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Direct 1,4-Addition of Aldehydes to Vinylketones

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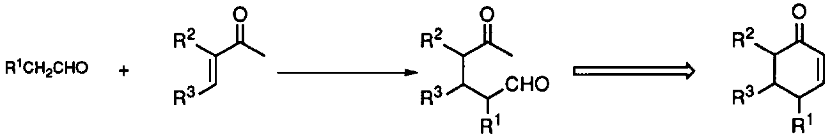
Abstract: Aldehydes directly add in 1,4-manner to vinylketones in the presence of 0.5 eq. of diethylaminotrimethylsilane without a solvent to give 5-ketoaldehydes.

Substituted 5-ketoaldehydes **3** have been important synthones especially for substituted cyclohex-2-en-1-one derivatives **4**[2] which have been versatile starting materials for natural products such as terpenoids. So far, these 5-ketoaldehydes **3** have been prepared mainly by the 1,4-addition of masked aldehydes, *i.e.*, morpholinoenamine of aldehyde,[3] alkyl or trimethylsilylenol ether of aldehyde in the presence of Lewis acid,[4] or diethylallylamine in the presence of a catalytic amount of Ru complex,[5] to vinylketones, because of the difficulty to generate enolates or enols of aldehydes directly. We report herein a novel synthesis of 5-ketoaldehydes **3** by an unprecedented 1,4-addition of unmasked aldehydes **1** to vinylketones **2** (Scheme 1).



1a $R^1=C_8H_{17}$
b $R^1=C_6H_{13}$
c $R^1=i\text{-Pr}$
d $R^1=PhCH_2$

2a $R^2=R^3=H$
b $R^2=H, R^3=Me$
c $R^2=Me, R^3=H$

3a $R^1=C_8H_{17}, R^2=R^3=H$
b $R^1=C_8H_{17}, R^2=H, R^3=Me$
c $R^1=C_6H_{13}, R^2=R^3=H$
d $R^1=C_6H_{13}, R^2=Me, R^3=H$
e $R^1=i\text{-Pr}, R^2=R^3=H$
f $R^1=PhCH_2, R^2=R^3=H$

4

Scheme 1

Among reagents investigated, we found diethylaminotrimethylsilane (Et_2NTMS) gave the best result (Table 1, entry 1 and 5). Use of chlorotrimethylsilane, triethylamine or tris(trimethylsilyl)amine recovered aldehyde **1** completely. The optimum amount of Et_2NTMS was 0.5 mol. equiv. (Table 1, entry 3, 4 and 5). Better yield was obtained without a solvent (Table 1, entry 2). The major side product in these reactions was the recovered starting aldehyde **1**. The reaction was carried out simply by stirring the reaction mixture at room temperature overnight under nitrogen atmosphere, and evaporation of excess reagents *in vacuo* followed by purification by medium pressure liquid chromatography provided 5-ketoaldehydes **3**. Some representative examples of the present reaction are shown in the Table 1. Conjugate addition of Et_2NTMS to methyl vinylketone **2a** was not a serious side reaction in spite of a recent report by Hosomi *et. al*,[6] probably because of the lower reaction temperature. TLC inspection did not suggest any intervention of enamine of the aldehyde **1**.

Table 1 1,4-Addition of Aldehydes to Vinylketones

Entry[a]	Aldehyde	Vinylketone	5-Ketoaldehyde	Yield (%)
1	**1a**	**2a**	**3a**	46[b]
2	**1a**	**2a**	**3a**	54[c]
3	**1a**	**2a**	**3a**	22[d]
4	**1a**	**2a**	**3a**	66[e]
5	**1a**	**2a**	**3a**	67
6	**1a**	**2b**	**3b**	15
7	**1b**	**2a**	**3c**	49
8	**1b**	**2c**	**3d**	35
9	**1c**	**2a**	**3e**	22
10	**1d**	**2a**	**3f**	58

[a] All reactions were conducted with 0.5 mol. equiv. of Et_2NTMS without a solvent unless otherwise indicated. All reagents were used directly from bottles. [b] Bis(dimethylamino)dimethylsilane (0.5 mol. equiv.) was used. [c] Dichloromethane was employed as a solvent with an equivalent of Et_2NTMS. [d] Et_2NTMS (0.2 mol. equiv.) was used. [e] A mol. equiv. of Et_2NTMS was used.

Although the exact mechanism of the present reaction remains obscure, comparison of net atomic charges of dimethylaminotrimethylsilane and chlorotrimethylsilane by semiempirical molecular orbital calculations (MOPAC, AM1, precise mode)[7] revealed that the charge separation between the silicon and hetero atoms was larger in the former. Namely, in dimethylaminotrimethylsilane, the silicon atom was more positive and nitrogen atom was more negative than the silicon and chlorine atoms of chlorotrimethylsilane, respectively. Thus, enhanced Lewis acidity of the silicon atom as well as basicity of the nitrogen atom of Et_2NTMS might play an important role in enolate formation of aldehydes and activation of vinylketone towards 1,4-conjugate addition.

In summary, the present reactions with its milder reaction conditions and simplicity of operation, opened novel entry to direct conjugate addition of aldehydes to electron-deficient olefins.

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