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Synthesis of β-hydroxymalonates: the direct aldol addition of malonates to aldehydes in the presence of $SiCl_4$ and *i*-Pr_2EtN

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ABSTRACT

The direct aldol addition of malonates to aromatic, hetero-aromatic and unsaturated aldehydes leading to β-hydroxymalonates is described. The stability of these products, the trimethyl silyl protection of the hydroxyl group as well as the role of both $SiCl_4$ and *i*-Pr_2EtN in attaining the final products are also discussed.

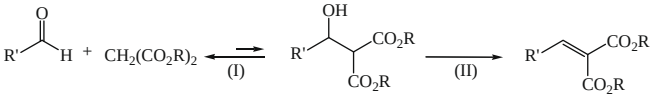
1. Introduction

In spite of the progress of organocatalysis[1] and metal-catalysed methodologies,[2] the aldol addition of readily enolizable 1,3-dicarbonyl compounds, such as β-ketoesters and malonates, to aldehydes still remains a difficult challenge. According to Sodeoka and co-workers, the most accepted explanation of this methodological gap is mainly attributed to the instability of the resulting β-hydroxymalonates and to the difficulty in generating efficient malonate nucleophiles.[3] Another reason can also be related to the inadequacy of the current methodologies that favour the elimination or the retro-aldol process instead of the aldol reaction (Scheme 1).[4] As a consequence, there are only few examples that describe efficient synthesis of β-hydroxymalonates and related compounds. The aldol addition of metal enolates of malonates has been successfully achieved only with α-alkoxy aldehydes in the presence of $ZnCl_2$.[5] Moreover β-hydroxymalonates have been obtained indirectly in oxy-Michael reactions,[6] and β-ketosters have been used as nucleophiles in the addition to activated aldehydes[7] and to acetals.[3,8] While free β-hydroxy adducts have been obtained only in one case,[7] the driving force for a general addition of methylene-active compounds seems related to the obtaining of the final products as O-protected compounds.[3,4,6,8] In this case the main disadvantage is the necessity of additional steps to obtain the corresponding free aldol adducts.

This lack is in contrast with the large use of malonates in organocatalysed Michael reactions[1] as well as in the Knoevenagel synthesis of alkylidenemalonates.[4] Moreover, even if β-hydroxymalonates are considered as the intermediates of Knoevenagel condensation (reaction II, Scheme 1), they have been isolated only rarely.[4]

In this complex framework, a straightforward aldol addition of methylene-active compounds to aldehydes should take into account the following conditions: (a) possibility to stop the reaction at aldol step and to suppress both the retro-aldol (I) and the elimination processes (II) (Scheme 1); (b) easy generation of nucleophile and (c) mild work-up to avoid product decomposition.

In the course of our studies about the use of Denmark's system,[9] silicon tetrachloride activated by a Lewis base, in vinylogous aldol reactions,[10] we realised that this system could be the ideal candidate for aldol addition of malonates to aldehydes for the following reasons. The selective activation of electrophilic functional groups in the presence of $SiCl_4$ allowed the use of many preformed nucleophiles such as silylenolethers and allylstannanes.[9,10] However, to the best of our knowledge, there is no report about the in situ gen-



Scheme 1. β-Hydroxymalonate chemistry: (I) retro-aldol, (II) Knoevenagel condensation.

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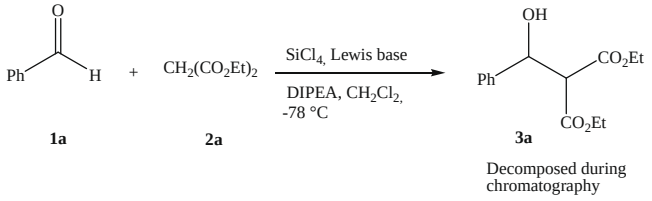
eration of the nucleophilic species. It is noteworthy that in $SiCl_4$-mediated reactions, *i*-Pr_2EtN is usually added to scavenge adventitious HCl. Our idea is to exploit the basicity of *i*-Pr_2EtN for the in situ generation of effective nucleophiles by the reversible deprotonation of activated methylene groups ($^{DMSO}pK_a$[4b] of dimethyl malonate and related esters is about 15.9).

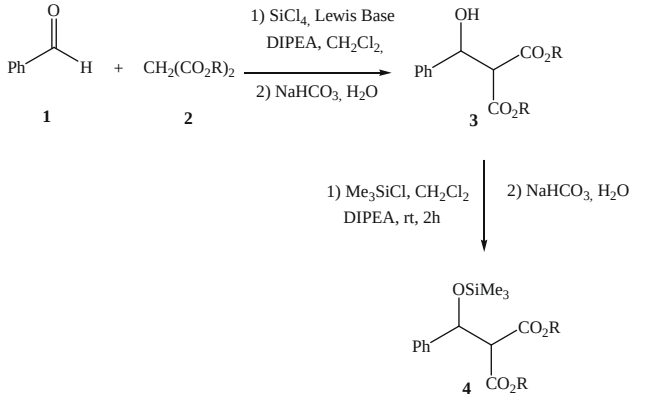
Another consequence of the activation of the carbonyl groups by $SiCl_4$ is the obtaining of the addition products as –O–$SiCl_3$-protected hydroxyl compounds.[9a,10b] Then these labile species are mildly hydrolysed in aqueous $NaHCO_3$ work-up to afford the final products. In this way, the formation of –O–$SiCl_3$-protected adducts could allow the addition of malonates to stop at the aldol step and suppress the undesired processes in Scheme 1.

On the basis of these ideas, herein, we disclose a reliable method for the aldol reaction of aromatic, hetero-aromatic and unsaturated aldehydes with malonates mediated by $SiCl_4$ and *i*-Pr_2EtN. In preliminary experiments, benzaldehyde, chosen as representative substrate, was submitted to treatment with diethyl malonate **2a** in the presence of $SiCl_4$ (1 equiv), *rac*-methyl *p*-tolyl sulfoxide, the Lewis base for the activation of $SiCl_4$ (1 equiv). and *i*-Pr_2EtN (2 equiv) under different reaction conditions (Scheme 2).

Preliminary experiments at −78 °C showed a rather low conversion, as analysed by ^1H NMR on the crude, for the presence of the starting materials. Unfortunately any attempt on purification of **3a** by chromatographic methods led to extensive decomposition.[6] In order to obtain a product easy to handle and with a better stability, we thought to protect the hydroxyl group as a trimethyl silyl ether (Scheme 3). The protection reaction, performed directly on the crude product **3a**, afforded **4a** only in a yield that probably reflected the poor efficiency of the first step (Table 1, entry 1). However, **4a** was easily purified by chromatography and isolated as a pure compound. Higher yields were obtained increasing the reaction temperature of the aldol addition at −20 °C (Table 1, entries 1–4). At −50 °C and at −20 °C, 4-Ph-pyridine-*N*-oxide was used as the Lewis base because of the decomposition of methyl *p*-tolyl sulfoxide (entries 2 and 3).



Scheme 2. Diethyl malonate addition to benzaldehyde in the presence of $SiCl_4$/*i*-Pr_2EtN.



Scheme 3. Aldol addition and trimethyl silylation.

Table 1
Aldol addition of malonate diesters to benzaldehyde under different reaction conditions

Entry	R	Lewis Base (1 equiv)	Temp. aldol step (°C)	Time (h)	Yield **4**[a] (%)
1	Et	*p*-tolyl-SO–Me	−78 °C	18	**4a** 15
2	Et	*p*-tolyl-SO–Me	−50 °C	18	**4a** 28
3	Et	4-Ph-PyNO	−50 °C	18	**4a** 28
4	Et	4-Ph-PyNO	−20 °C	7	**4a** 43
5	Me	4-Ph-PyNO	−20 °C	7	**4b** 44
6	*t*-Bu	4-Ph-PyNO	−20 °C	7	**4c** 55
7	*t*-Bu	4-Ph-PyNO	−20 °C	7	**4c** 82[b]

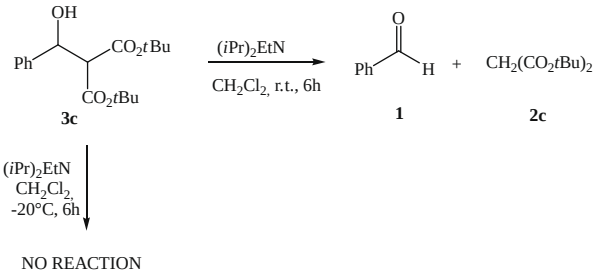
[a] Yields refer to chromatographic pure compounds.
[b] TMS protection was performed at −20 °C.

Then the reactivity of different alkyl malonates was examined under similar conditions (Table 1, entries 5–7). When the alkyl groups were changed to *tert*-butyl, a quantitative conversion of **3c** was observed, yielding an essentially pure compound (entries 6 and 7). However, TMS protection at rt of **3c** gave **4c** only in moderate yield with the concomitant isolation of the starting materials **1** and **2c** (Table 1, entry 6). Further optimisation of the protection reaction at −20 °C afforded **4c** in 82% yield calculated for the two consecutive steps (Table 1, entry 7).

The possibility of retro-aldol process at different temperature was confirmed by simple experiments, treating **3c** with *i*-Pr_2EtN in CH_2Cl_2 (Scheme 4).

The formation of the aldehyde and **2c** was observed only at rt while at −20 °C **3c** was quantitatively recovered unreacted. On the contrary neither at rt nor at −20 °C, the Knoevenagel products, corresponding to the dehydration of β-hydroxymalonates were detected.

Then, under the optimised conditions, a series of control experiments highlighted the importance of both $SiCl_4$ and *i*-Pr_2EtN to obtain the final products (Table 2). For example, when **2c** was reacted in the presence of $SiCl_4$ or *i*-Pr_2EtN alone, the starting materials were recovered unreacted (Table 2, entries 1–3). However comparable yields were obtained in the absence of the Lewis base, pointing out that in this case the activation of $SiCl_4$ was not necessary (Table 2, entries 4 and 5).



Scheme 4. Stability of β-hydroxymalonate in the presence of *i*-Pr_2EtN at rt and −20 °C.

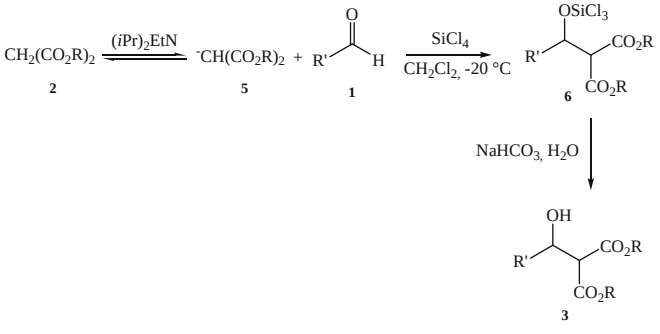
Table 2
Control experiments in the presence of *tert*-butyl malonate and benzaldehyde

Entry	$SiCl_4$ (equiv)	Lewis base 4-Ph-PyNO	*i*-Pr_2EtN (equiv)	Conversion **3c**[a] (%)
1	0	0	2	–
2	1	0	0	–
3	1	1 equiv	0	–
4	1	1 equiv	2	90
5	1	0	2	90

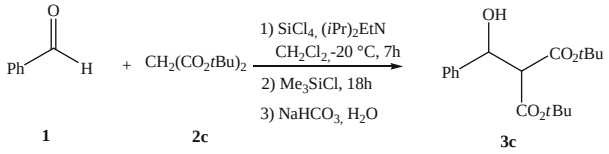
[a] Determined by ^1H NMR analysis on the crude.

On the basis of these experiments the pathway of the process can be proposed as reported in Scheme 5. The main steps are reasonably the reversible deprotonation of malonate **2** by *i*-Pr_2EtN, the activation of the aldehyde **1** and the in situ protection of **3** by means of $SiCl_4$. Even if we were unable to isolate the O–$SiCl_3$ intermediates **6**, any attempt of in situ TMS protection failed and we recovered **3c** in quantitative way (Scheme 6). This is a proof that, after the addition step mediated by $SiCl_4$, the hydroxyl group is not free for a further reaction.

Once the general features of the method were examined, we turned our attention to expand the substrate scope. Therefore a series of representative hetero-aromatic, unsaturated and aromatic aldehydes were reacted with *tert*-butyl malonate **2c** under the optimised conditions (Table 3, Scheme 7). As previously observed for benzaldehyde (Table 3, see also entry 1), the addition of *tert*-butyl malonate was particularly efficient and very good conversions of **3** were observed (Table 3, entries 3–9). Among the tested substrates, the electron-rich para-methoxybenzaldehyde showed a lower reactivity and a longer reaction time was required to attain a satisfactory result (Table 3, entries 2–3). Moreover the α,β-unsaturated aldehyde gave exclusively 1,2-addition (Table 3, entry 9) while the aliphatic aldehyde 3-phenylpropanal proved to be completely unreactive (Table 3, entry 10). As previously observed, in spite of the good purity of the crude products, any attempt at purification of **3** by chromatography was unsuccessful. Therefore we performed the same TMS protection of **3** and we obtained good to high yields of **4** for all the tested compounds. However, the isolated yields were lower for **4d**, **4e**, **4g** and **4l** for the formation of the starting materials **1** and **2c** as by-products (Table 3, entries 3, 4, 6 and 9). On the contrary the reaction of β-hydroxymalonate derivative of 2-Cl-benzaldehyde **3i** was slower probably for the steric hindrance of chlorine substituent. In this case, even after 24 h at 0 °C we observed on the crude product a mixture of about 50/50 of **3i**/**4i** and we obtained a 30% isolated yield of **4i** (Table 3, entry 8).



Scheme 5. Proposed mechanistic pathway for the aldol step.

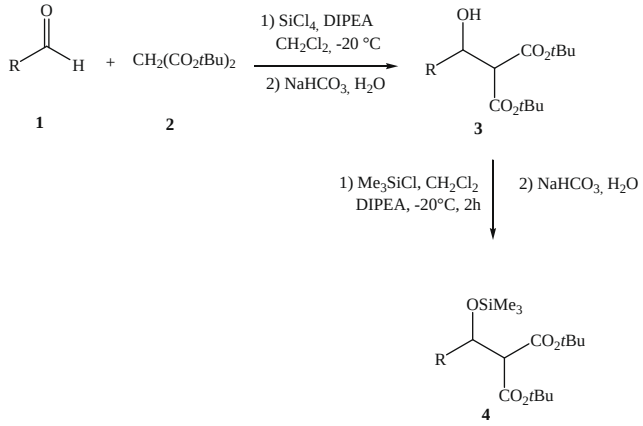


Scheme 6. Attempt at in situ TMS protection.

Table 3
Aldol addition of *tert*-butyl malonate to several aldehydes

Entry	R	Time (h)	Conversion **3** (%)[a]		Yield **4** (%)[b]	
1	Ph	7	**3c**	90	**4c**	82
2	4-$MeOC_6H_4$	7	**3d**	Low conv.		n.d.
3	4-$MeOC_6H_4$	24	**3d**	70	**4d**	58
4	4-$O_2NC_6H_4$	7	**3e**	65	**4e**	53
5	4-ClC_6H_4	7	**3f**	85	**4f**	80
6	4-CNC_6H_4	7	**3g**	75	**4g**	55
7	2-Furyl	7	**3h**	90	**4h**	85
8	2-ClC_6H_4	7	**3i**	75	**4i**	30[c]
9	PhCH=CH	7	**3l**	70	**4l**	59
10	$PhCH_2CH_2$	24		—		

[a] Conversions were determined on the basis of ^1H NMR analysis and mass balance of the crude product.
[b] Yields refer to chromatographic pure compounds.
[c] TMS protection was performed at 0 °C for 24 h.



Scheme 7. Aldol addition of *tert*-butyl malonate to several aldehydes.

In conclusion, we have described a very efficient direct aldol addition of malonates to aromatic, hetero-aromatic and unsaturated aldehydes to give β-hydroxymalonates. Both $SiCl_4$ and of *i*-Pr_2EtN were necessary to obtain the final products. Even if β-hydroxymalonates were obtained in high conversion, any attempt at purification of these materials by chromatographic methods led to extensive decomposition. Therefore we converted β-hydroxymalonates in more stable and easy to purify TMS-O-protected compounds.

Because of the uniqueness of this approach, further studies are currently underway to develop an asymmetric version and to expand the scope of the reaction with respect to both the electrophile and methylene-active components.

2. Experimental section

2.1. General procedure for aldol reaction

In a flame-dried, 2-necked, round-bottomed flask, malonate diester (1.1 equiv, 0.44 mmol) was added to a solution of *i*-Pr_2EtN (2.0 equiv, 0.80 mmol), $SiCl_4$ (1.1 equiv, 0.44 mL of 1.0 M solution in CH_2Cl_2) and aldehyde (0.40 mmol) in dry dichloromethane (2.0 mL) under nitrogen at −20 °C. At the end of the reaction, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with 15 × 3 mL of CH_2Cl_2 and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude oil was analysed by ^1H NMR and submitted to TMS protection.

2.2. General procedure for trimethyl silyl protection

Diisopropylethylamine (1.37 equiv, 0.55 mmol) and trimethyl silyl chloride (1.25 equiv, 0.50 mmol) were added to a solution of

the crude product **3** in dry dichloromethane (3.0 mL) at −20 °C under nitrogen. At the end of the reaction, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with 15 × 3 mL of CH_2Cl_2 and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude oil was purified by flash chromatography from hexane to 95:5 hexane/AcOEt mixture to afford the pure products **4**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.057.

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