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Practical Synthesis of (*E*)-α,β-Unsaturated Esters from Aldehydes

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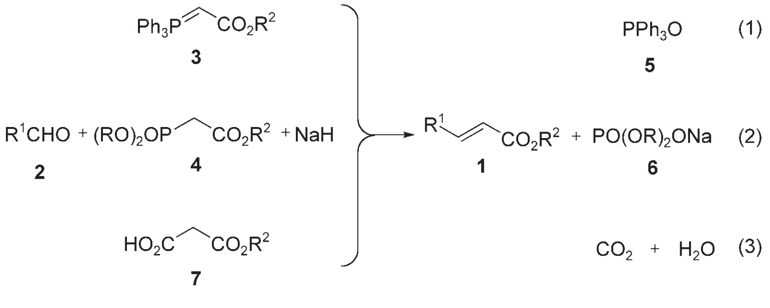
Abstract: Based on a modification of the Doebner–Knoevenagel reaction, a practical and highly efficient synthesis of α,β-unsaturated esters with excellent regio- and stereoselectivity was developed. The reactions are catalyzed by 4-dimethylaminopyridine in DMF at room temperature or below. Both aliphatic and aromatic aldehydes can readily be used in the process.

Keywords: atom economy; Doebner–Knoevenagel reaction; malonic acid half esters; (*E*)-stereoselectivity; α,β-unsaturated esters

The synthesis of α,β-unsaturated esters **1** from aldehydes **2** is a very common carbon-carbon bond forming reaction. Typically, the transformation is realized *via* the Wittig reaction [Eq. (1)] or Horner–Wadsworth–Emmons reaction [Eq. (2)] using alkoxycarbonylmethylene(triphenyl)phosphoranes **3** or trialkyl phosphonoacetates **4**, respectively.[1–3] Both reactions are reliable, high yielding, tolerate various functional groups, and are generally (*E*)-stereoselective. However, their main drawback, if there is one, concerns their rather modest atom economy, and as a result, considerable by-product formation. In the Wittig reaction the by-product is triphenylphosphine oxide **5**, which has to be removed chromatographically and disposed. The Horner–Wadsworth–Emmons variant has the advantage of producing a water-soluble phosphate salt **6** as the by-product, which can be removed *via* aqueous extraction. However, the Horner–Wadsworth–Emmons reaction typically requires the use of a strong base such as sodium hydride and the phosphate salt by-product **6** is produced in stoichiometric amounts which, especially on a large scale, can challenge waste-management.

An alternative yet rarely used methodology for the synthesis of α,β-unsaturated esters from aldehydes is the decarboxylative Knoevenagel-type reaction employing malonic acid half esters **7** [Eq. (3)].[4] This reaction has a significantly improved atom economy and the only by-products are water and carbon dioxide. Moreover, half-esters of malonates **7** are as inexpensive as the corresponding phosphorus-based reagents (e.g., **3** and **4**) and can also be obtained from inexpensive dialkyl malonates.[5,6]

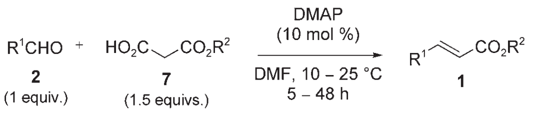
The much less frequent use of this Knoevenagel (or Doebner–Knoevenagel) reaction variant can be attributed to the generally required reaction conditions, which include using an excess of the malonic half ester, catalysis with piperidine in pyridine as the solvent, and elevated temperatures. Moreover, (*E*)- *vs.* (*Z*)-selectivity varies and, most importantly, in the reaction with enolizable aldehydes, not α,β- but rather β,γ-unsaturated esters (or their mixtures) are commonly obtained.[7] During several other projects we realized the need for a clean, by-product-free, and reliably selective methodology for the production of α,β-unsaturated esters from aldehydes that can be used on a large scale and does not require heating or strong bases. We therefore set



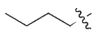
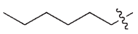
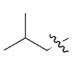
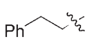
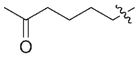
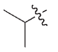
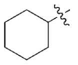
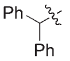
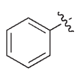
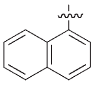
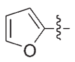
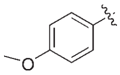
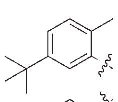
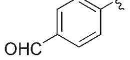
up a study aimed at overcoming the disadvantages of the traditional Wittig, Horner–Wadsworth–Emmons, and Knoevenagel reactions. Here we report our preliminary results of these studies culminating in the development of a highly practical and efficient synthesis of α,β-unsaturated esters from aldehydes. In our laboratories, this reaction is now the standard protocol for this important and often used transformation.

After screening a diverse set of reaction parameters we found that treating various aldehydes with malonic acid half esters (1.5 equivs.) in the presence of catalytic 4-dimethylaminopyridine (DMAP, 10 mol %) at room temperature or below in DMF, provided the corresponding unsaturated esters with the remarkable results [Eq. (4), Table 1].[8]

Table 1. A practical synthesis of α,β-unsaturated esters from aldehydes.



(4)

Entry	R^1	R^2	Yield[a]	*E*:*Z*[b]
1[c]		Et	91	95:5
2[c]		Et	95	96:4
3[c]		Et	90	95:5
4[c]		Et	91	95:5
5[c]		Et	91	98:2
6		Et	96	>99:1
7		Et	92	98:2
8[d]		Et	91	>99:1
9		Et	92	>99:1
10[d]		Et	92	>99:1
11[d]		*t*-Bu	87	99:1
12[d]		Bn	96	>99:1
13[d]		Et	92	>99:1
14		Et	90	>99:1
15		Et	99	>99:1
16[d]		Et	89	>99:1
17[d,e]		Et	93	>99:1

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[a] Yield of isolated product.
[b] Determined by GC.
[c] Reaction at 10 °C.
[d] Piperidine (10 mol %) as co-catalyst.
[e] Bis-enoate was obtained using 3 equivs. of **7**.

Overall, the yields of the isolated α,β-unsaturated esters are high in all investigated cases (87–99%, Table 1, entries 1–17). It turns out that catalysis with DMAP essentially shuts down the pathway leading to the undesired β,γ-isomer. Gratifyingly, the substrate scope is remarkably broad and both aliphatic (entries 1–9) as well as aromatic aldehydes (entries 10–17) can readily be used. With most aromatic aldehydes we found it to be of benefit to add a catalytic amount of piperidine (10 mol %) in addition to the DMAP. While high yields and selectivities are also obtained without added piperidine, its co-catalysis shortens reaction times in these cases by about 50%. In general, (*E*)/(*Z*)-selectivities are excellent being equal or exceeding a ratio of 95:5. In addition to ethyl esters ($R^2 = \mathrm{Et}$), both *tert*-butyl ($R^2 = t\text{-Bu}$) and benzyl esters ($R^2 = \mathrm{Bn}$) can be obtained with comparable efficiency. We have not yet fully studied the functional group tolerance of the reaction but entry 5 indicates that at least ketones remain unaffected in the process as long as a more reactive aldehyde is present as well. Remarkably, the substrate of this particular reaction, 6-oxoheptanal, could readily undergo a facile intramolecular aldolization[9] which, however, is not observed under our reaction conditions. The synthesis of ethyl *p*-methoxycinnamate (entry 15) serves as an illustration of a potentially industrial application of our reaction.[10] *p*-Methoxycinnamates are important UV-light absorbing ingredients of sunscreens.

Future studies in our laboratory will focus on exploring the full scope of this reaction and of similar decarboxylative carbon-carbon bond forming reactions.

Experimental Section

General Experimental Procedure

4-Dimethylaminopyridine (24.4 mg, 0.20 mmol) was dissolved in DMF (5 mL). The malonic acid half ester (3.00 mmol) followed by the aldehyde (2.00 mmol) were added, and the mixtures was stirred at 10 °C or room temperature until the aldehyde was consumed. The mixture was extracted with Et_2O and the organic layer was washed successively with NH_4Cl, water, $NaHCO_3$, and once again with water. After drying (Na_2SO_4) and filtering, all volatiles were evaporated under vacuum yielding, without any further purification, the pure α,β-unsaturated ester in good yields (87–99%).

Acknowledgements

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[5] Aldrich catalogue: (carbethoxymethylene)triphenylphosphorane (**3**, R^2=Et), 10 mmol *ca.* EUR 17.00, triethyl phosphonoacetate (**4**, R^2=Et), 10 mmol *ca.* EUR 2.00, monoethyl malonate (**7**, R^2=Et) 10 mmol *ca.* EUR 5.00, monoethyl malonate, potassium salt 10 mmol *ca.* EUR 2.00.

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