSOTf, and a trialkylamine. Residual TMSOTf activates acetal or nitrone electrophiles via a Mukaiyama-like pathway to provide β-methoxy or β-(silyloxy)amino nitriles respectively with minimal elimination byproducts.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxx. These data include MOL files and InChiKeys of the most important compounds described in this article.

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