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One-Pot Silyl Ketene Acetal-Formation Mukaiyama–Mannich Additions to Imines Mediated by Trimethylsilyl Trifluoromethanesulfonate

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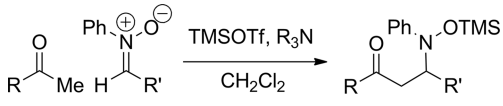
In the presence of trimethylsilyl trifluoromethanesulfonate and trialkylamine base, thioesters are readily converted into silyl ketene acetals in situ and undergo Mukaiyama–Mannich addition to *N*-phenylimines in one pot. The silyl triflate appears to play two roles, activating both the thioester and the imine. This process also works well when thioesters are replaced with amides, esters, or ketones. Products are isolated as desilylated anilines without the necessity of a deprotection step. Yields range from 65 to 99 %.

Introduction

The Mukaiyama–Mannich reaction occupies an honored position in the field of organic synthesis, providing a convergent route to complex β-amino carbonyl compounds through a carbon–carbon bond-forming process.[1,2] Significant advances have been made in this field, particularly with respect to the development of enantioselective variants,[3,4] three-component coupling reactions,[5,6] and proton- or hydrogen-bond-catalyzed reactions.[7] Each of these examples, however, relies upon the independent generation and purification of the silyl ketene acetal reaction partner, a mild nucleophile that usually requires activation of the imine acceptor with a Lewis acid in order to achieve the desired reactivity.

Previously, we reported the one-pot silyl ketene acetal-formation Mukaiyama–Mannich additions of thioesters and ketones to nitrones in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and an amine base [Equation (1)].[8,9] Because of the known affinity of silicon for Lewis basic oxygen species, nitrones were a logical target for our trialkylamine/TMSOTf system.[10] Activation at nitrogen, however, appeared to be a considerably greater challenge, because the nitrogen–silicon bond generated over the course of the reaction (ca. 85 kcal/mol) is considerably weaker than a silicon–oxygen bond (ca. 108 kcal/mol).[11] Nonetheless, the analogy to our previous work with *N*-phenylnitrones drew us to *N*-phenylaldimines as potential electrophiles. Furthermore, the *N*-monoalkylated aniline products share structural properties with a number of cardiovascular drugs such as methylclothiazide,[12] furosemide,[13] bumetanide,[14] and dabigatran etexilate[15] (Figure 1). We now describe the ability of TMSOTf to mediate the addition of thioesters, amides, esters, and ketones to *N*-phenylimines through a two-step, one-pot process.



(1)

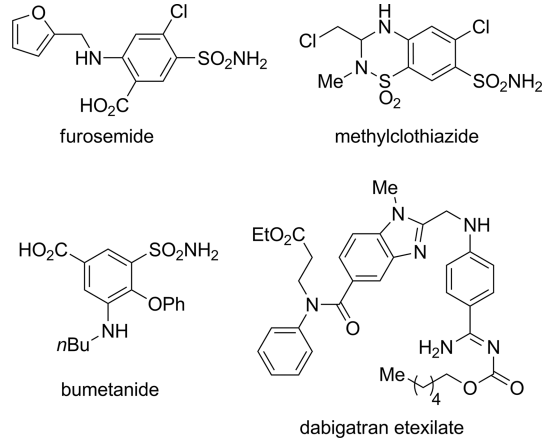


Figure 1. Some aniline-containing pharmaceuticals.

Results and Discussion

Initial discovery and optimization experiments were performed with acetophenone and the *N*-phenylimine derived

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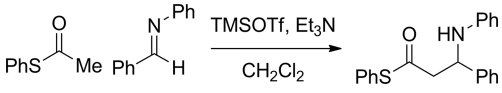
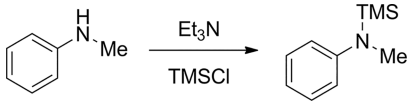
from benzaldehyde [(*E*)-*N*-benzylideneaniline], but generally inconsistent results (vide infra) prompted us to examine *S*-phenyl thioacetate as a more convenient enolate precursor. When the thioacetate was treated with TMSOTf, Et_3N, and the imine in CH_2Cl_2 at room temperature, high conversion (<90%) to the Mannich product was observed [Equation (2)]. Interestingly, desilylation of the product appeared to proceed spontaneously under the reaction conditions. When CH_2Cl_2 was substituted with other solvents (Et_2O, toluene, THF, cyclopentyl methyl ether) much lower conversion was observed.



(2)

A plausible mechanism is presented in Figure 2. Enolization of the thioester occurs conveniently by treatment with TMSOTf and Et_3N, a base that gave consistently better results than iPr_2NEt in terms of reproducibility and overall conversion for thioester substrates.[16] Activation of the imine appears to be accomplished by residual TMSOTf (vide infra), accelerating the Mukaiyama–Mannich addition and presumably yielding an *N*-silylated aniline as the product. Net silyl transfer from oxygen to another molecule of imine was facile as expected, but we were pleased to discover that spontaneous desilylation of the aniline nitrogen also occurs under the reaction conditions. This result stands in some contrast to literature precedent, which includes reports that *N*-alkylated anilines are readily silylated in the presence of TMSCl and Et_3N [Equation (3)],[17] conditions quite analogous to those employed here. The presence of a carbonyl conveniently positioned to hydrogen bond with the free aniline proton may provide a thermodynamic driving force for the exchange of the silicon group with the acidic proton on the nascent ammonium salt.



(3)

Given this apparent ability of the ammonium salt to act as a weak acid under the conditions, the possibility that it might be the activator of the imine warranted investigation. Brønsted acids have been shown to catalyze similar reactions through the protonation of nitrogen-based electrophiles, a motif recently demonstrated in aziridine openings[18] as well as Mukaiyama–Mannich additions.[19] In order to investigate this possibility, a number of control experiments were performed (Table 1). When the independently prepared the silyl ketene acetal of *S*-phenyl thioacetate was treated with imine in dichloromethane, only a trace of product was observed after 2 h (entry 1). Addition of 1.0 equiv. Et_3N·HCl to the reaction mixture did accelerate the reaction, but only 16% conversion was observed after 2 h (entry 2), suggesting that ammonium salts are not likely to be the active catalyst under our optimized conditions. In

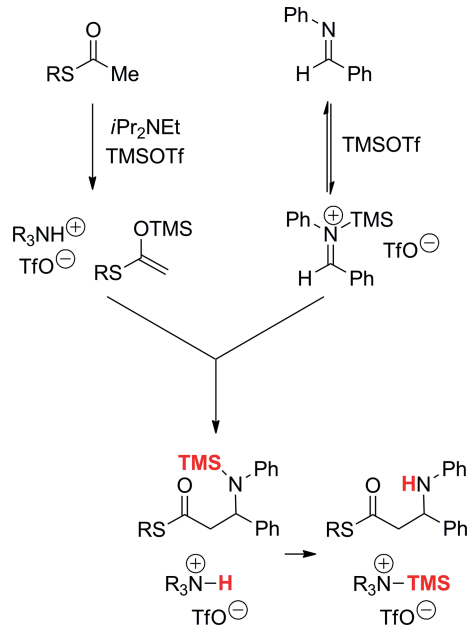
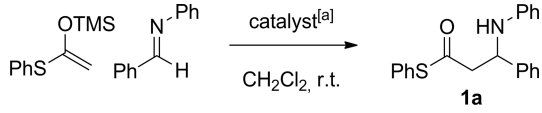


Figure 2. Proposed mechanistic scheme.

contrast, when the silyl ketene acetal and imine were treated with 1.0 equiv. TMSOTf and stirred for 1 h, 89% conversion to the Mannich product was observed (entry 3). These results suggest that the most likely catalyst is a cationic silicon species, and that desilylation of a preliminary *N*-silylated product occurs spontaneously under the reaction conditions.

Table 1. Identification of Lewis acid catalyst.



1a

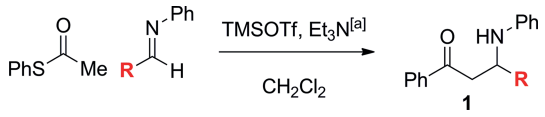
Entry	Catalyst	Conversion [%][b]
1	none	trace
2	Et_3N (1.0 equiv.)	0
3	Et_3N·HCl (1.0 equiv.)	16
4	TMSOTf (1.0 equiv.)	89

[a] Reaction conditions: 0.2 mmol silyl ketene acetal, 0.24 mmol imine, 0.2 mmol catalyst, 1.0 mL of CH_2Cl_2, room temp., 2 h. [b] Determined by ^1H NMR spectroscopy of the unpurified reaction mixture.

A variety of imines was tested under the optimized reaction conditions, including *N*-tosyl, *N*-phosphoryl-, *N*-alkyl-, and *N*-(4-methoxy)phenylimines, but only *N*-phenylimines showed consistently high reactivity (Table 2). Other imines typically reacted with 0–50% conversion under optimized conditions. A wide range of arylimines, including both electron-poor and electron-rich substrates, reacted in high yield with *S*-phenyl thioacetate (entries 1–6), except for the *p*-nitrobenzaldehyde derivative (entry 4). Initial conversion to product **1d** did appear to be quite high, affording >95% conversion as determined by ^1H NMR spectroscopy of the unpurified reaction mixture. The product was not stable to silica gel chromatography, however, and decomposed com-

pletely during attempted purification. Treatment of the silica gel with Et_3N or Et_2NH did not prevent decomposition, which appears to proceed primarily through retro-Mannich reaction as evidenced by recovery of the *S*-phenyl thioacetate. Nonetheless, other aryl aldimines were quite successful, including heteroaryl derivatives and the sterically challenging 2-naphthyl substrate (entries 7–9).

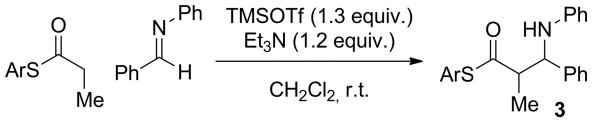
Table 2. Mannich reactions of *S*-phenyl thioacetate.



Entry	R	Product	Yield [%][b]
1	Ph	**1a**	81
2	4-MePh	**1b**	81
3	4-MeOPh	**1c**	75
4	4-NO_2Ph	**1d**	0[c]
5	4-FPh	**1e**	87
6	4-BrPh	**1f**	83
7	2-naphthyl	**1g**	84
8	2-furyl	**1h**	93
9	2-thiophenyl	**1i**	87

[a] Reaction conditions: 1.0 mmol thioester, 1.2 mmol imine, 1.3 mmol TMSOTf, 1.2 mmol Et_3N, 2.5 mL of CH_2Cl_2, room temp., 2 h. [b] Isolated yield after chromatography. [c] Product decomposed during purification on silica gel.

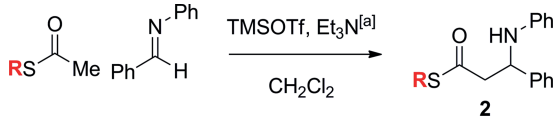
Extension to other thioesters was rapidly achieved (Table 3). Substitution on the aryl position of the thioester was easily tolerated (entries 1–3), including the sterically encumbered 2-naphthalenethiol derivative. Replacement of the aryl thiol-derived moiety with a benzyl mercaptyl group led to smooth reactivity, yielding the *S*-benzyl product **2d**. When the acetyl residue was replaced with a propionyl group, the typical high level of reactivity was maintained, providing product **3** in 98% yield [Equation (4)]. The reaction rate did slow significantly, however, requiring overnight stirring to achieve optimal conversion. Diastereoselectivity was moderate but significant (61:39 *anti*/*syn*[20,21] as determined by ^1H NMR spectroscopy of the unpurified reaction mixture).



(4)

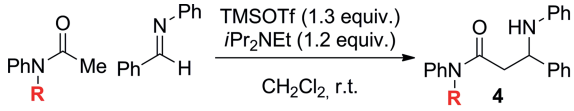
Amides are also excellent substrates.[22] Treatment of *N*-phenyl tertiary amides[23] with the benzaldehyde-derived *N*-phenylimine provided β-amino amides in very high yield [Equation (5), >95% yield in both cases]. These remarkably positive and consistent results suggest that *N*-aryl amides are powerful substrates in these reactions, and bear further study. It should be noted, however that when *N*-acetylmorpholine or *N*-methoxy-*N*-methylacetamide was employed as the enolate precursor, only very low yield was observed (6% and 36% yield, respectively).

Table 3. Mannich reactions of various thioesters.



Entry	R	Product	Yield [%][b]
1	4-FPh	**2a**	99
2	4-BrPh	**2b**	81
3	2-naphthyl	**2c**	74
4	benzyl	**2d**	84

[a] Reaction conditions: 1.0 mmol thioester, 1.2 mmol imine, 1.3 mmol TMSOTf, 1.2 mmol Et_3N, 2.5 mL of CH_2Cl_2, room temp., 2 h. [b] Isolated yield after chromatography.

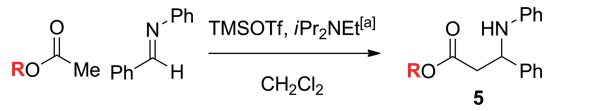


(5)

Mukaiyama–Mannich reactions of thioester and acyclic amide substrates[24] have been relatively unexplored and therefore constituted the primary focus of this study. In contrast, methyl ester derivatives have been widely used in Mukaiyama–Mannich reactions, albeit after independent synthesis and isolation of their silyl ketene acetal derivatives.[21,25] Although reliable methods already exist for the two-step version of this reaction for ester substrates, we were still eager to test our conditions. Somewhat to our surprise, application of the conditions optimized for thioesters to ester substrates was quite disappointing, generally providing <20% conversion even with extended reaction times. Ultimately, however, suitable yields could be achieved by simply increasing the stoichiometry of the TMSOTf from 1.3 to 1.7 equiv. As illustrated in Table 4, a range of acetate esters acted as effective substrates under these conditions, including the industrially friendly isopropyl acetate and the easily substituted phenyl acetate.

Upon evaluation of our success with thioester, amide, and ester enolate precursors, a reexamination of ketones was appropriate. Historically, aryl ketones have been the highest-performing substrates in our one-pot enol silane formation-carbon–carbon bond-forming reactions,[26] and in the present study they again provided acceptable yields for a range of aryl aldimines (Table 5). Nonetheless, these reactions were complicated by the consistent generation of a competing product. It was ultimately confirmed that the byproducts resulted from Friedel–Crafts attack of the *N*-phenyl group on the carbonyl, a phenomenon precedented in the literature[27] but not observed with other substrates in our study. The identity of this byproduct was confirmed through treatment of adduct **6a** with TMSOTf and

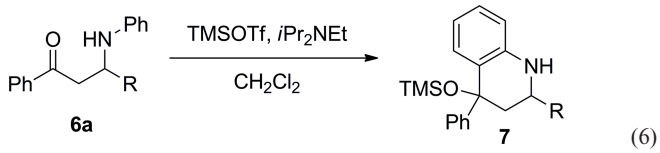
Table 4. Mannich reactions of various esters.



Entry	R	Product	Yield [%][b]
1	Me	**5a**	73
2	Et	**5b**	80
3	*i*Pr	**5c**	78
4	Ph	**5d**	69

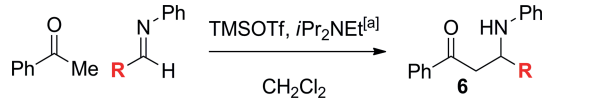
[a] Reaction conditions: 1.0 mmol thioester, 1.2 mmol imine, 1.7 mmol TMSOTf, 1.2 mmol iPr_2NEt, 2.5 mL of CH_2Cl_2, room temp., overnight. [b] Isolated yield after chromatography.

iPr_2NEt, which resulted in about 50% conversion to cyclic byproduct **7** as determined by ^1H NMR spectroscopy [Equation (6)]. Further optimization attempts failed to eliminate the generation of this class of byproducts under the reaction conditions. No evidence of analogous byproduct formation was observed for non-ketone substrates.



(6)

Table 5. Mannich reactions of acetophenone.



Entry	R	Product	Yield [%][b]
1	Ph	**5a**	82
2	4-MeOPh	**5b**	78
3	4-NO_2Ph	**5c**	68
4	4-FPh	**5d**	76
5	4-BrPh	**5e**	65

[a] Reaction conditions: 1.0 mmol thioester, 1.2 mmol imine, 1.3 mmol TMSOTf, 1.2 mmol iPr_2NEt, 2.5 mL of CH_2Cl_2, room temp., overnight. [b] Isolated yield after chromatography.

Conclusions

We have successfully developed the one-pot silyl ketene acetal-formation Mukaiyama–Mannich addition of thioesters to *N*-phenylimines. This methodology has been extended to include amide, ester, and ketone precursors, all of which provide products in deprotected form and in high yield. The TMSOTf appears to play two roles: first as a silylating agent that generates the requisite silyl ketene acetal intermediate, and second as a Lewis acid that activates the imine toward nucleophilic attack. Further study will be directed toward silyl triflate activation of other nitrogen-based electrophiles.

Experimental Section

General: Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. Methylene chloride was purified by passage through a bed of activated alumina.[28] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was stored in a Schlenk flask under inert atmosphere. Hünig's base (iPr_2NEt) was distilled from calcium hydride and stored in a Schlenk flask under inert atmosphere. All other chemicals were used as received or prepared according to literature precedent. Purification of reaction products was carried out by flash chromatography using silica gel (230–400 mesh). Analytical thin layer chromatography was performed on silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid stain, followed by heating.

General Procedure A. Mukaiyama–Mannich Reactions of Thioesters: To an oven-dried round-bottomed flask under N_2 atmosphere were added dichloromethane (2.5 mL), thioester (1.00 mmol), and Et_3N (167 μL, 121 mg, 1.20 mmol). Trimethylsilyl trifluoromethanesulfonate (235 μL, 289 mg, 1.30 mmol) was added dropwise. After 5 min, imine (1.20 mmol) was added, and the reaction mixture was stirred for 2 h. The reaction mixture was passed through a column of silica (2 cm × 1 cm) with dichloromethane. The solvent was removed in vacuo. Column chromatography of the residue (0–15% EtOAc/hexanes) provided the product.

General Procedure B. Mukaiyama–Mannich Reactions of Amides: To an oven-dried round-bottomed flask under N_2 atmosphere were added amide (1.00 mmol), dichloromethane (2.5 mL), and iPr_2NEt (209 μL, 155 mg, 1.20 mmol). Trimethylsilyl trifluoromethanesulfonate (235 μL, 289 mg, 1.30 mmol) was added dropwise. After 5 min, *N*-benzylideneaniline (217 mg, 1.20 mmol) was added, and the reaction mixture was stirred for 2 h. The reaction mixture was passed through a column of silica (2 cm × 1 cm) with dichloromethane. The solvent was removed in vacuo. Column chromatography of the residue (0–20% EtOAc/hexanes with 1% diethylamine) provided the product.

General Procedure C. Mukaiyama–Mannich Reactions of Esters: To an oven-dried round-bottomed flask under N_2 atmosphere were added *N*-benzylideneaniline (217 mg, 1.20 mmol), dichloromethane (1.0 mL), ester (1.00 mmol), and iPr_2NEt (209 μL, 155 mg, 1.20 mmol). Trimethylsilyl trifluoromethanesulfonate (308 μL, 378 mg, 1.70 mmol) was added dropwise, and the reaction mixture was stirred for overnight. The reaction mixture was passed through a column of silica (2 cm × 1 cm) with dichloromethane. The solvent was removed in vacuo. Column chromatography of the residue (0–20% EtOAc/hexanes) provided the product.

General Procedure D. Mukaiyama–Mannich Reactions of Acetophenone: To an oven-dried round-bottomed flask under N_2 atmosphere were added dichloromethane (2.5 mL), acetophenone (115 μL, 120 mg, 1.00 mmol), and iPr_2NEt (209 μL, 155 mg, 1.20 mmol). Trimethylsilyl trifluoromethanesulfonate (235 μL, 289 mg, 1.30 mmol) was added dropwise. After 5 min, imine (1.20 mmol) was added, and the reaction mixture was stirred for 2 h. The reaction mixture was passed through a column of silica (2 cm × 1 cm) with dichloromethane. The solvent was removed in vacuo. Column chromatography of the residue (0–5% EtOAc/hexanes) provided the product.

Acknowledgments

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