DOI: 10.1002/ejoc.201100120

Metal-Free S_N2' Decarboxylative Rearrangement of β-Keto Esters

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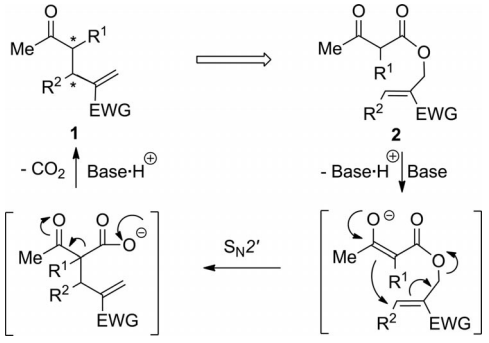
Keywords: Nucleophilic substitution / Reaction mechanisms / Organocatalysis / Rearrangement/ Decarboxylation

Treatment of 2-methoxycarbonyl- (or 3-cyano-)allyl acetoacetates with a tertiary amine or triphenylphosphane afforded α-methylene γ-substituted δ-keto esters (or nitrile) in satisfactory yields. Various bases and nucleophiles were tested to elucidate the mechanism. The results of the study strongly suggest an intermolecular pathway involving a S_N2'–decarboxylation–S_N2' cascade.

Introduction

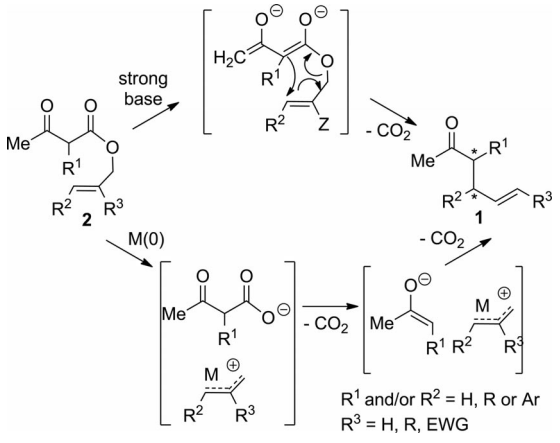
One of the major challenges in organic chemistry is the synthesis of highly functionalized molecules in a minimum of steps with efficient control of the stereochemistry. As a part of our research on organocatalytic approaches to C–C or C–H bond formation,[1] we envisaged a metal-free synthesis of δ-keto esters **1** from easily available allylic esters **2** (Scheme 1).



Scheme 1. Working hypothesis: base-catalyzed rearrangement of substituted allyl acetoacetates.

We anticipated that, in the presence of a base, an electron-withdrawing group (EWG = CO_2R, CN) on the double bond of **2** would facilitate the C–C bond formation through an intramolecular S_N2'[2,3] reaction of the β-keto ester enolate with displacement of the acetoacetate group and further decarboxylation of the latter. It is worth noting that intramolecular Michael additions of C-nucleophiles under organocatalytic conditions[4–7] have been relatively unexplored. "Intramolecular conjugated displacements" have been successfully applied to the synthesis of carbocycles[8] or nitrogen heterocycles.[9] In these reactions, a carbanion or an amine generated in situ reacted with an acrylate with substitution of an acetate (or a carbonate) group in the allylic position.[10] S_N2' reactions are also common reactions for intermolecular functional modifications of Morita–Baylis–Hillman adducts.[10,11]

From a slightly different point of view, the transformation we envisaged could be related to a base-induced Carroll reaction, which is a variant of the Claisen rearrangement (Scheme 2).[12] Although described a long time ago, applications of the Carroll reaction in organic synthesis have received little attention, probably because of the harsh thermal conditions required (typically higher than 180 °C)



Scheme 2. Carroll rearrangement catalyzed by a strong base or a transition metal.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900xxx.

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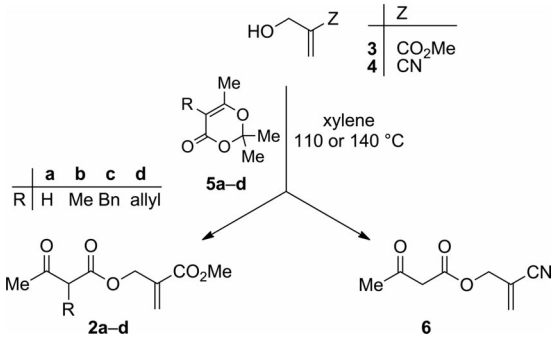
and because of its sensitivity to the structures of the substrates. Several methods have been designed to circumvent these limitations. The reaction can be accelerated by the use of strong bases[13] or a Lewis acid.[14] However, these methods suffer from the need for two equivalents of base and requires an additional step to carry out the decarboxylation. Recently, decarboxylations of allyl β-keto carboxylates catalyzed by transition metals (Ru,[15] Pd[16]) in the presence of chiral ligands have been successfully developed. Adsorption of β-keto esters on neutral alumina has also been used for the Carroll rearrangement of a precursor of zincophorin.[17] Under organocatalytic conditions, the treatment of an allylic alcohol with diketene in the presence of collidine[18] or 4-(dimethylamino)pyridine (DMAP)[19] afforded good yields of the rearranged product.

When the R^2 group of compound **2** (Scheme 2) was an electron-withdrawing group, Craig et al.[20] and You et al.[6] recently observed, under basic conditions, the formation of γ-lactone derivatives. A Michael addition of the keto enolate to the double bond could account for these observations. These results prompted us to describe our first results with model substrates **2** (R = H, Me, allyl, benzyl) and **6** (Scheme 3) and to demonstrate that their reaction in the presence of a nucleophile catalyst involves an S_N2'–decarboxylation–S_N2' sequence of the allyl acetoacetate rather than a base-catalyzed rearrangement.



Scheme 3. Synthesis of allyl acetoacetates **2a**–**d** and **6**.

Results and Discussion

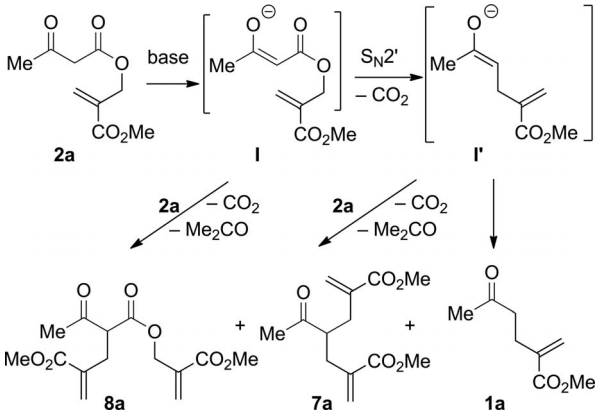
Allyl acetocetates **2** were prepared by reaction of the Baylis–Hillman adduct **3**[21] with 2,2,6-trimethyl-4*H*-1,4-dioxin-4-ones **5**[22] (Scheme 3). Nitrile **6** was obtained in a similar way from nitrile **4**[23] and dioxinone **5a**. Allyl ester **2a** could also be prepared in quantitative yield from alcohol **3** and diketene (1 equiv.) in the presence of DMAP (2 mol-%) in dichloromethane at room temperature for 24 h.

Initial attempts to study the formation of compounds **1** from allyl esters **2** were performed with **2a** and sodium hydride (1 equiv.) in tetrahydrofuran (THF) at 20 °C for 17 h. The expected product **1a**, together with diester **7a** and triester **8a**, were formed in 54, 14, and 29% molar ratio, respectively (Table 1, entry 1). The presence of products **7a** and **8a** could be explained by an intermolecular decarboxylation–S_N2' sequence involving two molecules of **2a** (Scheme 4).

Table 1. Tandem alkylation–decarboxylation of ester **2a**.

Entry	Base[a]	Conditions	*T* [°C]	Conv. [%]	Ratio [%][b]		
					1a	**7a**	**8a**
1	NaH	THF	r.t.	100	54	14	29
2	Cs_2CO_3, PTC[c]	CD_2Cl_2/H_2O (1:0.1)	r.t.	37	13	0	23
3	Et_3N[d]	CH_2Cl_2	r.t.	100	60–66	40–34	0
4	Et_3N	CH_2Cl_2 (0.05 or 0.2 M)	r.t.	100	67	33	0
5	Et_3N	MeCN	r.t.	100	67	33	0
6	Et_3N	toluene	r.t.	47	23	9	15
7	Et_3N	THF	r.t.	86	52	21	13
8	Et_3N	MeOH	r.t.	80	52	9	19
9	Et_3N	CH_2Cl_2	0	53	20	22	11
10	Et_3N	CH_2Cl_2	40	100	76	24	0
11	Et_3N	THF	65	100	77	23	0
12	Et_3N	MeOH	65	100	88	12	0

[a] Reagents and conditions: **2a** (0.1 M), base (20 mol-%), r.t., 17 h. [b] Determined from the ^1H NMR spectra of the crude product using 1,4-bis(trichloromethyl)benzene as an internal standard. All the products were isolated and characterized. [c] Phase-transfer conditions with NEt_3BnBr. [d] Reactions performed with Et_3N loadings of 25, 50, 100, or 150 mol-% gave similar results.



Scheme 4. Plausible reaction pathways for the transformation of **2a** under basic conditions.

To optimize the formation of **1a** we studied the reaction parameters in more detail. Phase-transfer catalysis in the presence of cesium carbonate and triethylbenzyl ammonium bromide led to a slow reaction in a mixture of $CDCl_3/H_2O$ (Table 1, entry 2); under these conditions, triester **8a** was the major product formed, even after a prolonged reaction time. In this context, homogeneous organocatalysis could be a valuable method to synthesize **1a** from **2a**. The application of organic bases were therefore tried. Triethylamine was chosen to avoid possible side reactions with the Michael acceptor.[24] Catalytic, stoichiometric, or an excess amount of Et_3N in dichloromethane at room temperature for 17 h (Table 1, entry 3) afforded the expected compound **1a** and the diester **7a** with total conversion of the starting material. Regardless of the amount of amine used, the ratio

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1a/7a was in the same range (Table 1, entry 3). Poor conversion (47%) and the formation of a mixture of triester **8a** (9%), diester **7a** (7%), and target compound **1a** (16%) was observed with a lower amount of Et_3N (5 mol-%, data not shown). Dilution had no effect on the ratio of **1a/7a**, as shown in Table 1, entry 4.

Different solvents were screened at room temperature. Acetonitrile (Table 1, entry 5) was as effective as dichloromethane. In toluene (Table 1, entry 6) and in THF (entry 7) the reaction was incomplete. A mixture of products was also formed when the reaction was performed in methanol (entry 8), although protic solvents were usually efficient in Michael addition of β-keto esters enolates.[25]

The influence of temperature was then studied. In dichloromethane at 0 °C (Table 1, entry 9), only half of the starting material reacted, and a mixture of **1a**, **7a**, and **8a** was formed. At 40 °C (Table 1, entry 10), **1a** and **7a** were formed as the sole reaction products with a slightly improved ratio of **1a/7a** (76:24). A similar result was observed in THF at 65 °C (Table 1, entry 11). In methanol at 65 °C (Table 1, entry 12) the ratio **1a/7a** was slightly improved, but other unidentified side products were also formed.

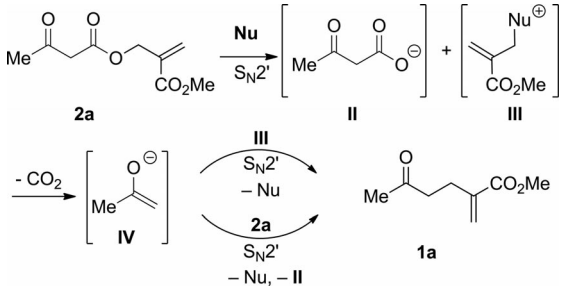
A deeper analysis of the formation of compounds **1a**, **7a**, and **8a** was undertaken by considering the ability of non-nucleophilic bases to catalyze the reaction and by monitoring the reaction by ^{1}H NMR and IR spectroscopy. In the presence of non-nucleophilic bases (Hünig's base, tri-*tert*-butylpyridine, proton sponge, and, to a less extent, tetramethylpiperidine, Table 2, entries 1–4), the conversion was poor and the triester **8a** was the main product formed.

Table 2. Reaction of **2a** in the presence of amines or triphenylphosphane.

Entry[a]	Catalyst	Time	Conv. [%]	Ratio [%][b]		
				1a	**7a**	**8a**
1	DIPEA	13 d	35	9	0	26
2	$(t\text{Bu})_3$Py[c]	13 d	0			
3	PS[d]	17 h	15	5	0	10
4	TMP[e]	13 d	94	36	45	13
5	DABCO	17 h	100	59	41	0
6	DBU	17 h	100	67	33	0
7	DMAP	17 h	100	69	31	0
8	Ph_3P	5 h	91	63	9	19
9	Ph_3P	46 h	95	67	12	16

[a] Reagents and conditions: catalyst (20 mol-%), solvent (CH_2Cl_2 or CD_2Cl_2), r.t. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product using 1,4-bis(trichloromethyl)benzene as an internal standard. [c] 2,4,6-*tert*-Butylpyridine. [d] Proton sponge or 1,8-diaminonaphthalene. [e] Tetramethylpiperidine.

In the presence of a nucleophilic catalyst (amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), or DMAP, Table 2, entries 5–7, or triphenylphosphane, Table 2, entries 8 and 9), the results were similar to those obtained with Et_3N. The higher nucleophilicity towards C-sp^2 centers of DBU,[26] Et_3N,[27] and DABCO[28] compared to that of Ph_3P[26] could account for the total conversion of the starting material observed with the amines. These results suggest that the transformation of **2a** into **1a** was not exclusively base-catalyzed but could also be mediated by a nucleophile. Thus, we can assume that an initial S_N2' reaction of the nucleophile[29] leads to the formation of cation **III** and acetoacetate anion **II** (Scheme 5). Rapid decarboxylation of this latter intermediate to acetone enolate **IV** and recombination of **IV** with **III** (through a second S_N2' reaction), would give **1a**. Such an S_N2'–decarboxylation–S_N2' sequence has been suggested when *N*-*p*-tolylsulfonyl-substituted carbamates were treated with DABCO to afford *N*-allyl allylamines.[30]



Scheme 5. Plausible reaction pathways for the transformation of **2a** under nucleophilic conditions.

Moreover, under the standard conditions, ^{1}H NMR spectroscopic monitoring of **2a** in the presence of Et_3N (Figure 1) showed that triester **8a** (which could not be isolated in pure form) was rapidly formed in the reaction mixture. As the reaction proceeded, the amount of **8a** decreased as a function of time, whereas those of compounds **1a** and **7a** increased by means of an S_N2' reaction (Scheme 4).

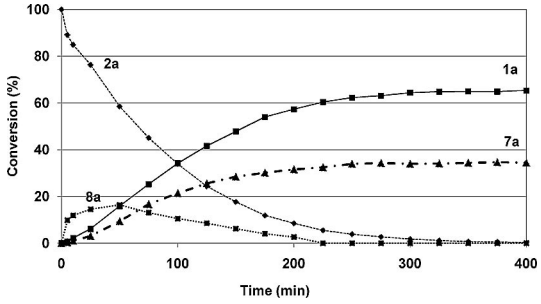
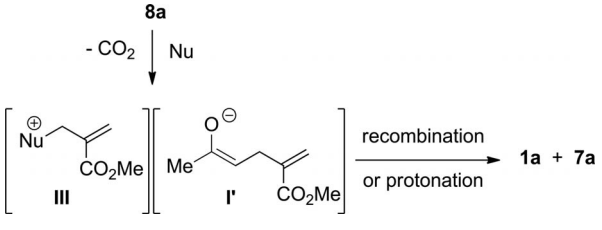


Figure 1. ^{1}H NMR spectroscopic monitoring the reaction of **2a** in the presence of Et_3N (20 mol-%) in CD_2Cl_2 (at room temperature).

Under nucleophilic conditions, we suggest an S_N2' decarboxylation cascade reaction takes place, leading to the formation of **1a** and **7a** via the intermediates **III** and **I′** (Scheme 6).



Scheme 6. Conversion of **8a** into **1a** and **7a** catalyzed by a nucleophile.

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To clarify the overall mechanism, the reaction of **2a** in the presence of a base (inorganic then organic) were monitored by in situ infrared spectroscopy. Spectra were recorded with a ReactIR™ 4000 instrument fitted with an immersible DiComp ATR probe.

The in situ IR monitoring of **2a** in the presence of NaH (1 equiv.) showed a band at 1591 cm^{-1}. This absorption is characteristic of the C=C band of an enolate,[31] and suggested that rapid conversion of **2a** into enolate **I** takes place (Figure 2). When the reaction was monitored for longer periods of time, this absorption band slowly disappeared (see the Supporting Information, Figure SI1).

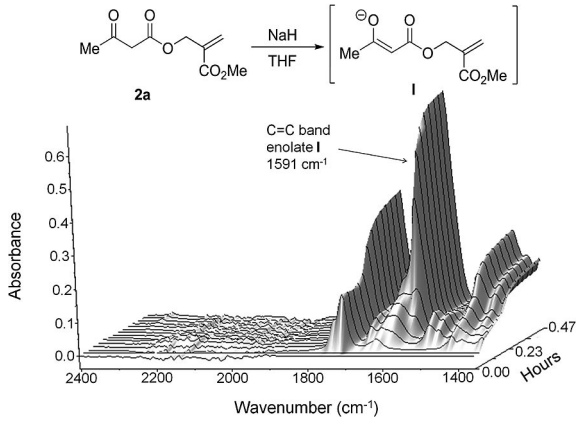


Figure 2. In situ IR monitoring of **2a** in the presence of NaH.

The reaction of **2a** in the presence of DABCO (1 equiv.) was monitored similarly. As soon as 25% of DABCO was added, an absorption band characteristic of carbon dioxide appeared at 2340 cm^{-1} (Figure 3). This band disappeared with time (CO_2 desorption, see the Supporting Information, Figure SI2). At the same time, a C=C absorption band clearly appeared at 1632 cm^{-1}. This band was attributed with confidence to the acetone enolate **IV** (see the Supporting Information, Figure SI3).

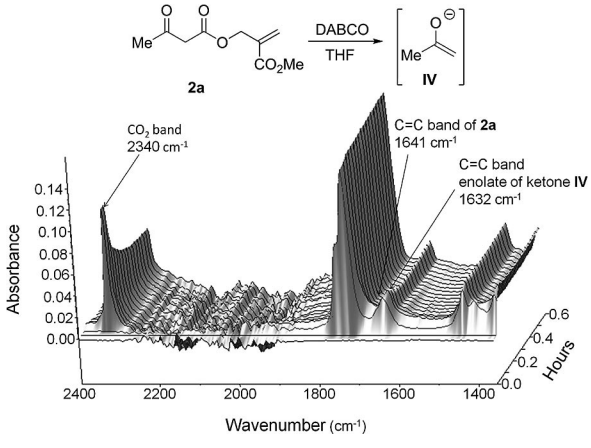
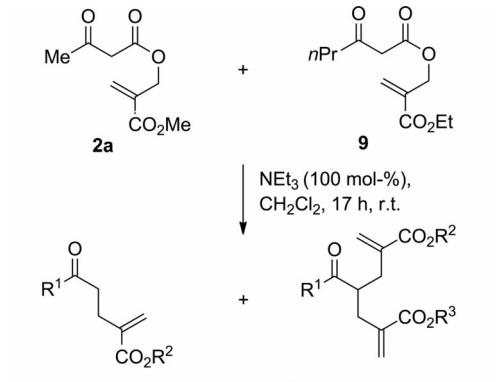


Figure 3. In situ IR monitoring of **2a** in the presence of DABCO.

These in situ IR monitoring experiments revealed that different initial pathways were followed, depending on whether a base or a nucleophile was used as catalyst. With one equivalent of base (NaH) the substrate was rapidly converted into its enolate **I**, whereas with a nucleophile (DABCO), spontaneous appearance of carbon dioxide and acetone enolate **IV** confirmed the nucleophilic sequence. Whereas the nucleophilic mechanism seems to operate immediately, even under catalytic conditions, the stoichiometric base-induced reaction takes place with a delayed time. Therefore, we can speculate that most of the products made in this reaction arose from an initial S_N2'–decarboxylation reaction sequence, leading the the formation of acetone enolate **IV**, which is capable of producing **1a** (Scheme 5) or undergoing the transformations observed under basic conditions (Scheme 4) through deprotonation of **2a**.

Finally, the reaction of methyl ketone methyl ester **2a** and propyl ketone ethyl ester **9** was investigated. Keto ester **9** was first synthesized by using the method previously described for keto ester **2a** (see the Supporting Information). Upon treatment with triethylamine (1 equiv.) for 17 h at room temperature, **9** afforded compounds **10** and **11** (77:23 molar ratio determined by ^1H NMR spectroscopic analysis).

A mixture of **2a** and **9** was then stirred at room temperature for 17 h in the presence of triethylamine (1 equiv.). Analysis of the reaction mixture by GC/MS showed that a cross-reaction had taken place with the formation of the four keto esters **1a**, **10**, **12**, and **14** in similar amounts (Scheme 7), together with the keto diesters **7a**, **11**, **13**, and **15**–**17**. These results strongly support the postulated intermolecular S_N2' reaction of allyl keto esters **2** and **9** in the presence of a nucleophile.



	R^1	R^2	ratio (%)
1a	Me	Me	16.3
10	*n*Pr	Et	17.7
12	Me	Et	13.8
14	*n*Pr	Me	13.7

	R^1	R^2	R^3	ratio (%)
7a	Me	Me	Me	10.4
11	*n*Pr	Et	Et	2.3
13	Me	Et	Et	5.8
15	*n*Pr	Me	Me	2.2
16	*n*Pr	Et	Me	4.0
17	Me	Et	Me	13.9

Scheme 7. Reaction of **2a** and **9** in the presence of Et_3N.

The reactivity of esters bearing a methoxycarbonyl (**2a**), a nitrile (**6**), or a hydrogen (**20**) on the allylic double bond were then compared (Scheme 8).

As expected, no reaction occurred with substrate **20**, bearing a monosubstituted allylic double bond, whereas nitrile **6** afforded the keto nitrile **18** in 78% yield, which was higher than that obtained with ester analogue **2a**.

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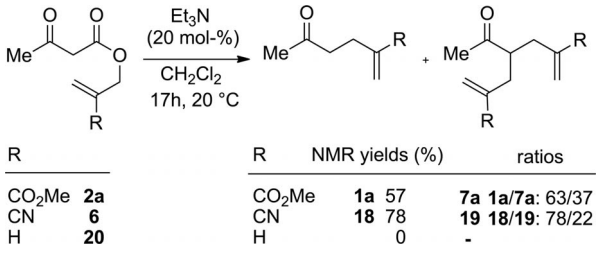
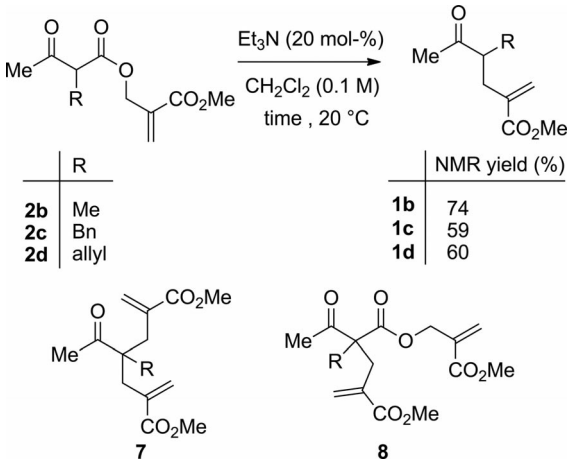


Scheme 8. Influence of the substituent on the double bond on the Et_3N-catalyzed reaction of allyl acetoacetates.

Moving to the α-methyl acetoacetate **2b** (Scheme 9), the reaction with 20 mol-% Et_3N in dichloromethane at room temperature was tested. The reaction was stopped after 17 h for comparison with the previous experiments. ^1H NMR analysis of the crude reaction mixture showed that 22% of the starting material was recovered and that the desired product **1b** was formed in 74% NMR yield, with no diester **7** being observed. However, the reaction product was contaminated by triester **8** (molar ratio **1b/8** of 96:4). At –20 °C (4 d), or at 40 °C (14 h), the amount of **8** formed was higher (ratio **1b/8**, 75:15 and 87:10, respectively, with complete conversion). Benzyl and allyl acetoacetates **2c** and **2d** were less reactive and required longer reaction times (7 and 5 d, respectively)[32] to afford the expected product **1c** or **1d** in 59 and 60% NMR yields, or 38 and 60% isolated yields. We were pleased to observe that the desired products were formed without any diester **7** or triester **8** being observed (Scheme 9). The absence of these side compounds is probably due to the presence of a substituent on the enolate, which prevents further addition that would lead to the formation of a quaternary carbon atom.



Scheme 9. Et_3N-catalyzed reaction of substituted allyl acetoacetates **2b**–**d**.

Conclusions

We have shown that acetoacetate allyl esters bearing an electron-withdrawing group on the double bond of the allylic moiety were easily transformed under tertiary amine (or phosphane) catalysis into α-methylene δ-keto esters or nitrile through a tandem S_N2'–decarboxylation–S_N2' sequence. By ^1H NMR and in situ IR analysis of the reactions carried out in the presence of various bases or nucleophiles, it was demonstrated that the use of a non-nucleophilic base led to low conversion of **1a**. With a nucleophilic base, the transformation of **2a** into **1a** was followed simultaneously by a base-catalyzed and a nucleophile-catalyzed pathway. A cross-experiment demonstrated that an intermolecular mechanism was operating. Therefore, we can conclude that the reaction only required a good nucleophile to proceed to completion. Although it has not been possible to avoid the formation of diester **7a** with the unsubstituted allyl acetoacetate **2a**, α-substituted β-keto esters afforded products **1b**–**d**, bearing a newly formed stereocenter, nearly exclusively and in good yields. This study, which unveiled the mechanism and determined the main parameters involved in the reaction, will enable the scope of the transformation to be broadened while preventing the formation of side products. These developments should also allow the stereochemical outcome of the reaction to be controlled. These aspects are under study in our laboratory.

Experimental Section

Typical Procedure for the Synthesis of Allyl Acetoacetates: To a stirred solution of dioxinone **5** (66.8 mmol, 1.02 equiv.) in xylene (31 mL) was added the allylic alcohol (65.5 mmol, 1 equiv.). The mixture was heated at 110 or 140 °C for 10 or 50–80 min, depending on the dioxinone used. After cooling, the mixture was concentrated under vacuum and xylene was removed by distillation (kugelrohr, 60 °C). The residue was purified by flash chromatography on silica gel.

Typical Procedure for the Decarboxylative Rearrangement: To a stirred solution of allyl ester (0.5 mmol, 1 equiv.) in the appropriate solvent (5 mL), was added the catalyst (0.1 mmol, 0.2 equiv.). The mixture was stirred at the given temperature for 17 h, then the solvent was evaporated. The residue was diluted in dichloromethane (5 mL) and saturated NH_4Cl (5 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization of the products.

Acknowledgments

We gratefully acknowledge the Ministère de l'Enseignement Supérieur et de la Recherche, Agence Nationale de la Recherche (ANR), "Mesorcat" (Programme Chimie Pour le Développement Durable CP2D), Centre National de la Recherche Scientifique (CNRS), Région Basse-Normandie, and the European Union (FEDER funding) for financial support.

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Received: January 27, 2011
Published Online: June 1, 2011

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