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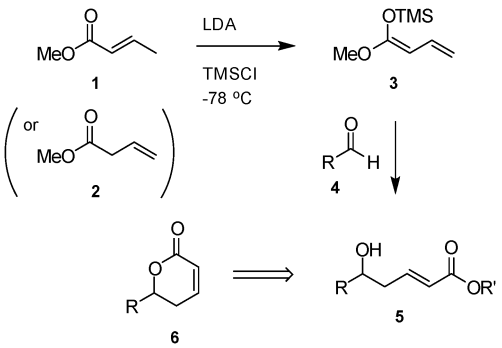
One-pot vinylogous aldol addition of β,γ-unsaturated esters under mild conditions†

İsmail Akçok and Ali Çağır*

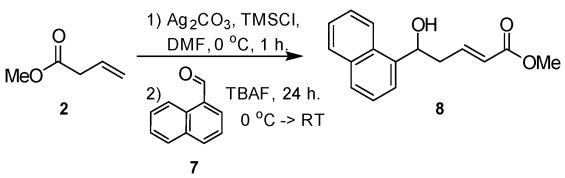
We described a one-pot vinylogous aldol addition of methyl 3-butenoate to aromatic aldehydes in the presence of silver salts and the TMSCl–TBAF mixture. The reaction can be done simply by sequentially mixing reagents *in situ*, and it does not require any catalyst or dienolate ether preparations prior 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-2*H*-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 acids[11] 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**) to aromatic aldehydes under mild conditions.

The aim of the study is to prepare 1-methoxy-1-(trimethylsiloxy)-1,3-butadiene (**3**) *in situ via* the reaction of methyl 3-butenoate (**2**) and trimethylsilyl cation which can be simply generated by 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



Scheme 1 Vinylogous aldol addition products as precursors of α,β-unsaturated-δ-lactones.



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

starting ester **2** with silver carbonate and TMSCl for one hour followed by the addition of TBAF and 1-naphhaldehyde 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.

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).

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

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

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

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

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[a] (%)
1	Ag_2CO_3	DMF [0.0625 M]	24	44
2	AgOTf	NMP [0.0625 M]	24	NP
3	AgOTf	THF [0.0625 M]	24	NP
4	AgOTf + Na_2CO_3	DMF [0.0625 M]	24	6
5	Na_2CO_3	DMF [0.0625 M]	24	39
6	AgOTf + Et_3N	DMF [0.0625 M]	24	NP
7	Ag_2O	DMF [0.0625 M]	24	19
8	$AgNO_3$	DMF [0.0625 M]	24	2

[a] Isolated yield. All reactants used were 1.00 eq. NP: No product.

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.

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 equivalents 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 the silyl source the yield of the reaction decreased to 25%, and this clearly shows that the silyl group plays an effective role in the reaction mechanism.

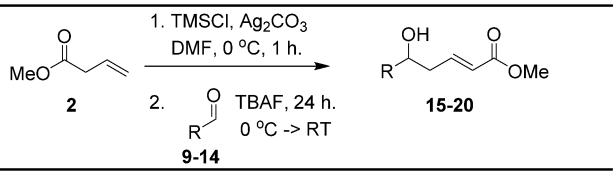
To check the applicability of the methodology, six different aldehydes were used under optimized reaction conditions. As can be seen in Table 4, yields of the reaction may be altered by the substituents present in the aromatic ring. Although the electron donating group causes a decrease, the electron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

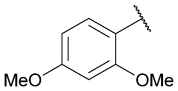
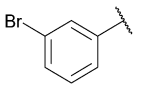
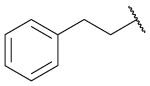
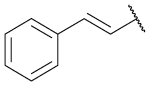
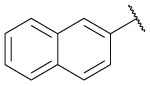
Table 3 Effect of the amount of Ag_2CO_3 and aldehyde on the preparation of α,β-unsaturated ester (**8**)[a]

Entry	Aldehyde 7 (eq.) [Conc.]	Ag_2CO_3 (eq.) [Conc.]	DMF (mL)	Yield (%)
1	1.00 [0.0625 M]	1.00 [0.0625 M]	4	44
2	1.00 [0.0625 M]	0.50 [0.03125 M]	4	55
3	1.00 [0.025 M]	0.50 [0.0125 M]	10	53
4	2.00 [0.125 M]	0.50 [0.03125 M]	4	75
5	2.00 [0.05 M]	0.50 [0.0125 M]	10	65

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

Table 4 Vinylogous aldol addition to different aldehydes. Conditions: methyl 3-butenoate (1 eq.), TMSCl (1 eq.), Ag_2CO_3 (0.5 eq.), aldehyde (2 eq.), TBAF (1 eq.)

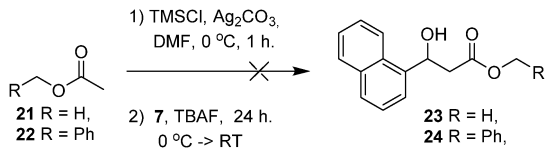


Aldehyde	Ar(R)	Yield[a] (%)
9		41
10		12
11		67
12		NP
13		28
14		69

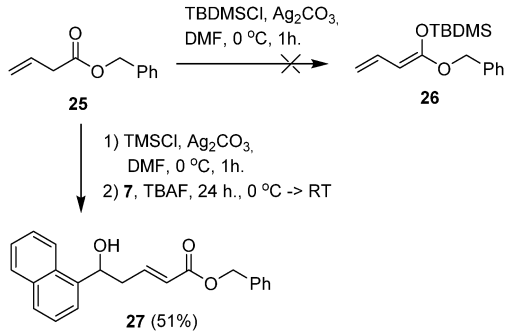
[a] Isolated yield.

To test the effectiveness of the reaction mixture two different acetate esters were used as enolate sources 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.

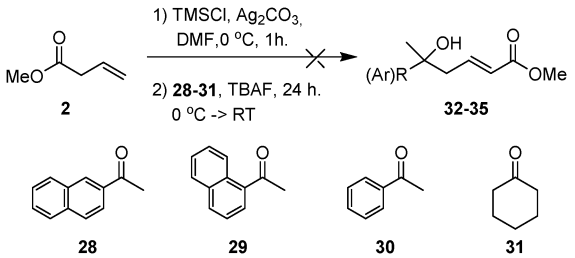
Earlier it was mentioned that the aim was to prepare 1-methoxy-1-(trimethylsiloxy)-1,3-butadiene (**3**) *in situ via* the reaction of methyl 3-butenoate (**2**) and the trimethylsilyl cation which can be simply generated by the reaction between silver salts and TMSCl. To identify such enol ether formation methyl



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



Scheme 4 Preparation of dienol silyl ether.



Scheme 5 Addition of methyl 3-butenoate to different ketones.

3-butenoate (**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 a product in 51% yield (Scheme 4).

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 in the α carbon of carbonyls.

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.

Experimental section

To a two-necked round bottom flask 34 mg of Ag_2CO_3 (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 an ice bath. Then 28 μL of methyl 3-butenoate (0.25 mmol, 1 eq.) and 33 μL of TMSCl (0.25 mmol, 1 eq.) were added sequentially. After stirring the solution for 1 h at 0 °C, 72 μL of 1-naphthaldehyde (0.5 mmol, 2 eq.) and 0.25 mL of 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 Et_2O (3 × 40 mL). The combined organic phase was dried over $MgSO_4$ and excess solvent was removed under reduced pressure. Purification of the crude product on a SiO_2 column (1 : 6 → 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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Notes and references

1 P. Kasaplar, O. Yilmazer and A. Cagir, *Bioorg. Med. Chem.*, 2009, **17**, 311.
2 P. Kumar and S. V. Naidu, *J. Org. Chem.*, 2006, **71**, 3935.
3 M. Kumar, A. Kumar, M. Rizvi, M. Mane, K. Vanka, S. C. Taneja and B. A. Shah, *Eur. J. Org. Chem.*, 2014, 5247.
4 M. J. Aurell, L. Ceita, R. Mestres, M. Parra and A. Tortajada, *Tetrahedron*, 1995, **51**, 3915.
5 H.-F. Chow and I. Fleming, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2651.
6 C. Camiletti, D. D. Dhavale, F. Donati and C. Trombini, *Tetrahedron Lett.*, 1995, **36**, 7293.
7 L. Ratjen, P. Garcia-Garcia, F. Lay, M. E. Beck and B. List, *Angew. Chem.*, 2011, **50**, 754.
8 P. Sawant and M. E. Maier, *Eur. J. Org. Chem.*, 2012, 6576.
9 G. Bluet and J. M. Campagne, *J. Org. Chem.*, 2001, **66**, 4293.
10 B. Bazán-Tejeda, G. Bluet, G. Broustal and J.-M. Campagne, *Chem. – Eur. J.*, 2006, **12**, 8358.
11 M. Christmann and M. Kalesse, *Tetrahedron Lett.*, 2001, **42**, 1269.
12 J. A. Gazaille and T. Sammakia, *Org. Lett.*, 2012, **14**, 2678.