Catalytic Synthesis of γ-Alkoxy-α-keto Esters

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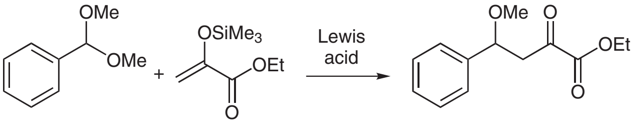
Abstract: Copper(II) triflate effectively catalyzes the reaction of (trimethylsilyloxy)acrylic esters and acetals to form γ-alkoxy-α-keto esters. The reaction proceeds under mild conditions providing products in good to excellent yields. The substrate scope was investigated, and it was demonstrated that the products could be converted into related compounds such as γ-hydroxy-α-keto esters and α-oximes.

Key words: copper(II)triflate, acetals, (trimethylsilyloxy)acrylic ester, γ-alkoxy-α-keto ester, α-oximes, γ-hydroxy-α-keto ester, Mukaiyama–aldol

(Trialkylsilyloxy)acrylic esters are interesting compounds containing both an electron-donating trialkylsilyloxy and an electron-withdrawing alkoxycarbonyl group at C1 of an olefinic core. Although they are easily accessible from the corresponding pyruvates and trimethylsilyl chloride,[1] only a few applications can be found in the literature. Those include the use of (trimethylsilyloxy)acrylic esters in the syntheses of hetusolonic and ulosonic esters[2] as well as tetrahydrocyclobuta[*c*]quinilon-3(4*H*)-ones.[3] Furthermore, radical reactions have been reported.[4] Most significant is their role as precursors for *syn*-β-amino-α-hydroxy acids[5] and β,γ-unsaturated α-keto esters.[6–9] Sugimura was the first to report a synthetic protocol for the formation of γ-alkoxy-α-keto esters,[10] which was then extended to the preparation of α-oxo-β,γ-unsaturated esters.[11] In the original report ethyl 2-(trimethylsilyloxy)acrylic ester (**2a**) was reacted with an acetal in the presence of a Lewis acid. In order to achieve reasonable results an excess of $BF_3 \cdot OEt_2$ in combination with temperatures below –30 °C was required. Apparently, the success of the reaction was limited by the acid sensitivity of both starting materials. The acrylic ester decomposed in the acidic medium, and the acetal quickly retransformed to the corresponding aldehyde. To the best of our knowledge, there has been no report on a catalytic version of this reaction. Considering its synthetic potential we decided to search for a Lewis acid that was sufficiently strong to catalytically promote this interesting C–C bond formation being at the same time mild enough to avoid the decomposition of the starting materials.

Because scandium triflate [$Sc(OTf)_3$] catalyzed a wide variety of organic reactions,[12] it became a prime candidate in our search. The reaction between (dimethoxymethyl)benzene (**1a**) and ethyl 2-(trimethylsilyloxy)acrylic ester (**2a**) was chosen as model system. In an initial attempt, 10 mol% of $Sc(OTf)_3$ was employed. After 30 minutes the desired α-keto ester **3a** was obtained in 77% yield (Table 1, entry 1). Several other metal triflates such as $Fe(OTf)_2$ and $Cu(OTf)_2$ also catalyzed the reaction.[13] Metal chlorides such as YCl_3 and $FeCl_2$ were inactive (entries 3 and 4). In contrast to $Cu(OTf)_2$, which furnished the keto ester in very high yield, $CuCl_2$ rendered the desired product only in trace amounts (entry 5). Use of $Cu(OTf)_2$ allowed to reduce the catalyst loading to 1 mol%, and under those conditions the keto ester was obtained in 85% yield (entry 8). Triflic acid proved to be too acidic, and even the use of 1 mol% led to an immediate decomposition of the reactants (entry 9).

Table 1 Effects of Various Lewis Acids on the Reaction between Acetal **1a** with Acrylic Ester **2a**



1a **2a** **3a**

Entry	Lewis acid (mol%)	Yield (%)[a]
1	$Sc(OTf)_3$ (10)	77
2	$Fe(OTf)_2$ (10)	73
3	YCl_3 (10)	traces
4	$FeCl_2$ (10)	traces
5	$CuCl_2$ (10)	traces
6	$Cu(OTf)_2$ (10)	99
7	$Cu(OTf)_2$ (5)	79
8	$Cu(OTf)_2$ (1)	85
9	TfOH (1)	–

[a] Yields after column chromatography.

In order to further optimize the reaction conditions, the influence of the solvent was investigated. Whereas no conversion or poor results were observed in reactions performed in diethyl ether or THF, dichloromethane proved to be the solvent of choice. Initially, the reactions were started at –78 °C and allowed to warm to 0 °C. Temperature studies revealed, however, that no deep cooling was required and that the reaction was best carried out in

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an ice bath (ca. 4 °C). Monitoring by TLC showed that the starting materials were completely consumed within 20–30 minutes when 10 mol% of $Cu(OTf)_2$ was employed as catalyst. Under those conditions, no significant side reactions occurred, and even without the common aqueous workup the analytically pure keto ester was isolated in nearly quantitative yield by simple column chromatography (Table 1, entry 6).

Next, the impact of a structural alternation of the acrylic ester silyl group was evaluated (Figure 1). Although compounds **2b** and **2c** bearing a dimethylphenyl silyl and a methyldiphenyl silyl group, respectively, proved to be more stable and suitable for purification by column chromatography, their use in the catalytic synthesis of α-keto ester **3a** remained inefficient. Compared to the reaction with **2a** the yields of that product were low (35% with **2b**, and 47% with **2c**).

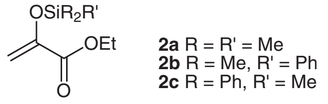
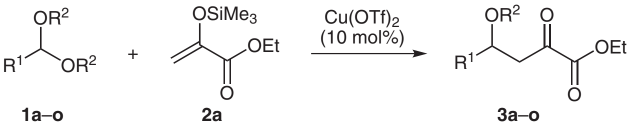


Figure 1 Ethyl (triorganylsilyloxy)acrylic esters applied in the reaction with **1a** to yield α-keto ester **3a**

Table 2 summarizes the substrate scope for catalyses performed under the optimal reaction conditions.[14] Except for (dibenzylmethyl)benzene (**1d**), which had to be prepared from benzaldehyde and trimethylsilyl-protected benzyl alcohol by $FeCl_3$ catalysis,[15] acetals **1** could easily be accessed in large quantities from the corresponding aldehydes and alcohols in the presence of hydrochloric acid. As mentioned before, (dimethoxymethyl)benzene (**1a**) reacted smoothly with ethyl 2-(trimethylsilyloxy)acrylic ester (**2a**) to give the desired γ-alkoxy-α-keto ester **3a** in almost quantitative yield (entry 1). The impact of the acetal moiety was determined by the following experiments. With (diethoxymethyl)benzene (**1b**), the corresponding keto ester **2b** was obtained in only 65% yield (entry 2). Diisopropyl acetal **2c** proved to be more reactive leading to product **3c** in 83% yield (entry 3). With the goal to introduce a cleavable ether group, dibenzyl acetal **1d** was applied. After a reaction time of only 20 minutes the corresponding keto ester **3d** was isolated in 69% yield (entry 4). Also an allyl ether could be formed, and **3e** was obtained in 76% yield starting from **1e** (entry 5).

Next, the influence of the substitution pattern of the aromatic ring was examined. To our delight various functional groups were tolerated. For example, *p*-methoxy-substituted aryl acetal **1f** reacted smoothly with **2a** to afford keto ester **3f** in 94% yield (entry 6). If the arene had a more electron-withdrawing group such as a nitro or halo substituent, the yields of the resulting keto esters were lower, but commonly still good (entries 8–12). Only in the catalysis with *p*-nitro-bearing **1h** the yield of **3h** remained unsatisfying (25%, entry 8). In none of those cases, neither extending the reaction time nor raising the temperature had a positive effect. Substrates with *ortho* substituents reacted remarkably well, and despite the steric hindrance at the reaction site of the respective starting materials the yields were good (entries 10–13). Thus, halo keto esters **3j** and **3k** were obtained in 69% and 63% yield, respectively (entries 10 and 11). Acetal **1l** having a bulky *ortho* nitro group gave the corresponding product (**3l**) in only 30% yield. Changing the catalyst to $Sc(OTf)_3$ increased the yield to 84% (entry 12). Also **1m**, prepared from 2-naphthaldehyde, reacted well, affording keto ester **3m** in 88% yield (entry 13). Reactions involving **1n** derived from 3-phenyl propanal and aliphatic acetal **1o** proved challenging, and the yields of the corresponding keto esters **3n** and **3o** were only 35% and 46%, respectively (entries 14 and 15).

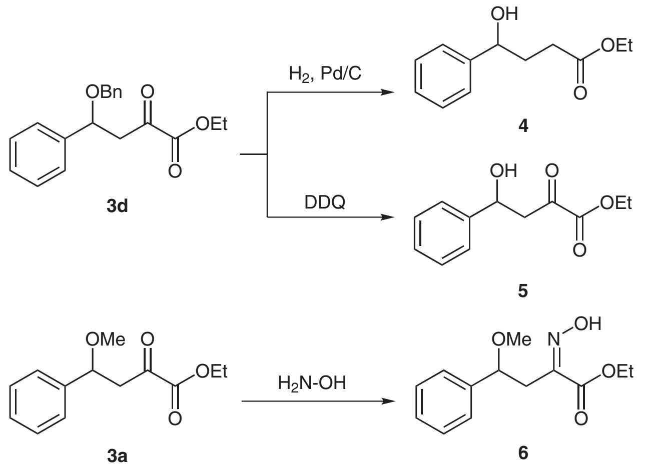
Table 2 Substrate Scope[a]



Entry	Product	R^1	R^2	Yield (%)[b]
1	**3a**	Ph	Me	99
2	**3b**	Ph	Et	65
3	**3c**	Ph	*i*-Pr	83
4	**3d**	Ph	Bn	69
5	**3e**	Ph	allyl	76
6	**3f**	$4-MeOC_6H_4$	Me	94
7	**3g**	$4-MeC_6H_4$	Me	51
8	**3h**	$4-NO_2C_6H_4$	Me	25
9	**3i**	$4-BrC_6H_4$	Me	73
10	**3j**	$2-ClC_6H_4$	Me	69
11	**3k**	$2-BrC_6H_4$	Me	63
12[c]	**3l**	$2-NO_2C_6H_4$	Me	84
13	**3m**	naphthyl	Me	88
14	**3n**	$PhCH_2CH_2$	Me	35
15	**3o**	hexyl	Me	46

[a] Reaction conditions: acetal **1**, $Cu(OTf)_2$ (10 mol%), acrylic ester **2** (1.5 equiv), CH_2Cl_2, 0 °C.
[b] After column chromatography.
[c] Use of 10 mol% of $Sc(OTf)_3$.

Because literature protocols described the removal of the γ-alkoxy substituents rendering synthetically useful β,γ-unsaturated keto esters by elimination,[11] we decided to focus our efforts on transformations retaining the dense functionalization of the products. The initial attempts targeted on the preparation of γ-hydroxy-α-keto ester **5** by debenzylation of **3d** (Scheme 1). To our surprise, utilizing a standard hydrogenation protocol with Pd/C in methanol led to overreduction, and instead of **5** hydroxy ester **4** was formed.[16] After several trials it was found that the desired benzyl cleavage was possible under oxidative conditions using 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) as reagent. In this manner γ-hydroxy keto ester **5** was obtained in 45% yield. With the goal to demonstrate a functional-group conversion of the α-keto moiety, γ-methoxy-α-keto ester **3a** was treated with hydroxylamine (Scheme 1). In this case, a smooth reaction occurred, and oxime **6** was obtained in 96% yield (Scheme 1). In the long run, the high efficiency of this process might render it interesting for the synthesis of substituted unnatural amino acid derivatives.



Scheme 1 Conversions of keto esters **3d** and **3a**

In summary, we developed a simple catalytic approach towards γ-alkoxy-α-keto esters, which proceeds under mild conditions in reasonable reaction times. No workup is required, and analytically pure products are obtained by simple column chromatography of the crude products. Various functional groups are tolerated, and depending on the substitution pattern good to excellent yields can be achieved. Straightforward functional-group conversions allow to access γ-hydroxy-α-keto esters and to address the α-keto group. Our current studies have the goal to develop a catalytic asymmetric version of this reaction and to find further applications of the densely functionalized products in organic synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **General Procedure for the Synthesis of the γ-Alkoxy-α-keto Esters**
$Cu(OTf)_2$ (0.04 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to 0 °C. The acetal (0.4 mmol) and the acrylic ester (0.6 mmol) were added, and the reaction was monitored by TLC. After consumption of the starting material, the crude reaction mixture was directly subjected to column chromatography to yield the pure products **3a**–**o**.
Ethyl 4-Methoxy-4-phenyl-2-oxobutyrate (3a)[17]
^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (t, $J = 7.14$ Hz, 3 H, CH_3), 2.98 (dd, $J = 16.8, 4.4$ Hz, 1 H, CH_2), 3.20 (s, 3 H, OCH_3), 3.41 (dd, $J = 16.8, 9.2$ Hz, 1 H, CH_2), 4.31 (q, $J = 7.14$ Hz, 2 H, CH_2), 4.73 (dd, $J = 9.2, 4.4$ Hz, 1 H, CH), 7.29–7.40 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$ (CH_3), 47.5 (CH_2), 56.7 (OCH_3), 62.4 (CH_2), 78.9 (CH), 126.4 (Ar), 128.0 (Ar), 128.5 (Ar), 140.1 (Ar), 160.6 (CO), 191.8 (CO) ppm.

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