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The $CeCl_3 \cdot 7H_2O$–NaI system as promoter in the synthesis of functionalized trisubstituted alkenes via Knoevenagel condensation

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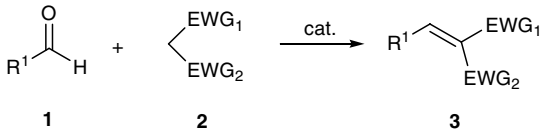
Abstract—The arylidene malonates with two different geminal carboxylate functions, a suitable class of substrates of several synthetic and pharmacological studies, are easily available through Knoevenagel condensation of ethyl *tert*-butyl malonate and different aromatic aldehydes. The results have increased the potentialities of $CeCl_3 \cdot 7H_2O$–NaI system as a type of water-tolerant green Lewis acid promoter for carbon–carbon bond forming procedures.

The development of promoted organic reactions using air-stable and water tolerant lanthanide salts as Lewis acid catalyst is one of the important and challenging subjects in organic synthesis chemistry.[1] In the last years, cerium trichloride heptahydrate ($CeCl_3 \cdot 7H_2O$) has attracted considerable attention because of its diverse applications as a promoter in organic synthesis.[2] In line with our group's interests in exploring new and potentially more concise procedures for carbon–carbon bond forming promoted by Lewis acids, we have increased the potentialities of the combination of $CeCl_3 \cdot 7H_2O$ with NaI.[3]

In these years, we have observed that the $CeCl_3 \cdot 7H_2O$–NaI system promotes the addition of CH-acidic compounds to different electrophiles.[4] In connection with our efforts on the synthesis of trisubstituted alkenes,[5] we have herein observed that our combination can be utilized as a green, mild, and efficient method for the Knoevenagel condensation (Scheme 1) of malonate derivatives (**2**) with aldehydes (**1**). The sequential reaction provides a new method for the synthesis of different multifunctional molecules (**3**) in a single operation. The corresponding alkylidene malonates appear as a suitable class of building blocks useful for the synthesis of natural and non-natural bioactive compounds.[6] In particular, the trisubstituted alkenes[7] derived from our procedure by Knoevenagel condensation with ethyl *tert*-butyl malonate (ETBM) could serve as excellent precursors to esters or acids 2-hydroxymethyl-3-aryl-2-propenoic, useful building blocks for the preparation of various biologically active molecules.[8]



1 **2** **3**

Scheme 1.

It is noteworthy that our procedure has not only increased the potentialities of $CeCl_3 \cdot 7H_2O$–NaI system, but it has also permitted to overcome the major restriction to the broad application of the Knoevenagel reaction, that is, the inability to arrest the coupling of aldehydes with 1,3-diesters at the monoaddition stage since these intermediates are highly Michael acceptors

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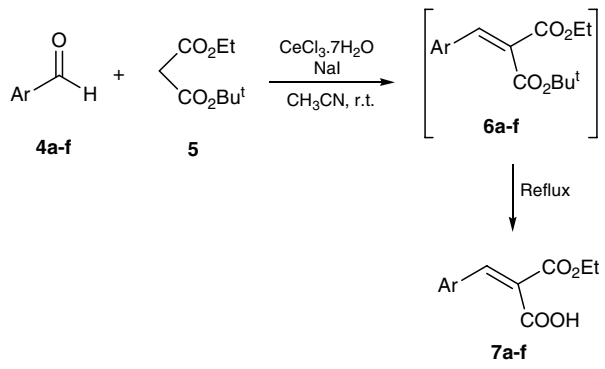
in their own right.[9] Further, from a close analysis of the literature methods for Knoevenagel condensation, we did not find any general procedure for the synthesis of arylidene-substituted unsymmetrical malonic acid derivatives,[10] versatile synthetic intermediates owing to the various possible transformations of the different carboxylic functionalities.[6b] However, when a monoester of malonic acid is used in the Knoevenagel condensation with carbonyl compounds, the decarboxylation occurs spontaneously during the reaction.[11]

In a preliminary experiment, the Knoevenagel reaction of benzaldehyde (**4a**) and ETBM (**5**) was explored to determine the optimal conditions (Scheme 2). We examined the influence of the reactants ratio and of the relative combination of the two promoter components on the reaction. We found that the best choice was a 1:1.2 ratio between **4a** and **5** in a ca. 0.1 M solution in acetonitrile[12] containing 1.35 equiv of $CeCl_3{\cdot}7H_2O$ and 1.35 equiv of NaI. The use of a higher excess of cerium(III) chloride (3.0 equiv) led to similar results, but lower amounts (e.g., 0.65 equiv) gave lower chemical yields.

The reaction temperature is also important. In fact, the first step of addition to the aldehyde moiety should be carried out at room temperature, but the dehydration and *tert*-butyl cleavage required a higher temperature to proceed to completion. When the process was carried out at room temperature, arylidenemalonate **6a** was observed in very low yield although formation of the initial adduct was observed.[13] Thus, after a first addition reaction at room temperature, the second step was conducted at reflux.[14] Under these conditions, selective deprotection of *tert*-butyl ester[15] was observed and unsymmetrical malonic acid derivative **7a** was obtained in good yield. This procedure proved to be general and could be applied to a range of aldehydes (see Table 1), and good results were in fact obtained with aromatic aldehydes.[16] NMR spectroscopy clearly showed malonate mono acid **7** as a unique product isolated without the presence of decarboxylation product. It should be noted that in the case of malonic acid addition to aromatic aldehydes our procedure gives, contrary to the results proposed by Weaver et al.,[17] no evidence of α,β-unsaturated malonic acids.

Except for the reaction of nicotinaldehyde (Table 1, entry 6), the reactions of other aldehydes were found



Scheme 2.

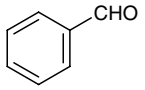
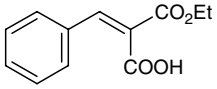
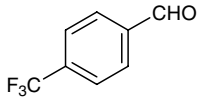
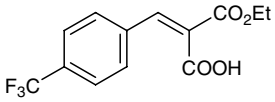
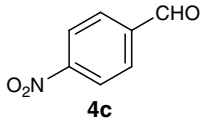
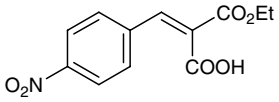
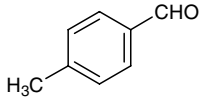
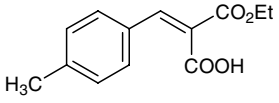
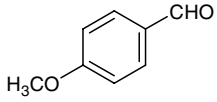
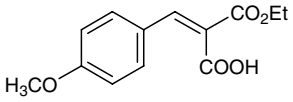
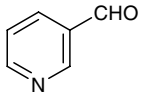
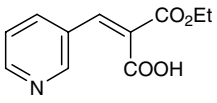
to be fairly stereoselective affording *E*-isomers in high yields.[10,18] In all cases, the olefinic proton signal for both diastereomers were clearly distinguishable in their ^1H NMR spectra. The olefin proton signal for *E*-isomer was downfield relative to the proton for the *Z*-isomer. This is in agreement with the principle that hydrogen cis-standing to the ester group shows a downfield shift.[19] Though the *E*-selectivity has generally been observed in all the cases, a satisfactory explanation is still not available at the present stage.

With aromatic aldehydes, this Knoevenagel reaction proceeds smoothly to give the desired arylidenemalonate derivatives. However, the electronic nature of the aryl substituents in the aldehydes has an effect on the rate of the reaction. It was found that electron-withdrawing substituted aromatic aldehydes favored this reaction (Table 1, entries 2 and 3), while the aromatic aldehydes bearing electron-rich group on the aromatic ring gave the corresponding trisubstituted alkenes after longer reaction time (Table 1, entries 4 and 5). The Knoevenagel reaction promoted by $CeCl_3{\cdot}7H_2O$–NaI system with electron-poor heteroaromatic aldehydes afforded the corresponding alkene in moderate diastereoselectivity, but with high yield (Table 1, entry 6). An alternative synthesis of the trisubstituted alkene **7** was tried by Knoevenagel condensation of cheaper ethyl hydrogen malonate,[20] but our procedure gave very low yield of adduct (GC–MS $< 5\%$), and many side products are formed. It is worthy to note that our procedure succeeded even in the presence of the coordinating heterocyclic nitrogen on this substrate, which could in principle affect the activity of a Lewis acid. In order to further investigate the scope of the methodology, we attempted the Knoevenagel reaction of the aliphatic aldehydes with ETBM (**5**). Unlike aryl aldehydes, adduct **6** was not observed and GC–MS analysis of the reaction mixture showed malonic acid half ester as the main product. Most probably, in our conditions, the alkylidenepropanedioic half esters are not stable and retro-aldol reaction takes place, and the starting aldehyde was recovered.

The mechanism of the reaction is not clear. Certainly, the acceleration effect caused by the addition of metal iodide (NaI) to $CeCl_3$ has already been observed by our group.[21] This effect might be rationalized by a halogen exchange reaction that leads to a more reactive species, but previous experimental evidences prove that CeI_3 shows a very poor activity as Lewis acid in various transformations.[22,23] A more plausible process is the disaggregation of the crystal lattice of $CeCl_3$ by NaI or which might lead to a notable increase in the Lewis acidity of the cerium available at the particle surface.

In conclusion, this letter clearly demonstrates the power and economic interest of a $CeCl_3{\cdot}7H_2O$–NaI promoted reaction in the field of synthetic organic chemistry. In fact, the procedure effects Knoevenagel reaction of aromatic aldehydes and malonate derivative efficiently.[24] The sequential reaction provides a new method for arylidenemalonate formation in a single operation. Extension of the present methodology to the synthesis

Table 1. Knoevenagel condensation of aromatic aldehydes **4** with ETBM (**5**) in the presence of $CeCl_3{\cdot}7H_2O$–NaI in acetonitrile

Entry	Aldehyde[a]	Time/h	Conditions	Product[b]	Yield[c] (%)	*E*:*Z*[d]
1	 **4a**	54 2.5	rt Reflux	 **7a**	80	77:23
2	 **4b**	40 1.5	rt Reflux	 **7b**	95	90:10
3	 **4c**	37 0.5	rt Reflux	 **7c**	97	93:07
4	 **4d**	62 3.5	rt Reflux	 **7d**	90	75:25
5	 **4e**	64 4.0	rt Reflux	 **7e**	85	80:20
6	 **4f**	42 1.5	rt Reflux	 **7f**	91	60:40

[a] All starting materials were commercially available.
[b] All products were identified by their IR, NMR, and GC–MS spectra.
[c] Yield of products isolated after workup.
[d] *E*:*Z* ratios determined by NMR.

of other trisubstituted alkenes, as well as studies dealing with the transformation of electron-withdrawing functionalities is currently under investigation and will be reported in due course.

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12. The use of other solvents (ether, THF, dichloromethane, nitromethane, DMF, toluene) led to lower yields. The best result (38% yield) was observed in nitromethane.
13. The major product identified by GC–MS was 1-(*tert*-butyl)-3-ethyl-2-[hydroxy(phenyl)methyl]malonate.
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16. A typical procedure for preparation of **7** is as follows: to a stirred suspension of aldehyde **4** (0.5 mmol) and cerium(III) chloride heptahydrate (0.25 g, 0.675 mmol) in acetonitrile (5 mL) was added sodium iodide (0.1 g, 0.675 mmol), followed by ETBM **5** (0.11 g, 0.6 mmol) and the resulting mixture was stirred at room temperature until complete consumption of aldehyde **4** (Table 1). Then the reaction mixture was refluxed until no intermediate **6** remains as monitored by GC. The reaction progress was monitored by withdrawing aliquots which were analyzed by GC, and the products were identified by GC–MS. After cooling, the reaction mixture was diluted with dichloromethane and treated with 0.5 N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were evaporated, the residue was dissolved in 10% $NaHCO_3$ solution (15 mL), and the bicarbonate layer was washed with ether. Bicarbonate solution was then made acidic to pH 3 and extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated to give arylidenemalonate **7** as an oil, which was spectroscopically pure. Spectral data of products not reported in the literature are listed as follows: compound **7b**: FTIR (neat): 2978, 1723, 1633 cm^{-1}; (*E*) ^1H NMR ($CDCl_3$, 200 MHz): δ 10.85 (bs, 1H), 7.93 (s, 1H), 7.67–7.55 (m, 4H), 4.30 (q, 2H, $J = 6.96$ Hz), 1.28 (t, 3H, $J = 7.00$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.7, 62.8, 113.1, 120.3, 121.0, 125.2, 127.6, 131.0, 131.4, 134.7, 160.8, 163.9; (*Z*) ^1H NMR ($CDCl_3$, 200 MHz) δ 10.85 (bs, 1H), 7.87 (s, 1H), 7.67–7.55 (m, 4H), 4.30 (q, 2H, $J = 7.02$ Hz), 1.25 (t, 3H, $J = 7.03$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 61.3, 112.9, 120.0, 120.8, 125.6, 127.2, 129.8, 131.2, 134.0, 134.7, 143.8, 165.3, 167.2. Anal. Calcd for $C_{13}H_{11}F_3O_4$ (288.23): C, 54.17; H, 3.84: Found: C, 54.13; H, 3.80. Compound **7d**: FTIR (neat): 2968, 1732, 1626 cm^{-1}; (*E*) ^1H NMR ($CDCl_3$, 200 MHz): δ 10.91 (bs, 1H), 7.91 (s, 1H), 7.55–7.20 (m, 4H), 4.36 (q, 2H, $J = 7.14$ Hz), 2.40 (s, 3H), 1.38 (t, 3H, $J = 7.12$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.9, 27.0, 63.0, 119.7, 128.0, 128.6, 132.3, 140.5, 144.6, 160.7, 163.2; (*Z*) ^1H NMR ($CDCl_3$, 200 MHz) δ 10.30 (bs, 1H), 7.85 (s, 1H), 7.55–7.20 (m, 4H), 4.26 (q, 2H, $J = 7.02$ Hz), 2.40 (s, 3H), 1.29 (t, 3H, $J = 7.08$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 27.0, 62.7, 120.5, 128.0, 128.6, 132.3, 140.5, 144.5, 165.0, 166.2. Anal. Calcd for $C_{13}H_{14}O_4$ (234.25): C, 66.65; H, 6.02: Found: C, 66.62; H, 5.98. Compound **7e**: FTIR (neat): 2982, 1731, 1634 cm^{-1}; (*E*) ^1H NMR ($CDCl_3$, 200 MHz): δ 11.03 (bs, 1H), 8.02 (s, 1H), 7.57–7.32 (m, 4H), 4.52 (q, 2H, $J = 7.32$ Hz), 3.86 (s, 3H), 1.29 (t, 3H, $J = 7.10$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.6, 54.6, 60.3, 117.1, 119.7, 120.9, 129.7, 142.1, 159.3, 160.8, 162.0; (*Z*) ^1H NMR ($CDCl_3$, 200 MHz) δ 10.64 (bs, 1H), 7.96 (s, 1H), 7.56–7.32 (m, 4H), 4.50 (q, 2H, $J = 7.10$ Hz), 4.00 (s, 3H), 1.21 (t, 3H, $J = 7.03$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.0, 55.3, 60.9, 116.9, 119.1, 120.8, 130.0, 143.0, 160.8, 164.9, 167.2; MS (EI) *m*/*z*: 206, 161, 134, 77, 65, 51. Anal. Calcd for $C_{13}H_{14}O_5$ (250.25): C, 62.39; H, 5.64: Found: C, 62.37; H, 5.58. Compound **7f**: FTIR (neat): 2975, 1730, 1625 cm^{-1}; (*E*) ^1H NMR ($CDCl_3$, 200 MHz): δ 10.00 (bs, 1H), 8.20–8.13 (m, 1H), 8.08–8.01 (m, 1H), 7.86–7.80 (m, 2H), 7.69 (s, 1H), 7.60–7.48 (m, 4H), 4.49 (q, 2H, $J = 6.99$ Hz), 1.32 (t, 3H, $J = 7.02$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.2, 59.4, 115.8, 123.9, 126.4, 126.9, 143.0, 143.5, 145.4, 163.7, 164.7; (*Z*) ^1H NMR ($CDCl_3$, 200 MHz) δ 10.23 (bs, 1H), 8.20–8.13 (m, 1H), 8.10–8.01 (m, 1H), 7.80–7.74 (m, 2H), 7.69 (s, 1H), 7.43–7.28 (m, 4H), 4.52 (q, 2H, $J = 6.14$ Hz), 1.29 (t, 3H, $J = 7.10$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.7, 61.8, 116.4, 123.5, 124.9, 129.5, 142.8, 144.0, 145.0, 165.9, 167.5; MS (EI) *m*/*z*: 177, 150, 92, 78, 53, 45. Anal. Calcd for $C_{11}H_{11}NO_4$ (221.21): C, 59.72; H, 5.01; N, 6.33: Found: C, 59.70; H, 4.96; N, 6.34.
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