



Chalcone and cinnamate synthesis via one-pot enol silane formation-Mukaiyama aldol reactions of ketones and acetate esters

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ABSTRACT

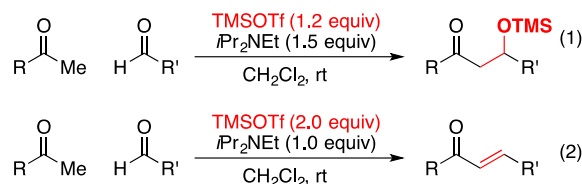
Aryl alkyl ketones, acetate esters, and acetamides undergo facile one-pot enol silane formation, Mukaiyama aldol addition, and dehydrosilyloxylation in the presence of an amine base and excess trimethylsilyl trifluoromethanesulfonate. The chalcone and cinnamate products are generally recovered in high yield. The relative stoichiometry of the trimethylsilyl trifluoromethanesulfonate and amine base reagents determines whether the reaction yields the β -silyloxy carbonyl product or the α,β -unsaturated carbonyl.

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The construction of chalcones and cinnamates via aldol condensation of ketones or esters with aromatic aldehydes is a staple of synthetic organic chemistry [1]. These syntheses are typically performed through the mediation of relatively strong bases like hydroxides and alkoxides. Construction of these valuable building blocks through a mild, Lewis acid-promoted Mukaiyama aldol pathway is relatively rare, however, and requires the preformation of an enol silane or related nucleophile [2]. In the course of our study of one-pot enol silane formation-Mukaiyama aldol and Mannich addition reactions promoted by trimethylsilyl trifluoromethanesulfonate (TMSOTf) [3], we recently discovered that either the β -silyloxy carbonyl or the α,β -unsaturated carbonyl aldol products can be produced in high yield, dependent upon the stoichiometry of the reagents. We report here that the use of a tertiary amine base and 2.0 equiv TMSOTf promotes the condensation of ketones, esters, or amides with aromatic aldehydes to yield α,β -unsaturated carbonyl products. This discovery emphasizes the versatility of the R_3N /TMSOTf system for the synthesis of various aldol products.

We previously reported that a one-pot enol silane formation-Mukaiyama aldol reaction occurs when a ketone and an aromatic aldehyde are subjected to a mixture of 1.5 equiv i -Pr₂NEt and 1.2 equiv TMSOTf, yielding the β -silyloxy carbonyl product (Eq. (1)) [3a,4]. Optimization attempts at that time were directed

solely toward maximization of the yield for the β -silyloxy carbonyl, but later results in our laboratory suggested that a change in the stoichiometry of the TMSOTf could significantly alter the product distribution to favor the α,β -unsaturated carbonyl. A brief optimization study showed that when the TMSOTf loading was increased to 2.0 equiv, rapid and efficient transformation of acetophenone and benzaldehyde to chalcone was effected in >95% conversion (Eq. (2)).

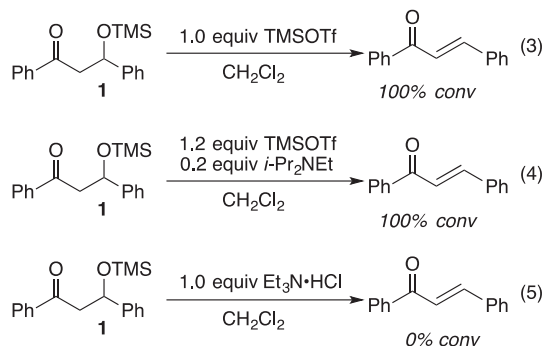


Presumably, formation of the chalcone product occurs through dehydrosilyloxylation of the initially formed β -silyloxy carbonyl product [5]. To provide evidence for this hypothesis, silyl ether **1** was first generated under our previously reported reaction conditions (1.5 equiv i -Pr₂NEt and 1.2 equiv TMSOTf) [3a]. The reaction mixture was then passed through a plug of silica with ether and concentrated in vacuo to yield a 91% by mass mixture of the desired product, where the remaining mass consisted of unreacted acetophenone and benzaldehyde. This mixture was redissolved in CH₂Cl₂ and treated with 1.0 equiv TMSOTf, which

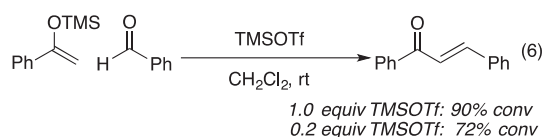
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resulted in 100% conversion to chalcone (Eq. (3)). In order to gauge the effect that residual trialkylamine base might play in the reaction, and to better duplicate reaction conditions that might occur at partial conversion, the experiment was repeated with 0.2 equiv *i*-Pr₂NEt and 1.2 equiv TMSOTf; identical results were observed (Eq. (4)). When β -silyloxycarbonyl **1** was treated with 1.0 equiv Et₃N·HCl, however, no elimination occurred, which suggests that trialkylammonium salts are not sufficiently acidic to activate the β position (Eq. (5)). These data corroborate the likely intermediacy of β -silyloxycarbonyl **1** in the reaction mechanism, and further suggest that coordination of TMSOTf to the silyl ether oxygen, rather than protonation by an ammonium salt, promotes the elimination reaction. Finally, it is noteworthy that the deprotected β -hydroxy analog of silyl ether **1** also undergoes elimination to form chalcone in the presence of TMSOTf, but for this deprotected substrate, retroaldol to regenerate acetophenone and benzaldehyde competes with elimination (58% retroaldol, 42% elimination). Based on these results, β -silyloxycarbonyl **1** appears to be the more likely intermediate in the reaction described in this manuscript.

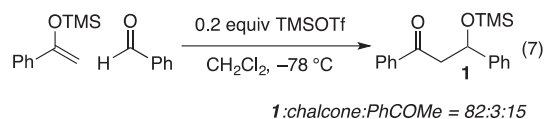


Although the ability of β -silyloxycarbonyl **1** to be converted to chalcone under the reaction conditions was now well established, generation of the final product via the intermediacy of an enol silane remained conjectural. Accordingly, the commercially available enol silane derived from acetophenone was subjected to benzaldehyde and 1.0 equiv TMSOTf in CH₂Cl₂. After 1 h, ¹H NMR spectroscopy of the reaction mixture showed 90% conversion to chalcone [3f] but no evidence of β -silyloxycarbonyl **1** (Eq. (6)) [6]. This experimental result is consistent with an enol silane intermediate in the reaction pathway. When the amount of TMSOTf in the reaction was decreased to 0.2 equiv, 72% conversion to chalcone was observed, but again no β -silyloxycarbonyl compound appeared in the ¹H NMR spectrum (Eq. (6)). These experiments highlight two important characteristics of this reaction. First, once formation of the enol silane is complete, only a catalytic amount of TMSOTf is necessary for both the addition and elimination steps to reach high conversion [7]. Second, because the β -silyloxycarbonyl product is not observed under these conditions, it must undergo elimination rapidly after formation.



It still remained to verify that the β -silyloxycarbonyl intermediate does in fact form under these reaction conditions, which are slight modifications of the conditions in our original report. Accordingly, the temperature was lowered to −78 °C and the

catalytic TMSOTf experiment was performed again (Eq. (7)). After 1 h under these conditions, generation of the β -silyloxycarbonyl was confirmed [8]. Analysis of the reaction mixture by ¹H NMR spectroscopy showed 82% β -silyloxycarbonyl **1**, 15% unreacted acetophenone, and only 3% chalcone. With these results in place, a reasonable mechanistic pathway can be proposed that accounts for all of the data. Conversion of the acetophenone to the enol silane occurs easily in the presence of TMSOTf and base, and residual TMSOTf catalyzes Mukaiyama addition to the aldehyde followed by elimination to yield the chalcone.



Although the strongly Lewis acidic reaction conditions described in Eqs. (3), (4), and (6) suggest an E1 mechanism for the elimination step, an E2 mechanism through the action of a mild base such as TfO[−] or trace H₂O cannot be ruled out, nor can a possible E1cb mechanism that proceeds via the enol silane. We further note that the elimination step of our proposed mechanism may yield HOTf or another hydronium analog as a byproduct, which may in turn catalyze further elimination reactions. As shown in Eq. (4), however, the β -silyloxycarbonyl intermediate undergoes elimination even when there is initially no possibility of an HOTf-like species; this result appears to verify that TMSOTf is capable of the *initiation* of the elimination reaction. When the standard reaction conditions were modified by an increase in the loading of amine base (up to 2.0 equiv) [9] in order to sequester adventitious acid, elimination was curtailed but not completely prevented. These results may be due to the neutralization of adventitious acid, but it should be noted that amine bases also interact reversibly with TMSOTf itself, which could also impact that rate of elimination.

An investigation of the scope of this aldol condensation reaction showed it to be general to a range of aryl alkyl ketones and aromatic aldehydes. As illustrated in Table 1, acetophenone condensed successfully with a range of benzaldehyde derivatives (entries 1–5). Similar reactions were attempted with both heteroaromatic and more sterically challenging aldehydes, most

Table 1
Reaction of Acetophenone with Various Aldehydes.

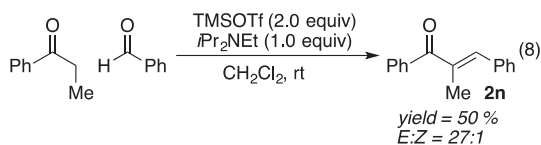
Entry	R	Product	Yield (%) ^b
1	Ph	2a	90
2	4-(MeO)C ₆ H ₄	2b	81
3	4-FC ₆ H ₄	2c	96
4	4-BrC ₆ H ₄	2d	91
5	4-(F ₃ C)C ₆ H ₄	2e	72
6	2-Naphthyl	2f	89
7	2-Furyl	2g	0
8	2-Thiophenyl	2h	82

^aReaction conditions: acetophenone (1.0 mmol), aldehyde (1.2 mmol), *i*-Pr₂NEt (1.0 mmol), TMSOTf (2.0 mmol), CH₂Cl₂ (1.0 mL), rt, 1 h. See [Supporting Information](#) for details.

^b Isolated yield after chromatography.

of which reacted in moderate to high yields (entries 5–7). Only the 2-furaldehyde substrate proved incompatible with the reaction conditions: reactions with this substrate were capricious and reproducible yields could not be obtained.

In addition to acetophenone, several other aryl methyl ketones were reacted under similar reaction conditions. As illustrated in Table 2, both electron-rich and electron-poor acetophenones reacted in high yield, as did the sterically encumbered 2-acetonaphthone (entries 1–4). In addition, the highly sterically encumbered, wholly aliphatic pinacolone underwent aldol condensation with benzaldehyde in good yield, which shows that the reaction scope is not limited to aryl ketones (entry 5). Propiophenone did not reach complete conversion after overnight reaction, but did provide a yield of 50% (Eq. (8)). Conversion did not appear to change significantly over 2–24 h time period, but the E:Z ratio increased from 3:1 at 2 h to 27:1 at 24 h [10].

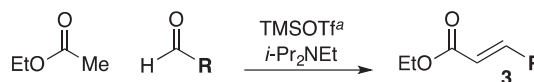


The scope of this convenient aldol condensation reaction is not limited to ketones. Both acetate esters and acetamides are reactive under similar conditions, although reaction times are substantially longer than with ketones. Ethyl acetate is particularly convenient because it can be used as both an enolate precursor and the solvent in the reaction, producing cinnamate esters in high yield (Table 3). Benzaldehydes were again suitable reaction partners, although electron-rich aldehydes in general did not afford high yields under these conditions. Notably, cinnamaldehyde reacted in 65% yield, producing an $\alpha,\beta,\gamma,\delta$ -unsaturated ester.

Interestingly, the electron-poor 4-(trifluoromethyl)benzaldehyde substrate was an outlier. When this aldehyde was reacted with ethyl acetate under the same reaction conditions described in Table 3, only the β -silyloxyester product was observed. Attempts to promote elimination of the β -silyloxyester to produce the cinnamate derivative failed. Neither resubmission of the silyl ether to the reaction conditions, heating the original reaction to reflux (77 °C), nor performing the experiment in CH_2Cl_2 produced any trace of the cinnamate. Nonetheless, deprotection of the observed

Table 3

Reaction of Ethyl Acetate with Various Aldehydes.

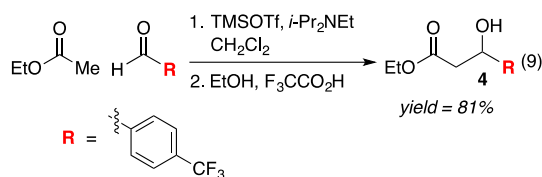


Entry	R	Product	Yield (%) ^b
1	Ph	3a	89
2	4-MeC ₆ H ₄	3b	98
3	4-(MeO)C ₆ H ₄	3c	69
4	2-furyl	3d	33
5	2-thiophenyl	3e	53
6	Cinnamyl	3f	65

^aReaction conditions: ethyl acetate (2.5 mL), benzaldehyde (1.0 mmol), *i*-Pr₂NEt (1.2 mmol), TMSOTf (2.2 mmol), rt, 16 h. See Supporting Information for details.

^b Isolated yield after chromatography.

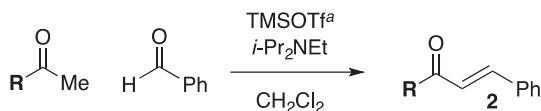
silyl ether with ethanol and trifluoroacetic acid yielded β -hydroxyester **4** in 81% yield from ethyl acetate (Eq. (9)). The failure of this very electron-poor substrate [11] to undergo elimination suggests that elimination may proceed via an E1 mechanism; the required carbocation derived from the trifluoromethylated product would be especially unstable and difficult to form. In addition, coordination of the silyl ether oxygen to TMSOTf (or another Lewis acid) may also be slowed by the nearby electron-poor aromatic ring, which would slow the elimination step regardless of the mechanism. The result illustrated in Eq. (10) does stand in some contrast with the reaction of acetophenone with 4-(trifluoromethyl)benzaldehyde (Table 1, entry 5), for which the chalcone product is observed. The difference between the 4-(trifluoromethyl)benzaldehyde results for ethyl acetate and acetophenone suggests that both stabilization of carbocationic character at the β position and the acidity of the α position influence the progress of the reaction. While these characteristics are consistent with an E1 reaction mechanism, they do not rule out an E2 pathway or an E1cb pathway that proceeds via an enol silane.



Given the success with ethyl acetate, the reaction of benzaldehyde in other convenient ester solvents was attempted. Both methyl acetate and isopropyl acetate were suitably reactive (Eq. (10)), but neither approached the success of ethyl acetate. Indeed, simple replacement of ethyl acetate with either methyl acetate or isopropyl acetate under otherwise identical reaction conditions as those described in Table 3 resulted in low conversions. After some further experimentation, it was discovered that incubation of the ester with TMSOTf and *i*-Pr₂NEt for fifteen minutes prior to addition of the aldehyde provided significantly higher yields. Nonetheless, it appears that ethyl acetate is an optimal substrate: First, it lacks the steric encumbrance of isopropyl acetate. More subtly, the ammonium salt byproducts generated under the reaction conditions appear to be more soluble in methyl acetate than in ethyl acetate, which may help drive the ethyl acetate reaction to higher conversion.

Table 2

Reaction of Benzaldehyde with Various Ketones.



Entry	R	Product	Yield (%) ^b
1	4-(MeO)C ₆ H ₄	2i	83 ^c
2	4-FC ₆ H ₄	2j	92
3	4-BrC ₆ H ₄	2k	95
4	2-Naphthyl	2l	86
5	<i>t</i> -Bu	2m	79

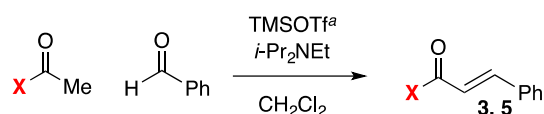
^aReaction conditions: ketone (1.0 mmol), benzaldehyde (1.2 mmol), *i*-Pr₂NEt (1.0 mmol), TMSOTf (2.0 mmol), CH_2Cl_2 (1.0 mL), rt, 1 h. See Supporting Information for details.

^b isolated yield after chromatography.

^c yield corrected to account for ~4% impurities.

Table 4

Reaction of Esters and Amides with Benzaldehyde.

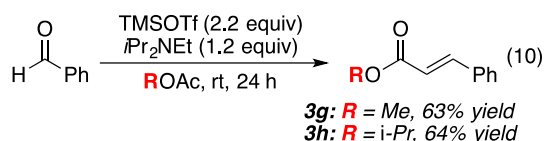


Entry	X	Product	Yield (%) ^b
1	MeO	3g	79
2	<i>i</i> -PrO	3h	85
3	PhO	3i	27
4	TMSO	3j	94 ^c
5	Me(MeO)N	5	93

^aReaction conditions: ester or amide (1.0 mmol), benzaldehyde (1.2 mmol), *i*-Pr₂NEt (1.2 mmol), TMSOTf (2.2 mmol), CH₂Cl₂ (2.5 mL), rt, 16 h. See [Supporting Information](#) for details.

^b Isolated yield after chromatography.

^c Isolated as the carboxylic acid, contaminated with <5% of an unidentified impurity.



When CH₂Cl₂ was employed as the reaction solvent, these esters were again suitably reactive as shown in [Table 4](#) (entries 1 and 2) [12]. When phenyl acetate was employed, poor conversion and multiple unidentified byproducts were observed. Moreover, product **3i** proved unstable to chromatography, and only a small amount could be isolated (entry 3). On the other hand, employment of trimethylsilyl acetate as the enolate precursor [3c] was very successful, providing cinnamic acid as the product in excellent yield (entry 4). Finally, extension of this method to the convenient Weinreb amide proceeded very well, yielding the cinnamide with great efficiency (entry 5).

In conclusion, the one-pot enol silane formation-Mukaiyama aldol reaction has been shown to provide different types of aldol products depending upon the stoichiometry of the TMSOTf. Past experiments have shown that when the amine base is in excess of the TMSOTf, the β-silyloxycarbonyl forms in high yield. The current work shows that an excess of TMSOTf with respect to amine base efficiently yields the α,β-unsaturated carbonyl. The reaction appears to be general to aryl alkyl ketones, acetate esters, and most unsaturated aldehydes.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tetlet.2018.06.066>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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- [5] The dehydration of β-hydroxycarbonyl compounds to yield chalcones in the presence of acids is well preceded, as highlighted in Ref. [2c].
- [6] We erroneously reported this reaction to yield no products in our original description of the one-pot enol silane formation-Mukaiyama aldol reaction (Ref. [3a]). For corrected data from our laboratories, which confirm the lack of β-silyloxycarbonyl products but do describe the formation of chalcone, see Ref. [3f].
- [7] Although this observation suggests that less than 2.0 equiv TMSOTf should be adequate to achieve full conversion from the ketone to the chalcone, experiments showed that 2.0 equiv TMSOTf was necessary to achieve full conversion at shorter, more desirable reaction times.
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