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Catalytic enamine reaction: an expedient 1,4-conjugate addition of naked aldehydes to vinylketones and its application to synthesis of cyclohexenone from *Stevia purpurea*

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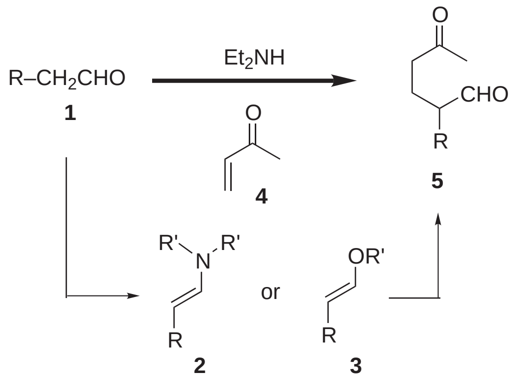
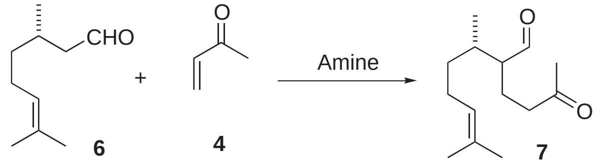
Abstract—Naked aldehydes directly add in a 1,4-manner to vinylketones in the presence of 0.2 equiv. of diethylamine in sealed tubes to provide 5-keto aldehydes. © 2001 Elsevier Science Ltd. All rights reserved.

Enamines **2**[1] have played an important role as very versatile nucleophiles for mild carbon–carbon bond forming reactions. One of these nucleophilic reactions, conjugate addition[2] of enamines **2** of aldehydes **1** to α,β-unsaturated carbonyl compounds, has been a powerful tool in the synthesis of γ-formyl carbonyl compounds (Scheme 1). As synthetic equivalents of enamines **2**, alkylenol or trimethylsilylenol ethers **3** of aldehydes **1** have been employed for the 1,4-addition to vinylketones in the presence of a Lewis acid.[3] Due to the difficulty in controlling reactions of enolates or enols of aldehydes, there had been no examples of direct conjugate addition of naked aldehydes to vinylketones so far until diethylamino(trimethyl)silane (DEATMS)-mediated conjugate addition was reported.[4] We delineate herein an alternative expedient synthesis of 5-keto aldehydes **5** by 1,4-addition of naked aldehydes **1** to 3-buten-2-one (MVK) **4** in the presence of a catalytic amount of diethylamine (DEA).

The reaction of citronellal **6** with MVK **4** was employed as a probe to find optimized reaction conditions (Scheme 2, Table 1). A catalytic amount of DEA gave a better yield than pyrrolidine when the reaction was carried out in a sealed tube to prevent evaporation of volatile DEA (Table 1, entries 1, 2 and 3). Among the solvents investigated, MeCN and toluene gave the best and comparable results (Table 1, entries 8 and 10). With 0.1 equiv. of DEA, a certain amount of citronellal **6** was recovered (Table 1, entries 5, 6 and 7). Higher temperature decreased the yield (Table 1, entry 9). Thus, the optimized reaction was carried out simply by



Scheme 1.



Scheme 2.

Keywords: aldehydes; amines; catalysis; enamines; Michael reactions.

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Table 1. Optimization of reaction condition in the conjugate addition of citronellal **6** to MVK **4**

Entry[a]	Solvent	Amount of amine (equiv.)	Product **7**	
			Time (h)	Yield (%)
1	CH_3CN	0.1	50	66
2[b]	–	1.0	23	28 (37)[c]
3	CH_3CN	0.2[d]	5	7[e]
4	*n*-Hexane	0.1	16	10[f]
5[c]	THF	0.1	19	43 (66)
6	CH_2Cl_2	0.1	15.5	45 (65)
7[c]	CH_3CN	0.1	16.5	50 (55)
8	CH_3CN	0.2	41	73
9[g]	Toluene	0.2	16	29 (59)[c]
10	Toluene	0.2	24	87
11[h]	Toluene	0.2	25	45 (80)[c]

[a] Reaction was carried out with 1.5 equiv. of MVK 4 at 80°C in a sealed tube.

[b] Reaction was carried out in an open vessel.

[c] Yield in parentheses was based on starting material consumed.

[d] Pyrrolidine was used.

[e] Citronellal **6** decomposed.

[f] Citronellal **6** could not be separable from by product.

[g] Reaction was carried out at 130°C.

[h] Reaction was carried out in the presence of 4 Å sieves.

heating the toluene solution of the substrates with 0.2 equiv. of DEA at 80°C overnight in a sealed tube. After the reaction, evaporation of the solvent in vacuo followed by purification by medium-pressure liquid chromatography provided 5-keto aldehyde **7** as a 1:1 diastereomeric mixture (NMR). No aqueous work-up was required.

Some representative examples of the present conjugate addition of various naked aldehydes are shown in Table 2. Taking the economy of the reaction into consideration, toluene or THF was employed as a solvent. In entry 2, the yield was low because of the volatile nature of the product. It is noteworthy that the reaction conditions were so mild that the acid-sensitive THP or TBS, and the base-sensitive acetyl protecting group survived. Not only MVK, but also 1-penten-3-one, 3-methyl-3-buten-2-one and methyl acrylate with citronellal **6** provided the conjugate addition product in 74, 10 and 7% yield, respectively. On the other hand, in the reaction of decanal **8** with cyclopentenone or vinylsulfoxide the aldehyde **8** was recovered. The present 1,4-conjugate addition was selective to contaminate no self aldol condensation product[5] of aldehyde except in the reaction of methyl acrylate with decanal **8**.

Table 2. Conjugate addition of various aldehyde **1** to MVK **4**

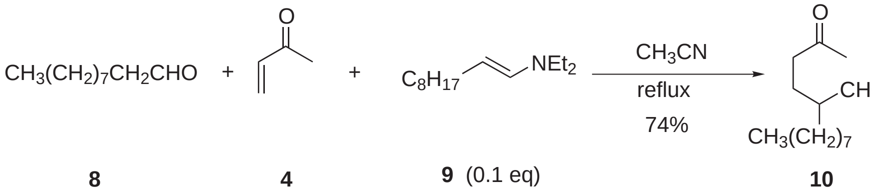
Entry[a]	Aldehyde **1**	Product **5** Yield (%)	
		THF	Toluene
1	$R=CH_3(CH_2)_7$	73	47
2	R = *i*-Pr	28	30
3	$R=PhCH_2$	62	60
4	$R=AcOC_8H_{16}$	61 (63)[b]	80 (83)[b]
5	$R=THPOC_3H_6$	55 (73)[b]	76
6	$R=TBSOC_8H_{16}$	–	75

[a] Reaction was carried out with 1.5 equiv. of MVK in the presence of 0.2 equiv. of Et_2NH at 80°C for 16 h in a sealed tube.

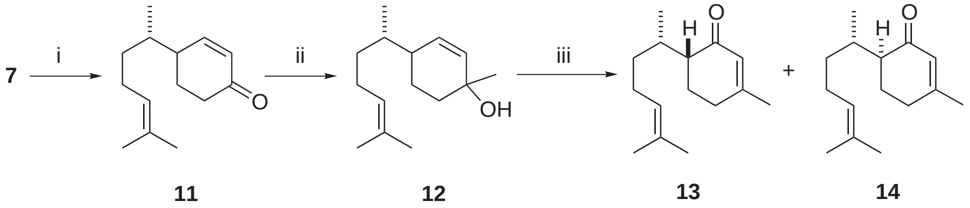
[b] Yield in parentheses based on starting material consumed.

The pathway of the present reaction is discussed as follows. When the reaction of citronellal **6** with MVK **4** in toluene was carried out in the presence of 4 Å molecular sieves powder, the yield of the 5-keto aldehyde **7** decreased to 45% along with 44% of recovered **6** (Table 1, entry 11). When diethylamino–enamine **9** was prepared according to the literature procedure[1a] it was quite unstable and partially hydrolyzed to a mixture of the enamine **9**, decanal **8** and DEA (1:0.85:0.70) during NMR measurement. Freshly distilled enamine **9** (0.1 equiv.) was added to the mixture of decanal **8** and MVK **4** in MeCN. The resulting solution was heated at reflux for 8 h to afford 1,4-conjugate addition product **10** in 74% yield, as shown in Scheme 3. These results suggest that the present reaction proceeds via in situ generated diethylamino–enamine **9** which drives the catalytic cycle to turn around in the presence of water as a mediator.[4] Pyrrolidino–enamine of decanal **8** (0.1 equiv.) also gave the 5-keto aldehyde **10** in 90% yield. Similarly, pyrrolidino–enamine of citronellal **6** (0.1 equiv.) provided the 5-keto aldehyde **7** in 91% yield.

Substituted 5-keto aldehydes **5**, thus obtained, have been important synthons especially for substituted 2-cyclohexenone derivatives which have been widely utilized as starting materials for a variety of natural and unnatural compounds. Cyclohexenone **13** was isolated[6] from *Stevia purpurea*, and its antipode has already been synthesized by Jefferies et al.[7] thereby correcting its absolute stereochemistry (Scheme 4). The 5-keto aldehyde **7** was transformed into the cyclohexenone **13** as a 1:1 diastereomeric mixture by a modified synthetic sequence in 64% overall yield. After medium-pressure LC separation, the less polar cyclohexenone **13** exhibited the same NMR spectral data as well as the optical rotation of the natural **13** {$[\alpha]_D$ −46° (*c* 3.1, $CHCl_3$), lit.[6] $[\alpha]_D$ −37° (*c* 3.7, $CHCl_3$)}.



Scheme 3.



Scheme 4. *Reagents and conditions*: (i) 5% KOH, Bu_4NOH, THF, Et_2O, 74%; (ii) MeLi, Et_2O, 95%; (iii) PCC, CH_2Cl_2, 91%.

In summary, we have offered a simple, efficient and practical 1,4-conjugate addition reaction of naked aldehydes **1** to vinylketones under milder reaction conditions. The present reaction would be easily applicable to large-scale preparations.

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