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Practical Synthesis of (*E*)-α,β-Unsaturated Carboxylic Acids Using a One-Pot Hydroformylation/Decarboxylative Knoevenagel Reaction Sequence

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Dedicated to Andreas Pfaltz on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Combining the regioselective room temperature/ambient pressure hydroformylation and a modification of the Doebner–Knoevenagel reaction allowed for the development of an efficient, one-pot procedure for the synthesis of (*E*)-α,β-unsaturated carboxylic acids. The reaction proceeds under mild conditions, tolerates a variety of functional groups and gives (*E*)-α,β-unsaturated carboxylic acids in good yields and with excellent regio- and stereocontrol. The practicability of this process has been demonstrated by a short protecting group-free synthesis of the queen honeybee pheromones 9-ODA [(*E*)-9-oxodec-2-enoic acid] and 9-HDA [(*E*)-9-hydroxydec-2-enoic acid].

Keywords: atom economy; Doebner–Knoevenagel reaction; hydroformylation; one-pot reaction; α,β-unsaturated carboxylic acids

An ideal target-oriented synthesis should consist of skeleton-constructing reactions only while avoiding unnecessary functional group interconversions, protection and deprotection steps.[1] If a synthetic target contains functional groups, those should be directly introduced in the course of the skeleton-expanding operation without the need for further manipulation.[2] This requires carbon-carbon bond forming reactions which proceed under mild conditions and tolerate the typical reactive functional groups of natural target structures such as alcohols, amines, carboxylic acids, etc. Furthermore, if such reactions would satisfy the criteria of atom economy, a highly efficient synthesis methodology should be the result.[3]

In this context we became interested in the functional subunit of α,β-unsaturated carboxylic acids, which represents a structural motif encountered in many natural product structures.[4] Several α,β-unsaturated acids and derivatives have been reported as pheromones.[5] Famous examples are, e.g., the honeybee queen compounds 9-HDA and 9-ODA.[6]

In spite of their widespread occurrence in synthetic targets, to the best of our knowledge there is no direct catalytic method for the construction of the α,β-unsaturated carboxylic acid motif meeting the criteria of atom economy.

Common synthesis methodology relies on two-step procedures resulting from (step 1) the construction of a corresponding α,β-unsaturated ester which is subsequently (step 2) saponified to liberate the acid.[5,7] The standard method for the construction of the α,β-unsaturated esters is a two-carbon chain elongation of an aldehyde by way of a Wittig or the related Horner–Wadsworth–Emmons olefination protocol.[8a–d] Although, this constitutes robust and reliable methodology, stoichiometric amounts of organophosphorus by-products are formed which have to be separated and disposed of. In this regard more attractive is the recently developed cross-metathesis protocol between terminal alkenes and acrylic esters with ethylene as the sole by-product.[8e,f] However, the problem of a subsequent ester hydrolysis step to liberate the desired carboxylic acid remains unsolved.

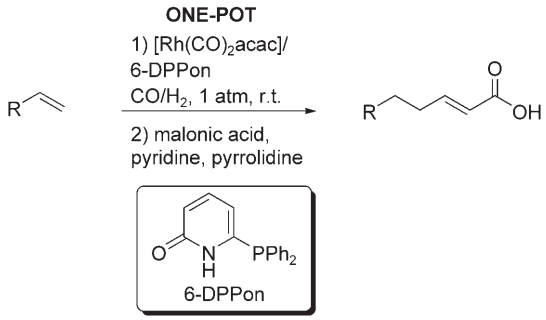
Based on similar considerations, a decarboxylative Knoevenagel-type condensation was recently suggested for the synthesis of α,β-unsaturated esters. This reaction has a significantly improved atom economy and only water and carbon dioxide are formed as by-products. Moreover it employs inexpensive starting materials – malonic acid derivatives. However, application of this methodology for the synthesis of α,β-un-

saturated carboxylic acids is described as limited. Yields for enolizable aliphatic aldehydes are low, the *E*/*Z*-selectivity varies and, most importantly, not α,β- but rather β,γ-unsaturated acids are obtained.[7,9] Accordingly, a clean, by-product free and selective methodology for the synthesis of α,β-unsaturated acids from aldehydes would be highly desirable. However, due to their intrinsic reactivity aldehydes are usually not particularly stable and isolation can be troublesome. Hence, a process combining an atom economic *in situ* aldehyde generation with a subsequent olefination process could be an interesting solution.[10]

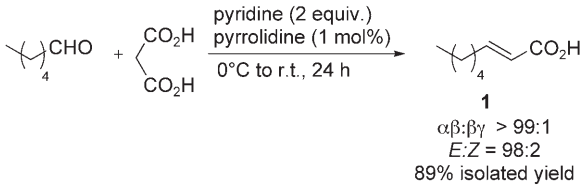
Herein, we report on the first one-pot hydroformylation/decarboxylative Knoevenagel reaction sequence, which constitutes a practical, atom economic and highly selective synthesis of α,β-unsaturated carboxylic acids (Scheme 1).

In a first step we tried to identify ideal reaction parameters for a clean and selective decarboxylative Knoevenagel condensation (Doebner–Knoevenagel) of aliphatic aldehydes. For this reason the influence of various reaction conditions on the reaction of capronaldehyde and malonic acid was studied (Table 1). Thus, preliminary experiments revealed that a combination of pyridine and a secondary amine catalyst gave most promising results. Employing catalytic amounts of pyridine (0.1 equiv.) and pyrrolidine (1 mol%) the chemoselectivity was high (α,β:β,γ = 96:4) but decarboxylation of the unsaturated diacid **3** (11.3%) was incomplete. Originally, DMF was used as solvent, which made the isolation of the reaction products troublesome. Interestingly, when pyridine (2 equiv.) was used as the solvent and reagent in the presence of catalytic amounts of pyrrolidine (1 mol%), (*E*)-oct-2-enoic acid was obtained in excellent yield (93%) and with high chemo- and stereoselectivity (α,β:β,γ > 98:2, *E*:*Z* > 99:1) (Table 1, entry 2). Other secondary amines were also effective as catalysts (Table 1, entries 3–5). Interestingly, with pyridine alone product **1** was formed highly selectively, but in low yield (50%, table 1, entry 6). Using pyrrolidine alone we observed full conversion of the aldehyde, but diacid **3** was the only product (Table 1, entry 7). Hence, there is cooperativity between these two base catalysts (*vide infra*). Dimethylaminopyridine, which has been described as an excellent catalyst for the synthesis of α,β-unsaturated esters, was not effective for this reaction (Table 1, entry 8).[7] With the optimized conditions in hand α,β-unsaturated carboxylic acid **1** was prepared on a preparative scale (50 mmol), and isolated in excellent yield and selectivity (Scheme 2).

In a next step we explored whether this decarboxylative Knoevenagel reaction could be coupled with an

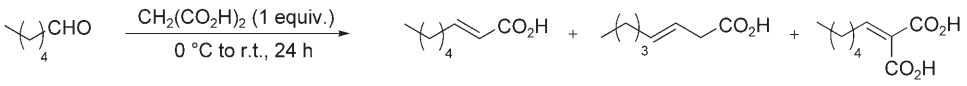


Scheme 1.



Scheme 2.

Table 1. Knoevenagel reaction optimization.



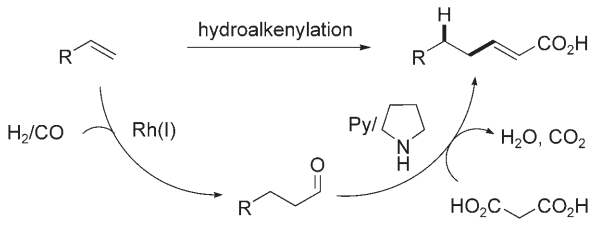
1 **2** **3**

Entry	Base 1	Equiv.	Base 2	mol [%]	NMR yield [%][a]	Ratio **1**:**2**
1[b]	pyridine	0.1	pyrrolidine	1	**1** (85); **2** (3.5); **3** (11.3)	96:4
2	pyridine	2	pyrrolidine	1	**1** (93); **2** (1.6)	>98:2
3	pyridine	2	piperidine	1	**1** (91); **2** (1.2)	>99:1
4	pyridine			1	**1** (88); **2** (1.8)	98:2
5	pyridine	2	Et_2NH	1	**1** (74); **2** (4.5)	94:6
6	pyridine	2	-	-	**1** (50)	>99:1
7	-	-	pyrrolidine	1	**3** (98)	-
8[c]	DMAP	2	pyrrolidine	1	**1** (22); **2** (11); **3** (66)	67:33

[a] 1H NMR detected, trimethoxybenzene as standard.
[b] DMF (6 M solution of the aldehydes) was added.
[c] THF (1 M solution of the aldehyde) was added. Formation of a precipitate was observed.

atom economic *in situ* generation of the required aldehyde. For this purpose we chose our recently developed regioselective room temperature/ambient pressure (RTAP) hydroformylation employing the self-assembling 6-DPPon/rhodium catalyst.[11]

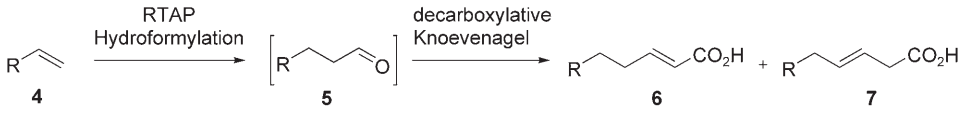
Such a one-pot regioselective hydroformylation/decarboxylative Knoevenagel reaction would install a C_3 extension of a terminal alkene, and would thus correspond to a formal and hitherto unknown cross-hydroalkenylation of a terminal alkene with acrylic acid (or related electron-poor alkenes) (Scheme 3).[12]

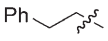
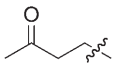
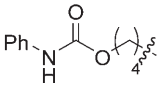
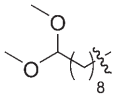
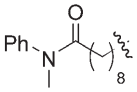


Scheme 3.

Initial experiments showed that the reaction conditions of the decarboxylative Knoevenagel are incompatible with the conditions of the RTAP hydroformylation protocol, which precluded a tandem process. However, a very efficient and practical one-pot process was developed. Thus, first hydroformylation was performed with [$Rh(CO)_2$acac]/6-DPPon as the catalyst precursor in a Schlenk tube under ambient pressure of synthesis gas at room temperature.[11] After 20 h the synthesis gas was replaced with argon and the nitrogen bases and malonic acid were added. After additional 20 h at 10 °C and 4 h at room temperature the reaction was complete and the α,β-unsaturated carboxylic acids were isolated by chromatography on silica in good overall yields and in high chemo- and stereoselectivity (Table 2, Experimental Section). The procedure turned out to be very reliable

Table 2. One-pot hydroformylation/Knoevenagel reaction.[a]

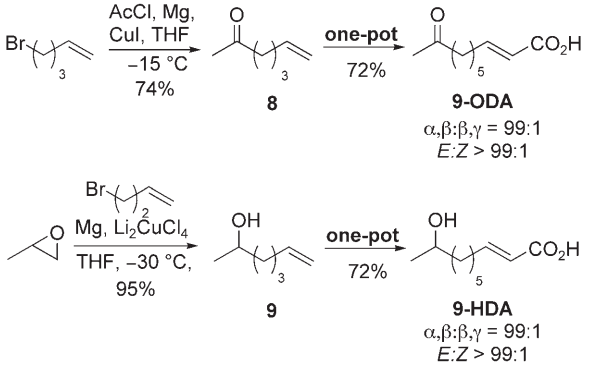


Entry	R	Conversion [%][b,c]	1:b[c]	Yield [%][d]	**5**:**6**[b]
1		**4** (quant.); **5** (quant.)	>99:1	77	>98:2
2		**4** (quant.); **5** (quant.)	99:1	78	97:3
3		**4** (quant.); **5** (quant.)	>99:1	68	98:2
4		**4** (quant.); **5** (quant.)	95:5	67	99:1
5		**4** (quant.); **5** (quant.)	99:1	75	99:1
6		**4** (quant.); **5** (quant.)	98:2	69	98:2
7		**4** (quant.); **5** (quant.)	99:1	68	99:1
8[e]		**4** (70); **5** (quant.)	99:1	71	98:2
9		**4** (quant.); **5** (98)	99:1	72	98:2
10		**4** (quant.); **5** (quant.)	99:1	77	98:2

[a] Conditions (hydroformylation): [$Rh(CO)_2$acac] (0.66 mol%), 6-DPPon (3.33 mol%), alkene (1 equiv.), CO/H_2 (1:1) 1 atm, THF [c_o(alkene) = 1.0 M], room temperature, 20 h, *Conditions* (Knoevenagel): malonic acid (1 equiv.), pyridine (2 equiv.), pyrrolidine (1 mol%), 20 h at 10 °C then 4 h at room temperature.
[b] Of alkene **4** (isomerization to the internal alkene < 5%), NMR detected.
[c] Of the intermediate aldehyde **5**, NMR detected.
[d] Isolated yield of product **6**.[e] Isolated yield referred to the Knoevenagel reaction.

and general for terminal alkenes. Many functional groups including, free alcohol functions as well as ketones, acetals, esters, amides and carbamates were tolerated.

To demonstrate the practicability of our methodology, a protecting group-free synthesis of the two honey bee pheromones, 9-ODA and 9-HDA, was envisioned (Scheme 4).[13,14] Thus, alkenes **8** and **9** were

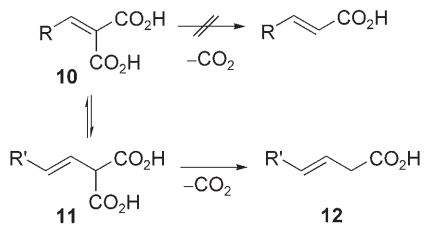


Scheme 4.

prepared by copper-catalyzed acylation and alkylation of the corresponding Grignard reagents, respectively.[15,16] Using our one-pot homologation the corresponding (*E*)-α,β-unsaturated acids 9-ODA and 9-HDA were obtained in good yields and perfect selectivity. To the best of our knowledge these are the shortest synthesis of these two honey bee pheromones which are completely free of protecting groups.[13,14]

Accordingly, the decarboxylative condensation of malonic acid presents an interesting, atom economic alternative to the more traditional carbon-carbon bond forming reactions. These and analogous processes are relatively rarely synthetically exploited because of the dominating controversy concerning the mechanism.

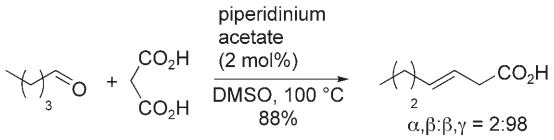
Mechanistic studies by Corey led to the proposal that decarboxylation of α,β-unsaturated malonic acids **10** can only proceed *via* β,γ-unsaturated intermediate **11** which then smoothly decarboxylates to the β,γ-unsaturated acid **12** (Scheme 5).[17] This mechanism probably operates during the condensation of malonic



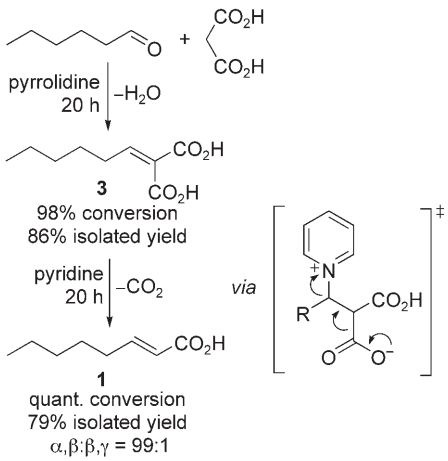
Scheme 5.

acid and aliphatic aldehydes catalyzed by piperidinium acetate in dimethyl sulfoxide at 100 °C (Scheme 6).[9a]

We reasoned that under our conditions an alternative mechanism is operative (Scheme 7). Thus, using pyrrolidine as the sole catalyst alkylidenemalonic acid **3** has been isolated and characterized. When **3** was



Scheme 6.



Scheme 7.

treated with pyridine a smooth decarboxylation took place and furnished the α,β-unsaturated acid **1**.

Hence, a two-step mechanism is most likely. The first step is a classical Knoevenagel condensation which is catalyzed by the secondary amine *via* formation of highly electrophilic iminium ion intermediates from the corresponding aldehyde with formation of diacid **3**. This step is fast (over 50% conversion after 30 min at 10 °C) and is followed by the much slower decarboxylation step initiated by pyridine (38% conversion after 10 h at 10 °C).[18] We propose that pyridine functions as a Lewis basic catalyst which undergoes conjugate addition to Knoevenagel product **3** followed by decarboxylation *via* the indicated transition state (Scheme 7).

In summary, conditions for the first general and highly selective decarboxylative Knoevenagel condensation with aliphatic aldehydes have been identified. This enabled the development of a new one-pot method for the direct synthesis of (*E*)-α,β-unsaturated acid starting from terminal alkenes. Thus, combining room temperature, ambient pressure regioselective hydroformylation with the decarboxylative Knoevena-

gel condensation (*E*)-α,β-unsaturated acids were obtained in good yields and with high chemo- and stereoselectivity. The process is mild, efficient, practical, atom economic and tolerates many functional groups. Interestingly, the overall transformation represents a formal cross-hydroalkenylation between a terminal alkene and acrylic acid, a reaction which is hitherto unknown. Future studies in our group will focus on exploring the full scope of this and related one-pot processes.

Experimental Section

General Procedure for the One-Pot Hydroformylation/Knoevenagel Reaction

Under an atmosphere of argon the olefin (150 equiv.) was added to a solution of 6-DPPon (5 equiv.) and $[Rh(CO)_2acac]$ (1 equiv.) in THF (1 M according to the olefin) at room temperature. The argon atmosphere was replaced by synthesis gas (balloon). The reaction mixture was stirred at room temperature and ambient pressure for 20 h.[11] Subsequently, synthesis gas was removed over 20 min by bubbling argon through the solution. The solution was cooled to 0 °C and malonic acid (150 equiv.), pyridine (300 equiv.) and pyrrolidine (1.5 equiv.) were added. The reaction mixture was warmed to 10 °C and stirred for 20 h at this temperature, and additional 4 h at room temperature. The reaction was finished by the addition of aqueous H_3PO_4 (20%, 10 mL). After phase separation, the aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over $MgSO_4$. The solvent was removed under vacuum. The product was purified by chromatography (SiO_2, petroleum ether:diethyl ether:acetic acid = 100:25:1 to 100:100:2).

Acknowledgements

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[18] For more details see Supporting Information.

