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FULL PAPER

One-Pot Enol Silane Formation-Mukaiyama–Mannich Addition of Ketones, Amides, and Thioesters to Nitrones in the Presence of Trialkylsilyl Trifluoromethanesulfonates

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Ketones, amides, and thioesters form enol silanes and add to *N*-phenylnitrones in one pot in the presence of trimethylsilyl trifluoromethanesulfonate and trialkylamine. The reaction is general to a range of silyl trifluoromethanesulfonates and *N*-phenylnitrones. The β-(silyloxy)amino carbonyl products are stable to chromatography and can be isolated in 63-99% yield.
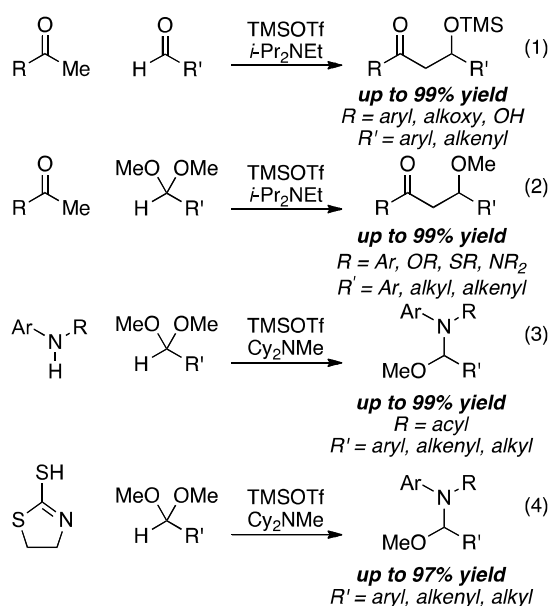
((Abstract Text----Continued))

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.xxxxxxxxx.

Introduction

The Mukaiyama–Mannich reaction is a proven method for the production of β-amino carbonyl compounds under mild conditions.[1] The addition of ester-derived silyl ketene acetals to nitrones[2] provides access to *N*-hydroxylated analogues of these Mannich adducts, and takes place readily in the presence of Lewis acids.[3] Additions by ketone-derived enol silanes are much more rare,[4] however, and additions by silyl ketene acetals derived from thioesters and tertiary amides are unknown. Furthermore, production of *N*-aryl-*N*-hydroxylated versions of these β-amino carbonyl compounds is very rare,[5] despite the ubiquity of aniline derivatives in the field of organic synthesis and the facile rearrangement of these compounds to provide isoxazolidines.

Our previous work with the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated one-pot enol silane formation-Mukaiyama aldol addition[6] has led to the development of several related reactions (eq 1-4).[7] We speculated that the mild TMSOTf-amine base conditions would be compatible with the addition of our in situ-generated enol silanes to nitrones, especially if residual TMSOTf could serve as Lewis acidic activating agent for the nitrone itself. Encouragingly, we found significant precedent for silyl triflate-catalyzed additions to nitrones in the literature. Catalysis by TMSOTf has been reported for additions to nitrones by certain ester-derived silyl ketene acetals,[8] and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) was recently reported to mediate the addition of enol silanes[9] and ester-derived silyl ketene acetals[9a,10] to silyl nitronates generated in situ. We now report our successful development of a one-pot enol silane formation-Mukaiyama–Mannich addition of ketones, amides, and thioesters to nitrones.

(1) R = aryl, alkoxy, OH; R' = aryl, alkenyl — up to 99% yield

(2) R = Ar, OR, SR, NR$_2$; R' = Ar, alkyl, alkenyl — up to 99% yield

(3) R = acyl; R' = aryl, alkenyl, alkyl — up to 99% yield

(4) R' = aryl, alkenyl, alkyl — up to 97% yield

Results and Discussion

We began the study by subjecting acetophenone and *N*,α-diphenylnitrone to TMSOTf and trialkylamine in various solvents (eq 5). Of the amine bases examined, *i*-Pr$_2$NEt most consistently provided the product in high conversion, although several others showed competence (Et$_3$N, Cy$_2$NMe, 2,6-lutidine). Toluene, THF, Et$_2$O, and CH$_2$Cl$_2$ were all compatible solvents for the reaction, with CH$_2$Cl$_2$ proving optimal for high conversion. Once this standard set of reaction conditions was established, we endeavored to determine the role of each reagent in the one-pot process through a series of control experiments. When commercial enol silane **1**, the putative intermediate in our reaction, was mixed with the nitrone in CH$_2$Cl$_2$, no reaction was observed regardless of the presence or absence of TMSOTf (eq 6). When 1.0 equiv *i*-Pr$_2$NEt was added to the same reaction mixture, conversion to the silylated product occurred. Finally, conversion increased from 59% to 95% when nitrone was added last to the reaction mixture instead of first.
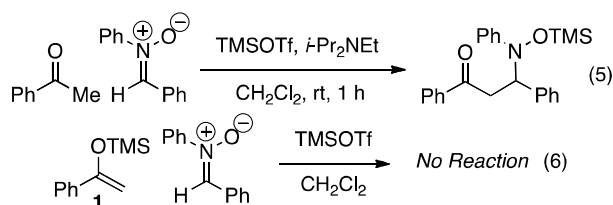
Based on these observations, we hypothesize that the nitrone outcompetes all other species for silylation, significantly slowing the formation of the necessary enol silane intermediate. Accordingly, enol silane formation must be allowed to take place prior to addition of nitrone to the reaction mixture in order to achieve high conversion. Furthermore, it appears that TMSOTf alone is not sufficiently Lewis acidic to catalyze Mukaiyama addition of the enol silane to the nitrone (eq 5);[11] the amine base may be playing an added role by acting as a Lewis base to activate the enol silane, similar to what we have observed for the related Mukaiyama aldol reaction.[7a]

After optimization of the reaction conditions was complete, we examined the scope of the ketones compatible with this reaction (Table 1). Electron-rich and electron-poor aryl methyl ketones were highly effective (entries 1-4), as were the bulky acetonaphthones (entries 5-6). Conversion dropped dramatically for propiophenone, never exceeding 50% even in the presence of additional TMSOTf and amine base.[12] Most alkyl-alkyl ketones provided intractable under the reaction conditions, but pinacolone was a successful substrate, achieving 74% yield (entry 7).

Table 1. Ketone scope.

Entry	R	Product	Yield (%)[b]
1	Ph	2a	94
2	4-methoxyphenyl	2b	89
3	4-fluorophenyl	2c	85
4	4-bromophenyl	2d	91
5	1-napththyl	2e	81
6	2-napththyl	2f	86
7	tBu	2g	74

[a] Reaction conditions: ketone (1.0 mmol), i-Pr$_2$NEt (1.2 mmol), TMSOTf (1.3 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). [b] Isolated yield after chromatography.

We next sought to extend this reaction to include carboxylic acid derivatives as enolate precursors. Because the addition of ester-derived silyl ketene acetals to nitrones is well known,[8-10] we chose to focus upon amides and thioesters. Both substrate classes were successful after slight modification of the reaction conditions (Table 2). Thioesters required 1.4 equiv i-Pr$_2$NEt and 1.5 equiv TMSOTf for the highest conversion, small increases from the optimal conditions for ketones. Thioesters derived from S-aryl thiols were highly effective (entries 1-3), and the thioester derived from benzyl mercaptan also provided good results (entry 4).

Table 2. Scope of carboxylic acid derivatives.

Entry	R	Conditions[a]	Product	Yield (%)[b]
1	PhS	A	3a	87
2	Me-C$_6$H$_4$-S	A	3b	93
3	naphthyl-S	A	3c	88
4	BnS	A	3d	70[c,d]
5	Ph$_2$N	B	3e	87
6	Ph(Me)N	B	3f	63

[a] Reaction conditions A: thioester (1.0 mmol), i-Pr$_2$NEt (1.4 mmol), TMSOTf (1.5 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). Reaction conditions B: amide (1.0 mmol), 2,6-lutidine (1.2 mmol), TMSOTf (1.3 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). [b] Isolated yield after chromatography. [c] Reaction was stirred 16 h. [d] Recovered as a mixture of product and S-benzyl thioacetate after chromatography; yield shown is corrected for presence of S-benzyl thioacetate.

Amides appeared to react somewhat less vigorously than ketones and thioesters, such that reduction of the nitrone via hydride transfer from the amine base was observed as a competing reaction.[13] Replacement of i-Pr$_2$NEt with 2,6-lutidine alleviated this problem, and both tertiary amides tested reacted with some efficiency (entries 5-6). Secondary amides did not yield the desired products, however, and were converted instead to silyl imidates[7c] that did not produce an isolable product.

The ability of a standard ketone acetophenone to add to a range of nitrones was examined next (Table 3). Acetophenone reacted well with nitrones derived from various aryl aldehydes, including both electron-rich and electron-poor electrophiles (entries 1-4). Heteroaryl nitrones also performed consistently well (entries 5-6). We were especially pleased to observe good reactivity for the cinnamaldehyde-derived nitrone, which provided the allylic silyloxyamine (entry 7). The aliphatic nitrone derived from cyclohexane carboxaldehyde also reacted, proving that enolization-prone substrates perform under our conditions, albeit in reduced yield (48% yield, entry 8). The N-aryl group appears to be essential to reactivity: nitrones bearing an N-methyl group or N-tert-butyl group were completely unreactive.

Table 3. Addition of acetophenone to various nitrones.

Entry	R	Product	Yield (%)[b]
1	4-methylphenyl	4a	93
2	4-methoxyphenyl	4b	94
3	4-fluorophenyl	4c	97
4	4-bromophenyl	4d	91
5	2-furyl	4e	89
6	2-thiophenyl	4f	88[c]
7	cinnamyl	4g	86
8	cyclohexyl	4h	48[c,d]

[a] Reaction conditions: acetophenone (1.0 mmol), i-Pr$_2$NEt (1.2 mmol), TMSOTf (1.3 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). [b] Isolated yield after chromatography. [c] Reaction time = 16 h. [d] Corrected yield. Product contaminated with 10% aldol byproduct (see supporting information).

Once the nitrone scope for acetophenone was established, the same set of nitrones was reacted with representative thioester *S*-phenyl thioacetate (Table 4). In general, the thioester reacted somewhat less vigorously than acetophenone, such that a slight change in reaction conditions was necessary to achieve optimal conversion in some cases. In those instances, *i*-Pr$_2$NEt was replaced Et$_3$N and the stoichiometry was increased slightly for the amine base (1.5 instead of 1.2 equiv). Again, nitrones derived from benzaldehydes and heteroaromatic aldehydes performed well (entries 1-6). The alkenyl substrate derived from cinnamaldehyde was also an excellent substrate (entry 7), as was the aliphatic cyclohexane-derived nitrone (entry 8).

Table 4. Addition of *S*-phenyl thioacetate to various nitrones

Entry	R	Conditions[a]	Product	Yield (%)[b]
1	4-methylphenyl	A	**5a**	92[c]
2	4-methoxyphenyl	B	**5b**	90
3	4-fluorophenyl	B	**5c**	89
4	4-bromophenyl	B	**5d**	76[c]
5	2-furyl	A	**5e**	86[c]
6	2-thiophenyl	B	**5f**	63[c]
7	cinnamyl	B	**5g**	87
8	cyclohexyl	B	**5h**	80

[a] Reaction conditions A: *S*-phenyl thioacetate (1.0 mmol), *i*-Pr$_2$NEt (1.2 mmol), TMSOTf (1.3 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). Reaction conditions B: *S*-phenyl thioacetate (1.0 mmol), Et$_3$N (1.5 mmol), TMSOTf (1.3 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). [b] Isolated yield after chromatography. [c] Reaction time = 16 h.

The substrate scope thus established, we next tested the ability of more robust silyl groups to participate in the reaction (Table 5). The standard diphenylnitrone was reacted with acetophenone in the presence of triethylsilyl trifluoromethanesulfonate (TESOTf), and an excellent yield of the TES-protected product resulted (entry 1). When TESOTf was replaced with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), the reaction again proceeded to completion overnight with very high yield (entry 2). Similar reactions with *S*-phenyl thioacetate were also successful (entries 3-4).

Table 5. Additions mediated by TESOTf or TBSOTf.

Entry	R$_3$SiOTf	R'	Base	Product	Yield (%)[b]
1	TESOTf	Ph	*i*-Pr$_2$NEt	**6a**	95
2	TESOTf	Ph	*i*-Pr$_2$NEt	**6b**	99
3	TBSOTf	PhS	Et$_3$N	**6c**	77[c]
4	TBSOTf	PhS	Et$_3$N	**6d**	76[c]

[a] Reaction conditions A: ketone or thioester (1.0 mmol), base (1.2 mmol), TMSOTf (1.3 mmol), nitrone (1.2 mmol), CH$_2$Cl$_2$ (5.0 mL). [b] Isolated yield after chromatography. [c] 1.5 mmol base used.

Conclusion

We have developed a one-pot enol silane formation-Mukaiyama–Mannich reaction for the addition of ketones, amides, and thioesters to *N*-phenyl nitrones. Enol silane formation occurs

rapidly in situ, and residual silyl triflate acts as a Lewis acid catalyst for addition to the nitrone in one pot. Isolation of the silylated products by chromatography is trivial. We anticipate that these compounds will find ready use within the synthetic community, because the utility of their derived isoxazolidines[8b,3c] is well established. Further investigation of these *N*-aryl nitrones under silylative conditions will be reported in due course.

Experimental Section

General. Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. Anhydrous CH$_2$Cl$_2$ was purified by passage through a bed of activated alumina.[14] Anhydrous *i*-Pr$_2$NEt was distilled and stored in a Schlenk flask under inert atmosphere. Commercial TMSOTf was transferred to a Schlenk flask and stored under inert atmosphere. Nitrones were used as received (*N*,α-Diphenylnitrone) or prepared according to literature precedent. Thioesters were used as received (*S*-Phenyl thioacetate) or prepared according to literature precedent. Amides were used as received (*N*,*N*-Diphenylacetamide) or prepared according to literature precedent. All other reagents were used as received. 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. Infrared spectra were recorded on an FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz spectrometer or 300 MHz spectrometer, and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 7.28 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded on a 125 MHz spectrometer or 75 MHz spectrometer, and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.0 ppm). High-resolution mass spectra were obtained by electrospray ionization. Melting points were determined using a capillary melting point apparatus.

General Procedure A. Addition of Ketones to Nitrones. To an oven-dried 10-mL round-bottomed flask under N$_2$ was added CH$_2$Cl$_2$ (5.0 mL), ketone (1.0 mmol), *i*-Pr$_2$NEt (210 L, 155 mg, 1.2 mmol), TMSOTf (235 L, 289 mg, 1.3 mmol). After 10 min, nitrone (1.2 equiv) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was passed through a silica gel plug (1 cm x 5 cm) with Et$_2$O and the solvent was removed by rotary evaporation. The product was purified by silica gel chromatography (0 to 2% EtOAc/Hexanes).

General Procedure B. Addition of Thioesters to Nitrones, mediated by Hunig's base. To an oven-dried 10-mL round-bottomed flask under N$_2$ was added CH$_2$Cl$_2$ (5.0 mL), thioester (1.0 mmol), *i*-Pr$_2$NEt (244 L, 181 mg, 1.4 mmol), TMSOTf (271 L, 333 mg, 1.5 mmol). After 10 min, nitrone (1.2 equiv) was added, and the mixture was stirred at room temperature for the indicated time. The reaction mixture was passed through a silica gel plug (1 cm x 5 cm) with Et$_2$O and the solvent was removed by rotary evaporation. The product was purified by silica gel chromatography (0 to 2% EtOAc/Hexanes).

General Procedure C. Addition of Thioesters to Nitrones, mediated by triethylamine. To an oven-dried 10-mL round-bottomed flask under N$_2$ was added CH$_2$Cl$_2$ (5.0 mL), thioester (1.0 mmol), Et$_3$N (214 L, 155 mg, 1.5 mmol), TMSOTf (235 L, 289 mg, 1.3 mmol). After 10 min, nitrone (1.2 equiv) was added, and the mixture was stirred at room temperature for the indicated time. The reaction mixture was passed through a silica gel plug (1 cm x 5 cm) with Et$_2$O and the solvent was removed by rotary

evaporation. The product was purified by silica gel chromatography (0 to 2% EtOAc/Hexanes).

General Procedure D. Addition of Amides to Nitrones. To an oven-dried 10-mL round-bottomed flask under N_2 was added CH_2Cl_2 (5.0 mL), amide (1.0 mmol), 2,6-lutidine (139 L, 129 mg, 1.2 mmol), TMSOTf (235 L, 289 mg, 1.3 mmol). After 10 min, nitrone (1.2 equiv) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was passed through a silica gel plug (1 cm x 5 cm) with Et_2O and the solvent was removed by rotary evaporation. The product was purified by silica gel chromatography (0 to 2% EtOAc/Hexanes).

Supporting Information (see footnote on the first page of this article): Details of experiments as well as spectral characterizations of the products prepared.
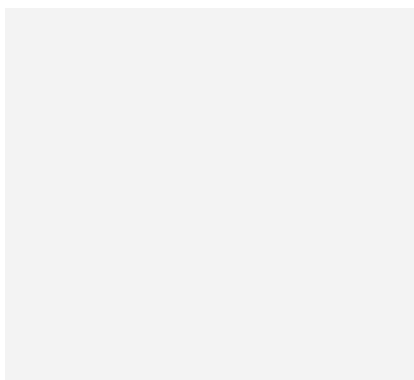
Acknowledgments

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[11] Note that more reactive silyl ketene acetals have been shown to react in the presence of catalytic TMSOTf. See reference 7a.

[12] No significant diastereoselectivity was observed.

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