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Solvent-free Mukaiyama aldol reaction of *O*-silyl dienolates catalyzed by benzoic acid

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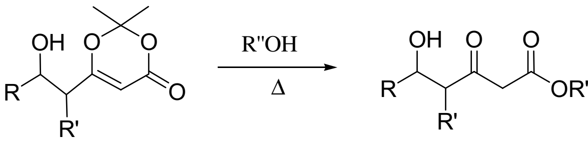
Abstract—The vinylogous aldol reaction of *O*-silyl dienolates deriving from 2,2-dimethyl-[1,3]-dioxin-4-ones proceeds in moderate to excellent yields in the presence of catalytic amounts of PhCOOH under solvent-free conditions. Modest to good yields can be obtained by using silica gel or 3 Å molecular sieves as heterogeneous catalysts.

In these last years an ever increasing interest has been aimed to solvent-free organic syntheses.[1] In fact, avoiding the use of volatile, often flammable, expensive and toxic solvents strongly reduces the waste production and many fundamental processes have proven to be achievable through efficient procedures characterized by high simplicity of set-up and work-up.

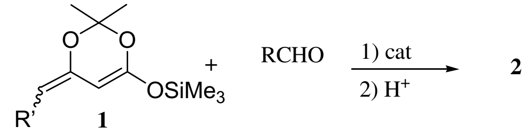
As well-documented in the literature, racemic and chiral compounds **2** are versatile intermediates in preparative organic synthesis[2] and, particularly, their easy conversion[3] in δ-hydroxy-β-ketoesters **3** (Scheme 1) has been conveniently exploited, as the key-step, in the preparation of several bio-active compounds.[4]



2 **3**

Scheme 1.

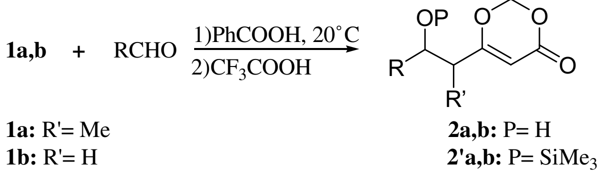
One of the typical approaches leading to compounds **2** is based on a Mukaiyama-type aldol condensation of *O*-silyl dienolates **1** promoted by Lewis acids such as $TiCl_4$[2b,5] or $BF_3{\cdot}Et_2O$[6] (Scheme 2).



Scheme 2.

A recent investigation[7] on the reactivity of compounds of type **1** pointed out their significant nucleophilic properties, so that the conversion **1** → **2** was found to take place in efficient way in the presence of a very weak Lewis acid as $SiCl_4$. Since solvent-free reactions very often exhibit rather high reaction rates, it seemed interesting to examine the reactivity of **1a**,**b** (Scheme 3) in Mukaiyama aldol condensations performed in the absence of solvent.

Nevertheless, a preliminary control experiment, carried out by using neat **1a** (*E*/*Z* mixture in a 3/5 ratio) and



Scheme 3.

Keywords: Aldol reaction; Molecular sieves; Silica gel; Silyl dienolates.

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Table 1. Benzoic acid-catalyzed Mukaiyama reaction of **1a** on RCHO

Entry	R	Reac. time (h)	Prod. **2a**	Yield[a] (%)	*syn*/*anti* dr[b]
1[c]	Ph	3	**2aa**	62	68/32
2[c]	2-Furyl	2.5	**2ab**	82	51/49
3[d]	Ph	3	**2aa**	18	68/32
4[d]	Ph	18	**2aa**	72	71/29
5	*p*-MeC_6H_4	24	**2ac**	96	58/42
6	*p*-$MeOC_6H_4$	2	**2ad**	96	57/43
7	$PhCH_2CH_2$	24	**2ae**	50	56/44
8	*p*-BrC_6H_4	2	**2af**	62	60/40
9	*p*-CNC_6H_4	2	**2ag**	60	54/46

[a] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by comparison of the spectroscopic data (^1H and ^{13}C NMR) with the ones reported in the literature.[9] In all entries RCHO/**1a** were used in 1/2 stoichiometric ratio. Typical experimental procedure: in a dried vial diene **1** (2 equiv, 1 mmol), benzoic acid (0.025 equiv) and aldehyde (1 equiv, 0.5 mmol) were mixed and stirred at 20 °C. The reaction was quenched by water (2 ml) and the organic layer extracted in Et_2O (3 × 5 ml). The crude was desilylated by Kruger and Carreira's procedure[8] and the resulting mixture purified by silica gel chromatography (eluent: $CHCl_3$–Et_2O 9/1).

[b] *syn*/*anti* diastereoisomeric ratios were calculated by ^1H NMR (400 MHz) analysis on the crude products **2a** by accurate integration of the signals relative to C*H*OH protons.[9]

[c] In these entries undistilled aldehydes were used.

[d] In this entry freshly distilled benzaldehyde was used.

benzaldehyde as representative reagents, afforded a rather surprising result: in fact, under the conditions reported in Table 1 (entry 1, no catalyst added) the formation of the *O*-silylated aldol **2′aa** was found to occur in rather fast way: the following desilylation by acidic treatment of the crude **2′aa**, according to Kruger and Carreira procedure,[8] afforded the free aldol **2aa** in appreciable yield and moderate diastereosectivity. An even better efficiency was observed by reacting **1a** with 2-furaldehyde under the same conditions (entry 2), although the corresponding aldol **2ab** was isolated in ~1/1 diastereoisomeric ratio. However, it is noteworthy that using freshly distilled benzaldehyde resulted in a dramatic drop of yield (entry 3). This latter result suggested the possibility that in entries 1 and 2 the presence of benzoic or furoic acids, deriving from the auto-oxidation of the corresponding aldehydes, could be responsible of the formation of the Mukaiyama aldols **2aa**,**ab**. In fact, undistilled benzaldehyde used in entry 1 was found to be contaminated by benzoic acid in a significant way (9%). The determining role exerted by the carboxylic acid was confirmed by performing the solvent-free reaction by using freshly distilled benzaldehyde in the presence of 0.025 equiv of PhCOOH (entry 4): in fact, after the usual treatment, the aldol **2aa** was isolated in good yield and appreciable diastereoisomeric ratio. In order to assess the level of general validity of this finding, several aldehydes were submitted to reaction with **1a** and in all the reported entries 4–9 the formation of the expected aldols **2a** was found to take place in moderate to very good yields, although a poor *syn*/*anti* selectivity was usually observed. These results are particularly interesting since many important preparative processes, including C–C bond formation reactions, may suffer the presence of protic acids since they often cause quenching or decomposition of the used nucleophiles, such as silyl enol ethers. However, recent reports[10] have shown that several nucleophiles sensitive to acidic conditions could be successfully reacted with carbonyl compounds, suitably activated by mild protic organo-catalysts through single or double hydrogen bonding.[11] The possible involvement in the conversion of type **1** → **2** of a hydrogen bond-promoted aldol reaction seemed to be reasonably confirmed by performing the experiment of entry 4 in the presence of *rac*-BINOL (3% mol) since aldol **2aa** was obtained in 73% yield (58/42 *syn*/*anti* ratio). Furthermore, the employment of the hindered 2,6-di-*tert*-butyl phenol (3% mol), as activator, required higher temperature (40 °C, reaction time 20 h) to change *p*-anisaldehyde into **2ad**, isolated in 74% yield, as 52/48 *syn*/*anti* mixture.

The same procedure showed to be successful with *O*-silyl dienolate **1b**, as confirmed by the data reported in Table 2 (entries 1–6).

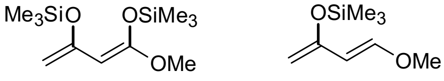
It is noteworthy that preliminary experiments performed on linear *O*-silyl dienolates, such as Chan's diene **4** and Danishefsky's diene **5** (Fig. 1) gave very poor results: in fact, under the typical conditions of entry 1 (Table 2) no evidence of formation of the corresponding vinylogous aldols could be detected and ^1H NMR analysis ($CDCl_3$) performed directly on the crude reaction mixtures, without any previous work-up, revealed only the presence of unreacted benzaldehyde and the products of decomposition of **4** and **5** (methyl 3-trimethylsilyloxy crotonate and 4-methoxy-but-3-en-2-one, respectively).

The employment of solvent-free conditions proved to be particularly convenient: in fact the experiment of entry 1 was repeated in CH_2Cl_2 solution (1 ml) and after 3.5 h a mixture of aldol **2ba** and *O*-silylated **2′ba** was isolated. The desilylation procedure afforded **2ba** in only 46% yield.

Table 2. Solvent-free benzoic acid-catalyzed Mukaiyama reaction of **1b** on RCHO

Entry	R	Reac. time (h)	Prod. **2b**	Yield[a] (%)
1	Ph	2	**2ba**	70
2	*p*-MeC_6H_4	2	**2bc**	72
3	*p*-$MeOC_6H_4$	2	**2bd**	85
4	$PhCH_2CH_2$	24	**2be**	40
5	*p*-BrC_6H_4	24	**2bf**	64
6	*p*-CNC_6H_4	2	**2bg**	61

[a] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by comparison of the spectroscopic data (^1H and ^{13}C NMR) with the ones reported in the literature.[9] In all entries RCHO/**1b** were used in 1/2 stoichiometric ratio.



4 **5**

Figure 1.

As previously reported,[5] in the past years $TiCl_4$ has represented the catalyst of choice for Lewis acid-catalyzed conversion **1** → **2**. For example, the formation of the aldol **2ba** was found to occur in 99% by performing the reaction in CH_2Cl_2 solution at −78 °C in the presence of stoichiometric amounts of the catalyst.[5b] In the attempt to compare the catalytic properties of PhCOOH and $TiCl_4$ the experiment of entry 1 (Table 2) was carried out under solvent-free conditions at room temperature in the presence of 0.05 equiv of $TiCl_4$ (reaction time 2 h). It is noteworthy that the above treatment again led to a mixture of **2ba** and **2′ba** and, after desilylation, pure **2ba** could be obtained in 68% yield, pointing out a very similar catalytic activity for both PhCOOH and $TiCl_4$ in the absence of solvent.

Keeping in mind that the employment of a heterogeneous catalyst could have allowed a significant improvement of the free-solvent procedure especially in terms of work-up and products isolation, the possibility to exploit the catalytic properties of Brønsted acidic silanol groups[12] situated on the surface of silica gel was examined. The preliminary results reported in Table 3 pointed out that, in spite of the weakly acidic character of the silanol groups, the formation of *O*-silylated products **2′a** took place in the presence of pre-activated silica gel; the usual desilylation procedure afforded the free aldols **2a** in acceptable yields although a modest diastereoselectivity was usually observed (entries 1–5).

As known, untreated molecular sieves exhibit intrinsic catalytic properties which are generally associated with the presence of Lewis and Brønsted acidic sites situated on the external and, most of all, internal surface. In particular, catalytic sites characterized by strong Brønsted acidity are origined by readily enolizable hydroxyl groups.[13] The experiments of entries 6–8 highlighted the capability of commercially available 3 Å molecular sieves to catalyze the conversion **1a**,**b** → **2′a**,**b** similarly to silica gel and the moderate efficiency can be reasonably attributed to the reduced pore dimensions, forcing therefore the reaction to take place only on the external surface of the heterogeneous catalyst.

Table 3. Solvent-free Mukaiyama aldol reaction of **1a**,**b** on RCHO promoted by silica gel and 3 Å molecular sieves

Entry	R	Reac. time (h)	Prod. **2a**,**b**	Yield[a] (%)	*syn*/*anti* dr[b]
1[c]	*p*-MeC_6H_4	18	**2ac**	49	80/20
2[c]	*p*-BrC_6H_4	24	**2af**	55	61/39
3[c]	*p*-CNC_6H_4	24	**2ag**	57	54/46
4[c]	$PhCH{=}CH$	24	**2ah**	40	55/45
5[c]	$PhCH_2CH_2$	24	**2ae**	38	51/49
6[d]	Ph	20	**2aa**	45	59/41
7[d]	*p*-MeC_6H_4	20	**2bc**	40	—
8[d]	*p*-$MeOC_6H_4$	20	**2bd**	50	—

[a] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by comparison of the spectroscopic data (^1H and ^{13}C NMR) with the ones reported in the literature.[9] In all entries RCHO/**1a**,**b** were used in 1/2 stoichiometric ratio.

[b] *syn*/*anti* Diastereoisomeric ratios were calculated by ^1H NMR analysis (400 MHz) on the crude products **2a** by accurate integration of the signals relative to C*H*OH protons.[9]

[c] Entries 1–5 were carried out on 0.5 mmol scale of RCHO in the presence of pre-activated (48 h at 120 °C) Merck chromatographic silica gel 60 (63–200 μm) (0.1 g).

[d] Entries 6–8 were carried out on 0.5 mmol scale of RCHO in the presence of activated (48 h at 120 °C) commercially available 3 Å molecular sieves purchased from Aldrich (pellets, 0.5 g).

In conclusion, the vinylogous aldol reaction of acid-labile masked forms of β-ketoesters was found to occur in satisfactory way under solvent- and metal-free conditions by activating the carbonyl functionality with benzoic acid; similar catalytic properties were exhibited by different protic organo-catalysts, such as *rac*-BINOL and 2,6-di-*t*-butyl phenol, although in all cases a modest stereoselectivity was usually observed. Alternatively, both activated silica gel and commercially available molecular sieves, characterized by the presence of Brønsted acidic sites on their surface, promoted the formation of the vinylogous aldols under heterogeneous conditions with acceptable yields.

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