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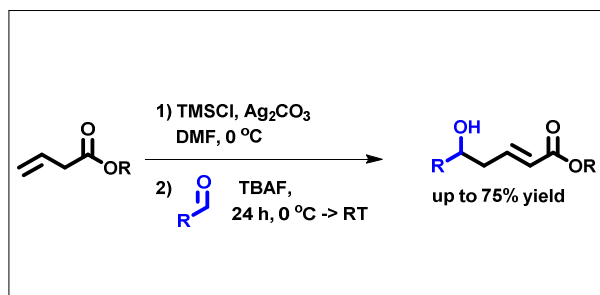
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One-Pot Vinylogous Aldol Addition of β,γ -Unsaturated Esters Under Mild Conditions

İsmail Akçok, and Ali Çağır*

A new methodology for the addition of β,γ -unsaturated esters to aldehydes was developed in TMSCl, Ag_2CO_3 , and TBAF mixture.





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LETTER

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İsmail Akçok and Ali Çağır*

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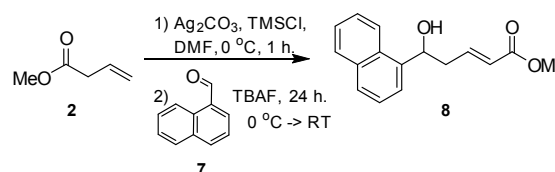
We described a one-pot vinylogous aldol addition of methyl 3-butenolate to aromatic aldehydes in the presence of silver salts and TMSCl-TBAF mixture. The reaction can be done simply by sequential mixing reagents in situ, and it does not require any catalyst or dienolate ether preparations prior to the reaction.

Synthesis of α,β -unsaturated- δ -lactones is of great importance to scientists because of their valuable antitumor, antibacterial, and antifungal activities.^{1, 2} Vinylogous aldol addition of esters (**1** or **2**) to aldehydes (**4**) produces unsaturated esters (**5**) which are valuable precursors for the synthesis of 6-alkyl or 6-aryl substituted 5,6-dihydro-2H-pyran-2-one derivatives (**6**).^{3, 4} In general, vinylogous aldol addition reactions of esters (**1** or **2**) to aldehydes (**4**) are performed by a two-step procedure. In the first step, starting esters (**1** or **2**) should be transferred to O-silyldienolate (**3**)⁵⁻⁹ and then purified by unreacted LDA and formed diisopropylamine by distillation before addition to aldehydes (Scheme 1).¹⁰ Such a distillation procedure may not be preferred for expensive starting esters because of their low yields. Alternatively, these reactions can be catalyzed by simple Lewis acids¹¹ and their complexes which can be prepared prior to the reaction.¹² Here we report a one-pot vinylogous aldol addition of β,γ -unsaturated ester (**2**) with aromatic aldehydes under mild conditions.

Scheme 1 Vinylogous aldol addition products as precursors of α,β -

unsaturated- δ -lactones

The aim of the study is to prepare 1-methoxy-1-(trimethylsilyloxy)-1,3-butadiene (**3**) in situ via the reaction of methyl 3-butenolate (**2**) and trimethylsilyl cation which can be simply generated from the reaction between silver salts and TMSCl. Then the addition of aldehyde would give the vinylogous aldol addition product (**8**). For this purpose 1-naphthaldehyde (**7**) was chosen as a model aromatic aldehyde for the optimization of reaction conditions (Scheme 2). Preliminary studies showed that pretreatment of starting ester **2** with silver carbonate and TMSCl for one hour followed by the addition of TBAF and 1-naphthaldehyde gave compound **8** with 39% yield. Interestingly, when the reaction was repeated in the absence of any one of the reagents, silver carbonate, TMSCl or TBAF, the reaction did not occur.



Scheme 2 One-pot vinylogous aldol addition to 1-naphthaldehyde

To investigate the effect of choice of solvent on reaction yield, reaction was carried out in 1.0 mL of THF, toluene, NMP, and DMF. All reactions were terminated after 24 hours and products were isolated. It seems that reaction proceeds faster in DMF and gives the highest yield of 39%. When the amount of DMF was increased to 4.0 mL the yield of the reaction increased to 44% but further dilutions of reactants in 10 mL of DMF slowed down the reaction and resulted in only 28% yield (Table 1).

Table 1. Effect of solvent on the preparation of α,β -unsaturated ester (**8**)*

Entry	Solvent [Conc.]	Yield (%)
1	THF [0.25M]	17
2	Toluene [0.25M]	16
3	NMP [0.25M]	16
4	DMF [0.25M]	39
5	DMF [0.0625M]	44
6	DMF [0.025M]	28

[*] Isolated yield. All reactants used were 1.00 eq.

*Department of Chemistry, Science Faculty İzmir Institute of Technology, Urla 35430, İzmir, Turkey. E-mail: alicagir@iyte.edu.tr

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To better understand the role of silver carbonate in the reaction, the reactions were carried out with different silver salts or sodium carbonate (Table 2). Again, all reactions were terminated in about 24 hours, and products were purified. In the presence of a weak base of silver triflate, silver nitrate, silver oxide or triethylamine, there were either poor yields or no reaction. On the other hand, when reactions were carried out with sodium carbonate or silver carbonate comparable yields were obtained (44 and 39% respectively). These findings imply that the basicity of the solution is quite important for the outcome of the reactions. Among the tested silver salts silver triflate was found to be the least effective. This might be because of the formation of trifluoromethanesulfonic acid during the enolization process. The presence of such a strong acid may shift the enol-keto tautomerism toward the carbonyl isomer.

Table 2 Effect of silver source and base on the preparation of α,β -unsaturated ester (**8**)

Entry	Silver source (and base)	Solvent [Conc.]	Time (h)	Yield* (%)
1	Ag ₂ CO ₃	DMF [0.0625M]	24	44
2	AgOTf	NMP [0.0625M]	24	NP
3	AgOTf	THF [0.0625M]	24	NP
4	AgOTf + Na ₂ CO ₃	DMF [0.0625M]	24	6
5	Na ₂ CO ₃	DMF [0.0625M]	24	39
6	AgOTf + Et ₃ N	DMF [0.0625M]	24	NP
7	Ag ₂ O	DMF [0.0625M]	24	19
8	AgNO ₃	DMF [0.0625M]	24	2

[*] Isolated yield. All reactants used were 1.00 eq.

On the other hand, the reaction gave low yield in the presence of silver nitrate, which can also produce a strong conjugate acid during the enolization step. As shown in Table 1, the rate of the reactions depends on the concentrations of the reagents. To further optimize the reaction conditions, reactions were performed in the presence of various amounts of aldehyde (**7**) and silver carbonate (Table 3). After 24 hours, a reaction with only 0.5 equivalent of silver carbonate for each aldehyde gave slightly better yield (55%). Addition of two equivalents of aldehyde to the reactions increased the yield up to 75%. When TBDMSCl was used as silyl source the yield of the reaction decreased to 25%, and this clearly shows that silyl group plays an effective role in the reaction mechanism.

Table 3 Effect of the amount of Ag₂CO₃ and aldehyde on the preparation of α,β -unsaturated ester (**8**)

Entry	Aldehyde 7 (eq.) [Conc.]	Ag ₂ CO ₃ (eq.) [Conc.]	DMF (mL)	Yield (%)
1	1.00 [0.0625 M]	1.00 [0.0625M]	4 mL	44
2	1.00 [0.0625 M]	0.50 [0.03125M]	4 mL	55
3	1.00 [0.025 M]	0.50 [0.0125M]	10 mL	53
4	2.00 [0.125 M]	0.50 [0.03125M]	4 mL	75
5	2.00 [0.05 M]	0.50 [0.0125M]	10 mL	65

[*] Isolated yield. All other reagents used were 1.00 eq.

To check the applicability of the methodology, six different aldehydes were used in optimized reaction conditions. As can be seen in Table 4, yields of the reaction may be altered by the substituents present on the aromatic ring. Although the electron donating group causes a decrease, the electron withdrawing group increases the yield. Enolizable aldehyde (**12**) gave no product formation whereas corresponding styryl substituted aldehyde (**13**) gave a product with 28% yield.

Table 4 Vinylogous aldol addition to different aldehydes. Conditions: methyl 3-butenolate (1 eq), TMSCl (1 eq), Ag₂CO₃ (0.5 eq), aldehyde (2 eq), TBAF (1 eq)

Aldehyde	Ar(R)	Yield* (%)
9		41
10		12
11		67
12		NP
13		28
14		69

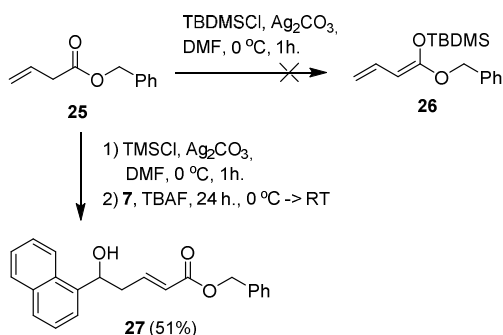
[*] Isolated yield.

To test the effectiveness of the reaction mixture two different acetate esters were used as an enolate source for aldol reactions (Scheme 3). In neither trial was product formation observed. This implies that the base is not strong enough to obtain acidic alpha-protons of acetates. A similar reaction was tried with N-methylpyrrolidinone and no enolization was observed in this attempt either.



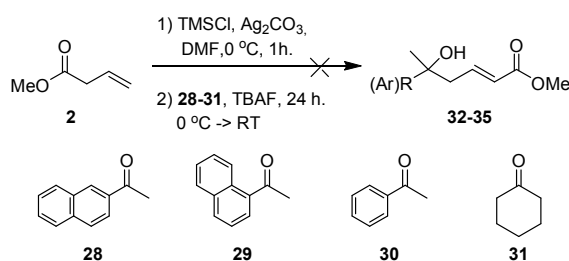
Scheme 3 Addition of acetate esters (**21** and **22**) to 1-naphthaldehyde

Earlier it was mentioned that the aim was to prepare 1-methoxy-1-(trimethylsilyloxy)-1,3-butadiene (**3**) in situ via the reaction of methyl 3-butenolate (**2**) and trimethylsilyl cation which can be simply generated from the reaction between silver salts and TMSCl. To identify such enol ether formation methyl 3-butenolate (**2**) was stirred with silver carbonate in DMF for 24 hours but no detectable reaction was observed. A similar preparation of silyl vinyl dienol ether (**26**) was also studied, starting with ester **25** and TBDMSCl, but no O-silyl dienol ether formation was observed. Additionally, vinylogous aldol addition of compound **25** to 1-naphthaldehyde gave compound **27** as product in 51% yield (Scheme 4).



Scheme 4 Preparation of dienol silyl ether

Lastly, similar to aldehyde **12** all additions of dienolate to the ketones (**28-31**) failed (Scheme 5). The current method cannot tolerate any acidic proton on the α carbon of carbonyls.



Scheme 5 Addition of methyl 3-butenolate to different ketones

A new selective enolization methodology for β,γ -unsaturated esters was developed and used in vinylogous aldol addition reactions. The exact reaction mechanism and the role of the reagents in the reaction are not clear yet, but reaction cannot be carried out in the absence of any one of the reagents, TMSCl, TBAF, and silver carbonate. The methodology does not require large amounts of starting materials, and it can be simply applied to small amounts of valuable aldehydes or vinyl acetate derivatives.

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Experimental Section

To a two-necked round bottom flask 34 mg of Ag₂CO₃ (0.125 mmol, 0.5 eq.) and 4 mL of anhydrous DMF were added. The mixture was stirred about 20 minutes at room temperature and cooled down to 0 °C in ice bath. Then 28 μ L of methyl 3-butenolate (0.25 mmol, 1 eq.) and 33 μ L of TMSCl (0.25 mmol, 1 eq.) were added sequentially. After solution was stirred 1 h at 0 °C, 72 μ L 1-naphthaldehyde (0.5 mmol, 2 eq.) and 0.25 mL TBAF (1.0 in M THF) (0.25 mmol, 1 eq.) were added to the reaction mixture. The final mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was poured into 30 mL of water and extracted with Et₂O (3x40 mL). Combined organic phase was dried over MgSO₄ and excess solvent was removed under reduced pressure. Purification of crude product on SiO₂ column (1:6 \rightarrow 1:4; EtOAc:Hexane) furnished 48 mg of (*E*)-methyl 5-hydroxy-5-(naphthalen-5-yl)pent-2-enoate (**8**) as yellow oil in 75% yield.

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