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# Mukaiyama addition of (trimethylsilyl) acetonitrile to dimethyl acetals mediated by trimethylsilyl trifluoromethanesulfonate

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**Mukaiyama addition of (trimethylsilyl)acetonitrile to dimethyl acetals mediated by trimethylsilyl trifluoromethanesulfonate**

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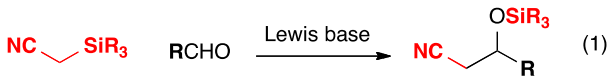
ABSTRACT

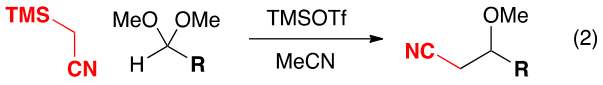
(Trimethylsilyl)acetonitrile reacts smoothly with dimethyl acetals in the presence of stoichiometric trimethylsilyl trifluoromethanesulfonate (TMSOTf) to yield β-methoxynitriles. The ideal substrates for this reaction are acetals derived from aromatic aldehydes. Elimination to the corresponding α,β-unsaturated nitriles is observed as the major product in the case of electron-rich acetals. A mechanistic hypothesis that includes isomerization of the silylnitrile to a nucleophilic N-silyl ketene imine is presented.

Aldol reactions of nitrile-derived enolate analogs have typically been carried out under very basic conditions and are often prone to retro-aldol reaction or dehydration to yield the α,β-unsaturated nitrile.[1] When nitriles are temporarily converted to α-silylnitriles, however, addition to aldehydes is known to proceed under Lewis basic conditions. Silyl transfer to the nascent aldolate produces a silyl ether not prone to reversion or elimination (eq 1). A variety of Lewis basic catalysts have proven capable of mediating this reaction, including cyanide,[2] fluoride,[3] acetate,[4] DMSO,[5] and phosphine derivatives.[6] Aldol reactions of the related silyl ketene imine nucleophiles have been rendered asymmetric by Denmark,[7] and certain silyl ketene imines have been generated in situ from α-aryl nitriles by Yoshimura and Tanino.[8]



(1)

We speculated that by replacement of the aldehyde with a dimethyl acetal and introduction of a Lewis acid, an oxocarbenium ion could be generated that would be attacked by the mild silylnitrile nucleophile. Our previous experience with the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to activate dimethyl acetals[9] suggested the investigation of its utility in this context. We now report that TMSOTf efficiently mediates the condensation of (trimethylsilyl)acetonitrile with dimethyl acetals in acetonitrile to provide β-methoxynitriles.



(2)

We began our study of the reaction of (trimethylsilyl)acetonitrile with dimethyl acetals under reaction conditions very similar to those reported by Mukaiyama for the acetate-catalyzed aldol reactions of α-silylnitriles with aldehydes.[4] In addition to the precedented strategy of employing a nucleophilic catalyst to activate the silylnitrile, we added the Lewis acidic TMSOTf to activate the acetal. We found early success with the combination TMSOTf and tetrabutylammonium

acetate in toluene, but control experiments quickly showed that only the TMSOTf was necessary to mediate the reaction. To our surprise, a search of the literature revealed no similar Lewis acid-mediated additions of silylnitriles to acetals. Accordingly, we surveyed the ability of several common, mild Lewis acids to facilitate this transformation.

In the first round of experiments, 25 mol% catalyst ($LiClO_4$, $MgBr_2$•$OEt_2$, $ZnBr_2$, $Yb(OTf)_3$, $In(OTf)_3$, $Cu(OAc)_2$, $BF_3$•$OEt_2$, or TMSOTf) was added to a solution of (trimethylsilyl)acetonitrile and benzaldehyde dimethyl acetal in $CH_2Cl_2$. After 1 h, only TMSOTf showed any reactivity (8% conv). Intrigued by the apparently unique reactivity of TMSOTf, we conducted further optimization experiments under stoichiometric conditions (Table 1). When the amount of TMSOTf was increased to 1.2 equiv, an increase in reactivity was observed after 1 h in $CH_2Cl_2$ (33% conv, entry 1). A survey of common reaction solvents showed that acetonitrile was optimal, providing 62% conv after 1 h (entry 5). At this point, the original set of Lewis acids was re-tested under stoichiometric conditions (entries 6-13). Again, most of the potential catalysts effected no desired reactivity. Other than TMSOTf, only $BF_3$•$OEt_2$ showed any success, providing 23% conversion to the desired product (entry 7).[10] Accordingly, we chose to focus on TMSOTf as the Lewis acid of choice for this transformation.

**Table 1**
Optimization


| entry | Lewis acid | solvent | conditions[a] | conv (%)[b] |
|---|---|---|---|---|
| 1 | TMSOTf | $CH_2Cl_2$ | A | 33 |
| 2 | TMSOTf | toluene | A | 57 |
| 3 | TMSOTf | CPME | A | 47 |
| 4 | TMSOTf | $Et_2O$ | A | 25 |
| 5 | TMSOTf | MeCN | A | 62 |
| 6 | TMSOTf | MeCN | B | 70 |
| 7 | $BF_3$•$OEt_2$ | MeCN | B | 23 |
| 8 | $LiClO_4$ | MeCN | B | 0 |
| 9 | $MgBr_2$•$OEt_2$ | MeCN | B | 0 |
| 10 | $ZnBr_2$ | MeCN | B | 0 |
| 11 | $Yb(OTf)_3$ | MeCN | B | 0 |
| 12 | $In(OTf)_3$ | MeCN | B | 0 |
| 13 | $Cu(OAc)_2$ | MeCN | B | 0 |

[a]Conditions A: 0.20 mmol acetal, 0.20 mmol (trimethylsilyl)acetonitrile, 0.20 mmol TMOSTf, solvent, 1 h. Conditions B: 0.22 mmol acetal, 0.24 mol catalyst, 0.16 mmol (trimethylsilyl)acetonitrile, 250 μL solvent, 1 h.

[b]Determined by $^1$H NMR spectroscopy of the unpurified reaction mixture

Once the optimal solvent and Lewis acid were identified, the reaction time was extended to 16 h to achieve full conversion with the benzaldehyde dimethyl acetal substrate. When the reaction was performed on a 1.0 mmol scale, 82% isolated yield of desired methyl ether **1a** was achieved.

A description of the further scope of this reaction is illustrated in Table 2. Acetals derived from halobenzaldehydes were especially effective (entries 2-4). Tolyl-substituted product **1e** (entry 5), however, suffered a slightly depressed yield because elimination to the cinnamonitrile derivative proved facile under the reaction conditions and during chromatography. Indeed, when product **1e** was purified and resubjected to TMSOTf in acetonitrile for a further 24 h, 43% conversion to the cinnamonitrile was observed.[11] On the other hand, electron-poor acetals delivered the desired methyl ether products **1** quite smoothly (Table 1, entries 6-7), and bulky aromatic groups were also well tolerated (entries 8-9). Although unbranched aliphatic acetals (e.g., propionaldehyde dimethyl acetal, acetaldehyde dimethyl acetal) afforded no desired products under these conditions, the branched cyclohexyl derivative provided 25% yield (entry 10).

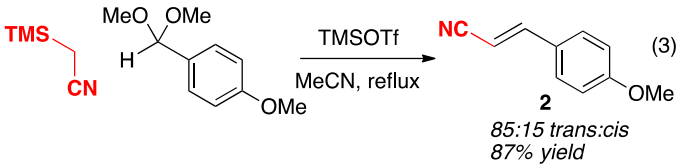
**Table 2**
Reaction scope


| entry | R | product | yield (%)[b] |
|---|---|---|---|
| 1 | Ph | **1a** | 85 |
| 2 | 4-$FC_6H_4$ | **1b** | 90 |
| 3 | 4-$ClC_6H_4$ | **1c** | 81 |
| 4 | 4-$BrC_6H_4$ | **1d** | 85 |
| 5 | 4-$MeC_6H_4$ | **1e** | 68 |
| 6 | 4-$NO_2C_6H_4$ | **1f** | 71 |
| 7 | 4-$CF_3C_6H_4$ | **1g** | 82 |
| 8 | 1-naphthyl | **1h** | 59 |
| 9 | 2-naphthyl | **1i** | 80 |
| 10 | cyclohexyl | **1j** | 25 |

[a]Reaction conditions: 1.0 mmol acetal, 1.2 mmol TMSOTf, 1.4 mmol (trimethylsilyl)acetonitrile, 5 mL MeCN, 16 h, rt.

[b]Isolated yield after chromatography

When the strongly electron-rich anisyl derivative was used, cinnamonitrile **2** was observed to be the major reaction product, even at shorter reaction times (eq 3). Accordingly, the reaction conditions for this specific substrate were re-optimized to favor α,β-unsaturated product **2**. When the reaction was stirred at reflux for 1 h, an 87% yield of the cinnamonitrile (85:15 trans:cis) was obtained. Other electron-rich acetals (2-furyl, 2-thiophenyl), however, decomposed under all reaction conditions and yielded no identifiable products.

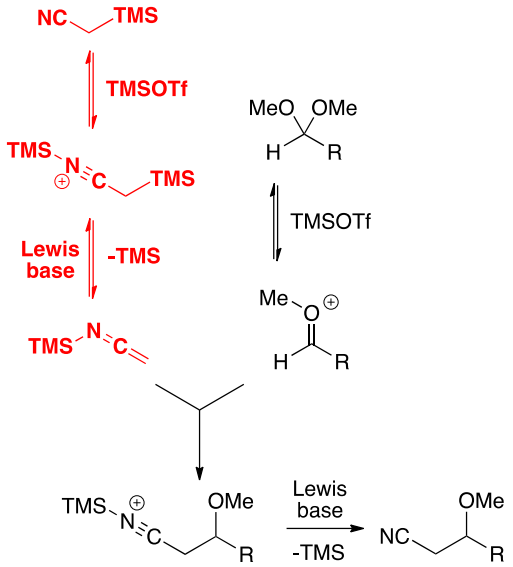



Despite the apparent simplicity β-methoxynitriles **1a-j**, to our knowledge only products **1a** and **1i** have ever been synthesized in the literature[12] and even in those cases no spectral data was reported, which demonstrates the importance of our new methodology. Accordingly, efforts were

made to extend the reaction scope to related species. For example, (trimethylsilyl)acetonitrile was replaced with 3-phenyl-2-(trimethylsilyl)propionitrile (**3)** and moderate reactivity was observed (50-80% conv under various conditions). Unfortunately, the desired β-methoxynitrile could not be separated chromatographically from unreacted nitrile **3** or the major byproduct, the desilylated parent nitrile (3-phenylpropionitrile). In another series of experiments, the acetal was replaced with either cyclohexanone dimethyl ketal or trimethyl orthobenzoate, but only hydrolysis products were observed when they were treated with (trimethylsilyl)acetonitrile and TMSOTf.

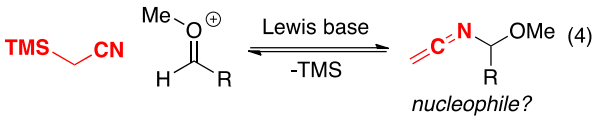
With the scope and limitations of the reaction thus established, we performed preliminary experiments toward elucidating the mechanism of this interesting reaction. Any compelling mechanism must include some rationale to explain why TMSOTf is so much more effective than other Lewis acids, as well as an explanation for how C-alkylation of the nitrile occurs. Our proposed mechanistic scheme is outlined in Figure 1. Activation of dimethyl acetals with TMSOTf is well documented to supply the oxocarbenium electrophile.[13] Of greater interest here is the activation of the (trimethylsilyl)acetonitrile, which is highlighted in red. Coordination of a TMS group to the nitrile provides a bis-silylated cation prone to desilylation at either of two positions. Desilylation at carbon may be carried out by one of the weak Lewis bases in solution, such as the acetonitrile solvent, the trifluoromethanesulfonate anion, or the TMSOMe generated by the breakdown of the dimethyl acetal. This process generates the key N-silylated ketene imine, an intermediate not easily accessible from (trimethylsilyl)acetonitrile with metallic or protic Lewis acids. Mukaiyama addition of the silyl ketene imine to the oxocarbenium ion and silyl transfer then provides the final product.[14]

Figure 1. Proposed Mechanistic Scheme



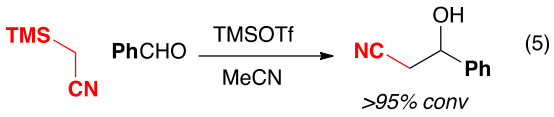

Although this mechanism accounts for the regiochemistry of the reaction (i.e., C-alkylation of the (trimethylsilyl)acetonitrile), the intermediacy of the silyl ketene imine remains unconfirmed. When (trimethylsilyl)acetonitrile is mixed with TMSOTf in $CD_3CN$, no silyl ketene imine is evident by $^1H$ or $^{13}C$ NMR spectroscopy. Direct activation of the silylnitrile at carbon by a Lewis base in solution cannot be ruled out and would be in accord with previously reported reactions.[2,3,4,5,6] Nonetheless, none of the Lewis bases present under our conditions appear to be as potent as those reported to activate similar silylnitriles in the absence of TMSOTf (i.e., $F^-$, $NC^-$, $AcO^-$, $R_3P$). Therefore, we propose that preliminary activation of the silylnitrile by coordination

of a TMS group at nitrogen prior to desilylation at carbon is the most likely course of the reaction. Alternatively, the (trimethylsilyl)acetonitrile nitrogen might directly attack the oxocarbenium ion, temporarily forming an N-(alkoxy)alkylated ketene imine that could attack another oxocarbenium ion and generate the desired product (eq 4). Such a pathway, however, would be accessible to all Lewis acids and not just TMSOTf, which does not match the reactivity profile documented in Table 1.




In addition, we have confirmed that the silylnitrile is a necessary component of the reaction mixture: subjection of the acetal to TMSOTf in acetonitrile in the absence of the preformed α-silylnitrile yields no methyl ether products. It is also conceivable that the reaction is catalyzed by trace amounts of trifluoromethanesulfonic acid (TfOH) in the mixture, but when the TMSOTf was premixed with a drop of water in acetonitrile prior to addition of the acetal and (trimethylsilyl)acetonitrile, which would presumably generate TfOH in situ, only hydrolysis of the acetal and formation of $(TMS)_2O$ was observed. The same result was observed when *p*-toluenesulfonic acid ($TsOH•H_2O$) or camphorsulfonic acid was employed as the catalyst instead of TMSOTf. To further investigate the possibility of catalysis by TfOH, a mild base was added to the reaction mixture to neutralize any Brønsted acids present. Accordingly, 25 mol% of the mild amine base 2,6-lutidine was added to the standard reaction conditions and 100% conversion to the β-methoxynitrile was still observed. When the amount of 2,6-lutidine was raised to 100 mol%, 74% conversion to products was observed, but the products consisted of a complex mixture including elimination products (trans:cis:desired = 2:1:1). Catalysis under these conditions by an ammonium salt like lutidinium triflate is highly unlikely: No reaction other than acetal hydrolysis was observed when pyridinium *p*-toluenesulfonate (PPTS) was used in place of TMSOTf. Taken as a whole, these results strongly suggest that TfOH is not an active participant in the reaction.

In conclusion, we have discovered a new reaction between (trimethylsilyl)acetonitrile and dimethyl acetals to yield β-methoxynitriles, providing a series of products not previously synthesized in the literature. The reaction is especially effective with acetals derived from benzaldehydes, and may proceed through a silyl ketene imine generated in situ. Although the course of our experiments led first to acetal electrophiles, future work targets additions to other electrophiles. Indeed, preliminary experiments show that the addition of (trimethylsilyl)acetonitrile to benzaldehyde (eq 5) proceeds smoothly under reaction conditions otherwise identical to the acetal chemistry described above. We look forward to reporting on this and further reactions in due course.

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## Supplementary data

Supplementary data associated with this article can found in the online version. These data include MOL files of the most important compounds described in this article.

### References and notes


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10. Conceivably, $BF_3$•$OEt_2$ may catalyze the reaction by acting as either a Lewis acid or a fluoride source. For ample evidence of fluoride catalysis of related reactions, see reference 3.
11. An additional byproduct that gives $^1$H NMR spectra consistent with insertion of acetonitrile into the C-O bond of product **1e** is also observed. This byproduct has been tentatively identified as a methyl imidate, but characterization is incomplete.
12. For a two-step synthesis of compound **1a** from α-cyanoacetophenone, see (a) Coady, T. M.; Coffey, L. V.; O'Reilly, C.; Lennon, C. M. *Eur. J. Org. Chem.* **2015**, 1108-116. For a two-step synthesis of compound **1i** from 2-naphthaldehyde, see: (b) Ellingboe, J. W.; Lombardo, L. J.; Alessi, T. R.; Nguyen, T. T.; Guzzo, F.; Guinosso, C. J.; Bullington, J.; Browne, E. N. C.; Bagli, J. F.; Wrenn, J.; Steiner, K.; McCaleb, M. L. *J. Med. Chem.* **1993**, *36*, 2485-2493.
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14. For examples of Mukaiyama additions of silyl ketene imines to aldehydes, anhydrides, and nitrones, see references 7 and 8.