Communication

Towards a Scalable Synthesis and Process for EMA401. Part II: Development and Scale-up of a Pyridine- and Piperidine-free Knoevenagel-Doebner Condensation

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Towards a Scalable Synthesis and Process for EMA401. Part II: Development and Scale-up of a Pyridine- and Piperidine-free Knoevenagel-Doebner Condensation

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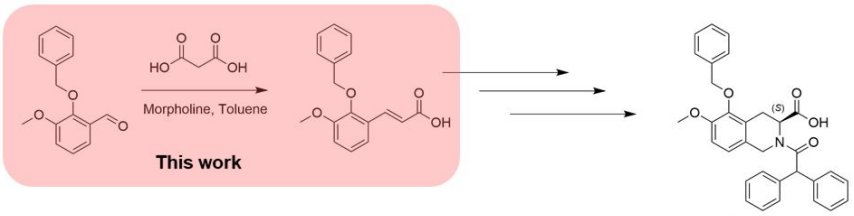
Graphical abstract



- Development of a Knoevenagel-Doebner condensation process ✓
- Successful scale-up (two times 12.5 kg, 84 and 87 % yield) ✓
- Substrate scope for general application ✓

15 examples, up to 99 % conversion

ABSTRACT During the route scouting of EMA401 (**1**), an angiotensin II type 2 antagonist, we identified the synthesis of key amino acid intermediate **2** *via* its cinnamic acid derivative **3** as a streamlined option. In general, cinnamic acids can be synthesized from the corresponding aldehyde in a Knoevenagel-Doebner condensation in pyridine with piperidine as an organocatalyst. We aimed at replacing both of these reagents and found novel conditions in toluene as the solvent and morpholine as the organocatalyst. Scale-up of the process allowed production of 25 kg of the cinnamic acid **3**, which was of required quality for process development on the subsequent phenylalanine ammonia lyase-catalyzed step. The modified conditions were found to be widely applicable to alternative aldehydes, and so of relevance to practitioners of chemical scale-up.

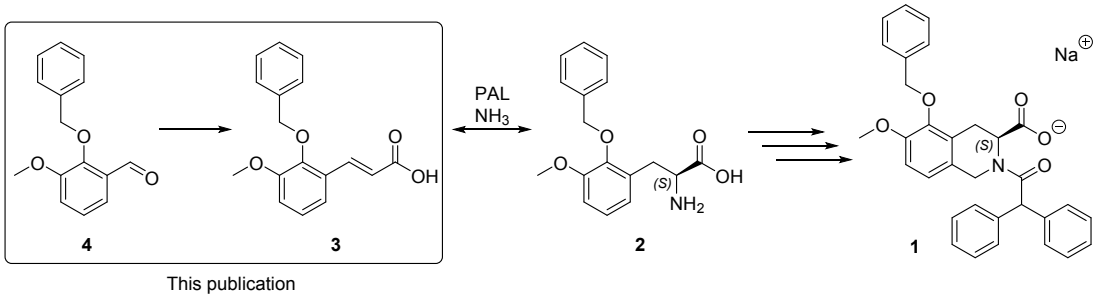
KEYWORDS Knoevenagel-Doebner, scale-up, cinnamic acid, pyridine-free, piperidine-free

Introduction

During the route scouting of EMA401 (**1**), several potential routes to the key amino acid intermediate **2** were evaluated.[1] One of the options identified relied on the phenylalanine ammonia lyase (PAL) catalyzed conversion of cinnamic acid **3** to amino acid **2** (Scheme 1).[2] To support our development program, we needed access to kilogram quantities of cinnamic acid **3**. We envisioned that the cinnamic acid could be made by a condensation reaction with benzylated *ortho*-vanillin **4**, an intermediate we had available in several kilograms as it was as a common intermediate for many of the proposed approaches to amino acid **2**.[1] In a first screening employing either Perkin condensation conditions, the use of catalytic DBU,[3] or the Doebner modification of the Knoevenagel condensation,[4] we found that the latter conditions proved most suitable for our substrate (Table 1, entry 1). The standard condition for a Knoevenagel-Doebner condensation employs pyridine as the solvent and piperidine as the organocatalyst. Since their first reports, a plethora of reports for Knoevenagel and Knoevenagel-Doebner condensation conditions replacing toxic or hazardous reagents have been published. Recently, Allais and co-workers developed a Knoevenagel-Doebner condensation to *p*-hydroxycinnamic acids with L-proline and malonic acid in EtOH,

yielding the naturally occurring acids in high yields.[5,6] The preparation of cinnamic acids in water was reported using microwave irraditation.[7] In addition, “solvent-free” Knoevenagel-Doebner conditions have also been reported recently, using ammonium bicarbonate as a catalyst and yielding the corresponding cinnamic acids in high yields.[8]

We aimed at replacing both piperidine and pyridine for several reasons: 1) piperidine is a precursor substance of narcotics,[9] and so its usage is complicated by bureaucratic tracking and control paper processes, 2) pyridine is possibly carcinogenic to humans and hazardous to the aquatic environment,[10,11] and 3) using an acidic quench as the work-up would have yielded large amounts of aqueous waste not suitable for the waste water treatment plant. With a large scale commercial manufacturing in mind, we aimed at developing conditions using more benign reagents and solvents following published solvent selection principles.[12,13]

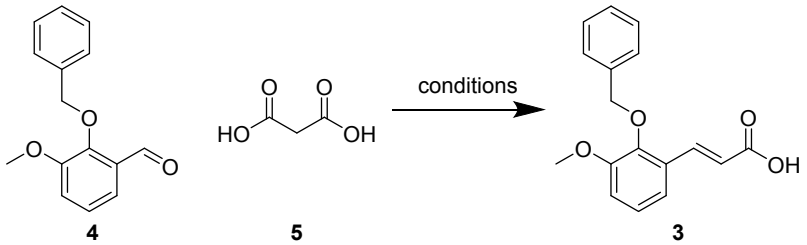


Scheme 1. Synthetic route to EMA401 (**1**) *via* the key intermediate amino acid **2**. Amino acid **2** can be prepared from cinnamic acid derivative **3**, which is itself prepared in a Knoevenagel-Doebner condensation starting from aldehyde **4**.

Experimental Details

Several alternatives to piperidine as the organocatalyst could be identified in an initial screening (Table 1). In particular, morpholine (entry 2), pyrrolidine (entry 3) and β-alanine (entry 4) showed comparable reactivity to piperidine (entry 1) in pyridine. Other secondary amines such as piperazine or L-proline generally showed lower or no conversion in our screenings. We selected morpholine as the reagent of choice, considering the HSE properties, the large-scale availability and pricing, the performance in the screening, as well as the compatibility with the process conditions (*vide infra*).

Table 1. Solvent and amine reagent screening for the conversion of aldehyde **4** to cinnamic acid **3**.



4 **5** **3**

Entry	*Solvent*	*Amine reagent*	*Temperature*	*Time*	*Conversion to 3*
1	Pyridine	Piperidine	100 °C	2 h	98%
2	Pyridine	Morpholine	100 °C	2 h	>99%
3	Pyridine	Pyrrolidine	80 °C	2 h	>99%
4	Pyridine	β-Alanine	100 °C	2 h	>99%
5	Morpholine	-	100 °C	2 h	5%
6	Pyrrolidine	-	80 °C	2 h	<1%
7	DBU	Morpholine	85 °C	2 h	<1%
8	TEA	Morpholine	85 °C	2 h	24%
9	DIPEA	Morpholine	85 °C	2 h	12%
10	4-Methylmorpholine	Morpholine	105 °C	2 h	99%

11	THF	Morpholine	90 °C[1)]	20 min[1)]	80%
12	MeTHF	Morpholine	80 °C	3.5 h	95%
13	CPME	Morpholine	94 °C	7 h	>99%
14	DMSO	Morpholine	94 °C	2 h	>99%
15	*t*-Amyl alcohol	Morpholine	94 °C	7 h	>99%
16	*i*PrOH	Morpholine	80 °C	7 h	>95%
17	Toluene	Morpholine	94 °C	7 h	>99%
18	Xylenes	Morpholine	110 °C	3.5 h	83%
19	Heptane	Morpholine	97 °C	3 h	2%
20	H_2O	Morpholine	94 °C	7 h	<1%

Conditions: 1–5 v/w solvent with 1.05–1.2 eq. of malonic acid and 0.12–0.25 eq. of the amine reagent. 1) microwave

We then tried to run the reactions in pure organocatalyst as the solvent. Running the reaction in neat morpholine (entry 5) or pyrrolidine (entry 6), however, only led to minor conversion with mostly starting material detected by HPLC. A screening of the ratio pyridine/morpholine showed that only mixtures above 10:1 (v/v) were efficient at catalyzing this reaction, with ratios up to 50:1 (v/v) giving good conversion, albeit at a

lower rate. Reactions using pyridine as the solvent at 5 g substrate scale were performed with a pyridine/morpholine ratio of 10:1 (v/v). Conversion of aldehyde **4** was usually complete within 2 h, but the reactions afforded very thick suspensions after a very exothermic quench with aqueous acids, and the material generated under these conditions tended to stick to the walls of the reactor. With mechanical cleaning of the reactor, isolated yields of cinnamic acid **3** of around 90% could be obtained. We then set out to screen for alternatives to pyridine as the reaction solvent, focusing first on amine-based solvents. Alternative nitrogen bases led to low conversion (DBU, entry 7) or the formation of gels (TEA, entry 8, DIPEA, entry 9). When 4-methylmorpholine was used, a conversion of 99% was observed in 2 hours (entry 10). However, a self-ignition temperature of 167 °C of 4-methylmorpholine would have required additional safety measures for production in a pilot plant environment.[14] We therefore continued our screening with common organic solvents.[12,13] A minimal boiling point of 60 °C was imposed, since the decarboxylation of the dicarboxylic acid intermediate **V** (Scheme 2) took place at around 70 °C. Gratifyingly, most of the solvents tested gave good to excellent conversion. THF (entry 11), MeTHF (entry 12), CPME (entry 13), DMSO (entry

14), *t*-amyl alcohol (entry 15), *i*PrOH (entry 16), toluene (entry 17) and xylenes (entry 18) all gave conversions of >80% after 2–7 h at temperatures above 80 °C, while heptane (entry 19) and water (entry 20), gave only minor conversion with mostly unreacted starting material detected by HPLC. Although DMSO seemed to be the best solvent for the given reaction, it was excluded from further screenings, due to safety considerations and the formation of darkly colored solutions. Out of the solvents screened, we favored MeTHF, *t*-amyl alcohol and toluene due to their fast reaction, and their high and clean conversion.

When *t*-amyl alcohol was used on a 5 g scale, full conversion could be achieved in 2 h. However, upon cooling the reaction mixture, the desired product precipitated rapidly as a hard solid, which caused stirrers to block and produced crusts which were not easily washed out of the reactor. Modifying the conditions did not help to overcome these issues in a manner we felt was acceptable for scale up.

Next, we ran the reaction in MeTHF on 5 g scale. The product was formed in 4 hours at a jacket temperature (JT) of 94 °C. The high solubility of cinnamic acid **3** in MeTHF (14.7wt%), further increased by the presence of morpholine (*vide infra*) meant that large

volumes of antisolvent, heptane in our case, were required to achieve a well stirrable and transferable suspension with reasonable isolated yields of the product.

In an initial screening with toluene at 94 °C, the reaction took 7 h for full conversion. When repeating the reaction and heating to JT = 110 °C, we were pleased to find that full conversion with only very few by-products could be achieved in 2 h. In addition, toluene is about seven times less expensive than MeTHF.

Based on these results, we went back to check the suitability of different secondary amines as organocatalysts in toluene at a loading of 0.1 eq. Under these conditions, only morpholine lead to full conversion in 5 h, while L-proline (26%), pyrrolidine (17%), β-alanine (8%) and piperazine (5%) gave significantly lower conversions.

Based on this initial screening for the conditions we then moved our attention to developing a process on 10–20 g of aldehyde **4** in a double jacketed glass reactor. When charging the reactor with all starting materials (aldehyde **4**, malonic acid (**5**), and morpholine) and suspending them in toluene, we noted that at temperatures between 25–50 °C, a gum-like substance was formed *in situ*, which was sticking to stirrers and walls and impeded stirring, but dissolved again at temperatures above 50 °C. We

reasoned that this might be caused by the formation of morpholinium salts. Therefore, we decided to dose morpholine as a solution in toluene at IT = 55–65 °C. Running the process in this manner, the formation of the gum-like intermediate was no longer observed.

In our small scale (5g) screening reactions, 1.05–1.20 eq. of malonic acid had been sufficient to achieve full conversion. In our initial trials however, we were not able to achieve full conversion of aldehyde **4** and observed the formation of a dark yellow color when extending the reaction time.[15] This led to the isolation of the desired product as a yellow solid, however, with no impurity observed by HPLC or ^{1}H NMR. The yellow color could only be removed by extensive washing with toluene, incurring a consequent reduction of the yield. We speculated that the yellow impurity might be caused by polymerization. Indeed, when stirring a 1:1 mixture of aldehyde **4** and cinnamic acid product **3** with morpholine at 110 °C, we observed the formation of a strong yellow color, with concomitant consumption of both reaction partners and without apparent formation of a new by-product detectable by HPLC. Heating both aldehyde **4** and cinnamic acid **3** in separate reactions in the presence of morpholine to reflux did not

lead to the formation of a yellow color and HPLC showed that the two compounds were reasonably stable. Based on these observations, we pre-supposed that it is crucial to achieve full conversion in a reasonable time, before the stated assumed polymerization occurs in a follow-up reaction. Given that incomplete conversion occurred even when employing 1.2 equivalents of malonic acid, we hypothesized that the decomposition of malonic acid is a competing side-reaction and hence that the equivalents of malonic acid are critical for achieving full conversion and high yield and purity of the isolated cinnamic acid **3**. This hypothesis was corroborated by the following experiments. A DSC (see supporting information (SI)) of malonic acid (**5**) shows a first endotherm starting at 82 °C (minima at 92 °C), indicating decomposition, and a strong second endotherm starting at 119 °C (minima at 136 °C), which corresponds to the reported melting point of malonic acid.[14] In a second experiment, a suspension of malonic acid and morpholine were gradually heated in toluene and the stability of malonic acid assessed over 17 h. By off-line ^{1}H NMR analysis, no peak for the methylene group of malonic acid was detected, but a singlet at 1.91 ppm was observed instead, indicating the formation of acetic acid by CO_2 elimination. Based on these results, we extended the equivalents of

malonic acid and found that 1.3 eq. are required to achieve full conversion of aldehyde **4** and prevent the formation of a strongly yellow colored product.

To remove the water formed during the reaction, a Dean-Stark trap was routinely used in all reactions.[16] For safety reasons, the release of CO_2 was monitored by volume in selected experiments and it was found that CO_2 is formed over the entire reaction time of approx. 1.5–2 h above ca. 80 °C, with no accumulation or sudden release of CO_2 observed. Generally, after 2 h in refluxing toluene, full conversion of aldehyde **4** (< 1a% by HPLC) was found. In the plant, it was deemed impractical to sample the reactor with refluxing toluene and so for HSE reasons it was hence decided to increase the reaction time at reflux to 3 h to ensure full conversion without the need for an in-process control (IPC). Further experiments showed that up to 24 h at 110 °C did not have a detrimental effect on yield and purity of the isolated product. After complete conversion, the mixture was cooled to 20 °C with a gradient of 0.5 K/min. At a temperature of 30–40 °C, a sudden precipitation of the voluminous, cotton-candy-like product occurred. We observed that the product did not settle when stirring was stopped, and the addition of more toluene did not afford a suspension which allowed emptying the reactor through its

bottom valve. A screening of different additives indicated that only the addition of EtOH helped to break the surface tension and ensured that the suspension could be transferred onto the filter. Since the cinnamic acid **3** is highly soluble in ethanol, the amount employed was minimized to 0.25 v/w with respect to aldehyde **2**. As the solubility of cinnamic acid **3** in toluene is also significantly increased in presence of morpholine (*vide infra*, SI), heptane was added as an anti-solvent to decrease the loss of product in the mother liquor. Twice the volume of toluene was used to reduce the solubility of cinnamic acid **3** in the reaction solvent system. To purge residual product, the lab glass reactor was rinsed with a mixture of toluene, ethanol and heptane corresponding to the final solvent ratio obtained before filtration. When going to the plant, a stainless steel reactor was used and it was found that the suspension could be entirely transferred to the filter, with no crusts or residual product visible in the reactor. For all development done after the initial scale-up, the reactor was consequently washed with heptane only.

After drying, the cinnamic acid **3** thus obtained was pure by HPLC, but contained 3–5 mol% of morpholine as determined by ^{1}H NMR. Since at this point in the project, and

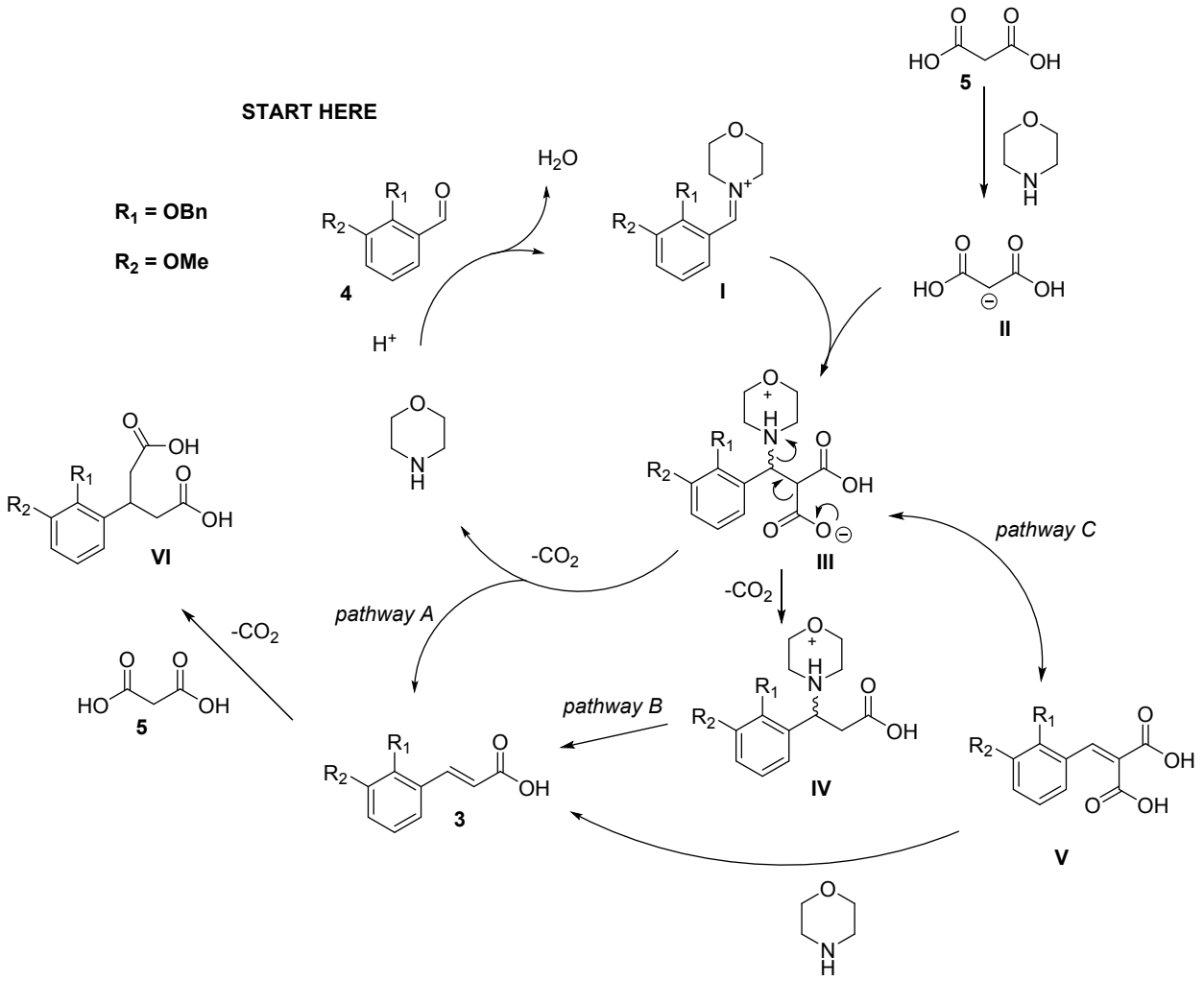
more specifically of enzyme evolution,[2] it was not clear if morpholine was compatible with the subsequent enzyme-catalyzed step, we aimed at further purifying the cinnamic acid **3**. This was done in a straightforward manner by suspending the crude compound in an aqueous acid, followed by filtration and drying. Hydrochloric acid proved to purge morpholine efficiently in an initial finding, but due to its incompatibility with some materials of construction and the potential to form ethyl chloride in the presence of EtOH, we searched for alternative acids. Employing sulfuric acid lead to the formation of yellow impurities during drying of cinnamic acid **3**, even with only traces of sulfuric acid present in the wet product after extended washing of the filter cake with H_2O. When using 10% citric acid, we were able to purge morpholine, and one additional wash with H_2O was sufficient to purge the citric acid. We serendipitously had also noted that the addition of acetonitrile helped purging the by-product **VI** (Scheme 2). Therefore, a 10% citric acid solution was mixed with acetonitrile (85:15 v/v) for the first wash, followed by a second wash with H_2O. Upon treatment of the compound with the aqueous layer, the aspect changed from voluminous needles to broad platelets. In order to obtain a powder-like substance, cinnamic acid **3** was finally re-slurried in heptane and filtered.

Subsequent drying afforded the desired compound in 86–92% yield with >99.8% purity, and no morpholine detected by ^{1}H NMR. Crucially for scale-up, starting materials, product, solutions and suspensions were not found to have a critical heat release in safety experiments. Only neat malonic acid showed an exotherm in safety experiments, which was safe to control under the process conditions.

Mechanistic considerations

The mechanism of the Knoevenagel-Doebner condensation outlined in Scheme 2 is adapted from textbooks as well as a computational study investigating *p*-hydroxycinnamic acid and the formation of vinyl phenols,[17] similar to the recently reported work on L-proline mediated condensations.[5] After formation of iminium **I**, and attack by malonate **II**, intermediate **III** can undergo three different fragmentation pathways to cinnamic acid **3**. Pathway A by direct fragmentation, pathway B through formation of the morpholine adduct **IV** and subsequent elimination, or pathway C *via* dicarboxylic acid intermediate **V**. We observed both intermediates **IV** and **V** by LC-MS,

while intermediate III was never observed. Intermediate V was shown by LCMS to accumulate at lower temperatures, which is consistent with our finding that no CO_2 release was observed below 70 °C. Compound V could be prepared and it was shown to convert to cinnamic acid 3 in 2 h (86% conversion) in the presence of morpholine, while <1% conversion was observed when no morpholine was added to the reaction mixture, highlighting the dual catalytic activity of the organocatalyst as base and nucleophile. Dicarboxylic acid VI was observed as a by-product, presumably formed by the 1,4-addition of malonic acid to cinnamic acid 3 and subsequent de-carboxylation. Both acids V and VI were found as trace impurities (<0.1a%) in some batches of isolated cinnamic acid 3, but were not deemed critical as they were not expected to interfere with the subsequent enzyme-catalyzed step.



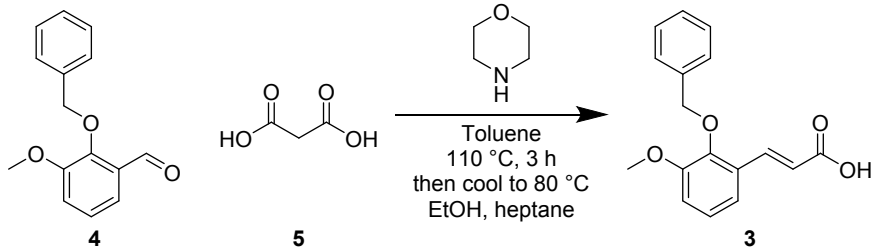
Scheme 2. Catalytic cycle of the Knoevenagel-Doebner condensation with the key intermediates **III**, **IV** and **V** for the synthesis of cinnamic acid **3**, and the proposed explanation for the formation of dicarboxylic acid by-product **VI**.

Process intensification after first scale-up

With the experience gained in the first scale-up, we aimed at further streamlining the process. A screening performed on the subsequent PAL-catalyzed step revealed that morpholine concentrations higher than those generally observed in isolated cinnamic acid **3** (3–5mol%) were acceptable.[2] Hence, the aqueous washes and the final heptane wash of the filter cake of cinnamic acid **3** were no longer required. This allowed usage of a standard filter instead of a stirred filter dryer. In addition, as described above, the filter cake only required a displacement wash of the mother liquor with heptane when using a stainless steel reactor. The product thus generated in the lab was successfully employed in use-tests within the subsequent PAL-catalyzed step.

In addition to the changes above, we used a Crystal16 to determine the cloud point of the precipitation of cinnamic acid **3** during cooling of the mixture at the end of the reaction. We aimed at avoiding a spontaneous precipitation of product **3** upon cooling when running the reaction at higher concentration, and before the addition of EtOH. While the transition points of cinnamic acid **3** in toluene without EtOH were found to be 79–85 °C (4 v/w toluene wrt aldehyde **4**, 0.15 eq. morpholine, see SI), the cloud point could be significantly reduced to 44–46 °C after the addition of EtOH (0.1 v/w wrt **4**),

while the clear point remained at 81–82 °C. As the cloud point was not critical anymore once EtOH had been added, we set up another experiment to determine the dependency of the cloud point on the dilution in toluene and the equivalents of morpholine (see SI). Based on this second screening, we selected 0.165 eq. of morpholine at 3 v/w dilution since the cloud point of <70 °C is low enough to prevent spontaneous precipitation before EtOH addition. This could be confirmed on a 20 g scale. We further found that the equivalents of malonic acid could be reduced to 1.2 eq. as a consequence of the higher concentration, which led to reduced formation of the dicarboxylic acid by-product **VI**. This proved to be crucial as **VI** and other less soluble impurities led to spontaneous nucleation at temperatures >70 °C. With this solvent system combined with heptane as anti-solvent at 70–80 °C, precipitation occurred after approx. 33% of the total heptane volume (4 v/w wrt aldehyde **4**, see SI), resulting in a thick but stirrable suspension, which was further mobilized by the addition of the remaining 67% of the heptane. In conclusion, the concentration could be increased by a factor of 2, with a reduction of the PMI from 47.1 to 7.3 (Scheme 3), and following this protocol on 20 g scale, cinnamic acid **3** could be isolated in 98% yield.[18]



4 **5** **3**

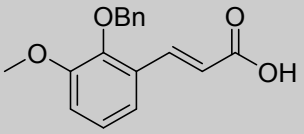
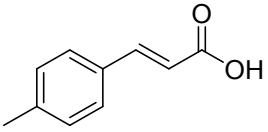
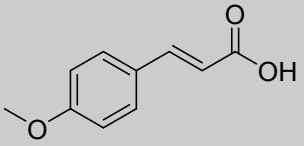
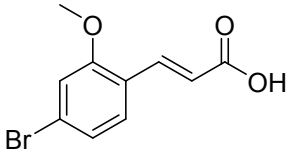
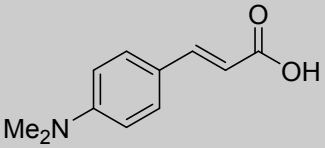
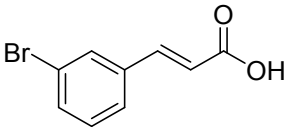
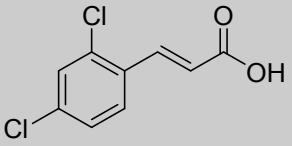
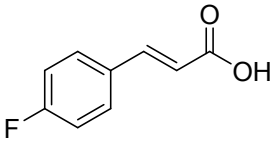
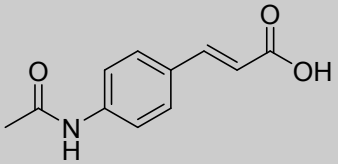
Scale-up Process		Streamlined Process
Charge aldehyde **4** (1.0 eq.)		Charge aldehyde **4** (1.0 eq.)
Charge malonic acid (1.3 eq.)		Charge malonic acid (1.2 eq.)
Charge toluene (5 v/w)		Charge toluene (2.75 v/w)
Heat to 110 °C		Heat to 110 °C
Charge morpholine (0.2 eq.) as a solution in toluene (1 v/w) at 55-65 °C		Charge morpholine (0.165 eq.) as a solution in toluene (0.25 v/w) at 55-65 °C
Stir at 110 °C for 3 h		Stir at 110 °C for 3 h
Cool to 80 °C		Cool to 80 °C
Add EtOH (0.25 v/w)		Add EtOH (0.1 v/w)
Add heptane (12 v/w)		Add heptane (4 v/w)
Cool to 20 °C and stir for 2 h		Cool to 20 °C and stir for 0.5 h
Filter the suspension		Filter the suspension
Rinse reactor and wash filter cake with a mixture of toluene/EtOH/heptane 1:0.04:2 (total 5 v/w)		Rinse reactor and wash filter cake with heptane (2 v/w)
Re-slurry the filter cake with 10% citric acid/MeCN (85:15 v/v, total 10 v/w) and filter		Dry wet product
Re-slurry filter cake with H_2O (10 v/w) and filter		
Re-slurry filter cake with heptane (10 v/w) and filter		
Dry wet product		
PMI =47.1		*PMI = 7.3*

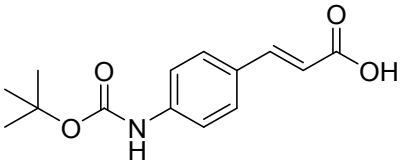
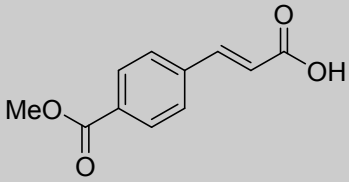
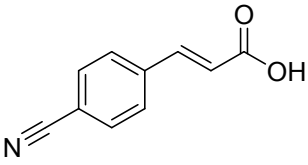
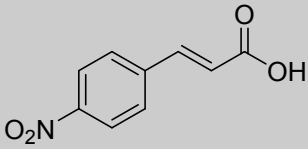
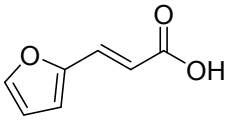
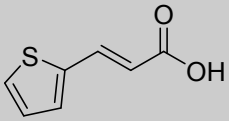
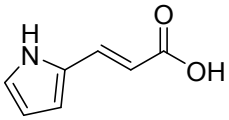
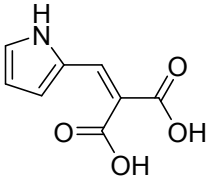
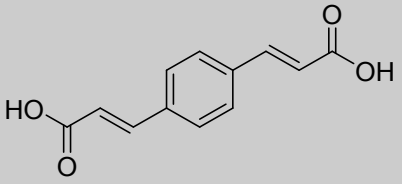
Scheme 3. Comparison of first process used in scale-up and second process after additional streamlining.

Scope of the newly developed conditions

The applicability of the reaction conditions developed for the actual intermediate of EMA401 were then tested on a series of aromatic aldehydes (Table 2). Since the work-up procedure was optimized for the desired cinnamic acid **3** and not applicable for all types of substrates, screening products were not isolated and conversions are stated according to LC-MS or HPLC data. The conditions gave good to excellent conversion for electron-rich (entry 1–5) and electron-poor (entry 6–13) aromatic compounds, as well as heterocyclic substrates (entry 14+15). Like for the actual substrate, substituents in the *ortho*-position to the aldehyde were well tolerated. Interestingly, pyrrole-2-carboxaldehyde (entry 16) did not afford the desired product but underwent full conversion to the corresponding analogue of intermediate **V**. Terephthalaldehyde (entry 17) gave the corresponding dicarboxylic acid in 24%, with many other intermediates observed by LCMS.

Table 2. Screening of various aldehydes using the newly developed conditions in toluene/morpholine.

Entry	Product	Conversion / a%[1)]	Reaction Time / h
1		>99[2)]	2
2		99[3)]	3
3		90[2)]	4
4		70[3)]	1.5
5		48[2)]	3
6		92[2)]	2.5
7		75[3)]	3
8		87[3)]	22
9		91[3)]	3

10		87[3)]	3
11		81[3)]	22
12		70[3)]	3
13		89[2)]	2
14		82[2)]	4
15		77[3)]	22
16		Dicarboxylated product observed[3), 4)] 	3
17		24[3)]	3

Conditions: Aldehyde (1.0 eq., 20 mmol) in toluene (20 mL) with morpholine (0.2 eq.) and malonic acid (1.3 eq.) heated to 110 °C for 3 h. 1) For the conversion, the integration of all peaks except the solvent peak and the injection peak were taken into account, 2) Samples analyzed with HPLC at 228 nm, 3) Samples analyzed with LCMS at a wavelength range of 210–450 nm; 4) structure proposed based on LCMS data.

Experimental Section: Synthesis of (2*E*)-3-[2-(Benzyloxy)-3-methoxyphenyl]prop-2-enoic acid (**3**)

Scale-Up Process run on 2 times 12.5 kg

Aldehyde **4** (1.0 eq.) and malonic acid (**5**) (1.3 eq) were suspended in toluene (5 v/w wrt **4**) and heated to IT = 110±5 °C. At IT = 55–65 °C, morpholine (0.2 eq) in toluene (1 v/w wrt **4**) was added over 3–5 min. The mixture was heated using a Dean-Stark trap at IT = 110±5 °C for 3 h and cooled to IT = 75–80 °C. EtOH (0.25 v/w wrt **4**) was then added over 5 min, followed by heptane (12 v/w wrt **4**) added over 30 min, and the mixture was cooled to 20 °C over 2 h. A white precipitate was formed. The mixture was stirred at 20 °C for 2 h and filtered.

The reactor was rinsed with a mixture of toluene/EtOH/heptane 1:0.04:2 (v/v/v, total 5 v/w wrt **4**). The filter cake was dried under nitrogen and suspended in a mixture of 10wt% citric acid/acetonitrile 85:15 (v/v; total 10 v/w wrt **4**), stirred for 10 min, and filtered. The filter cake was suspended in H_2O (10 v/w wrt **4**), stirred for 10 min, filtered and dried under nitrogen. The white solid was suspended in heptane (10 v/w wrt **4**), stirred for 10 min, filtered and dried under vacuum at 50 °C until dryness affording the cinnamic acid **3** as a white, voluminous powder (84–87% yield).

M.p.: 156 °C;[19] ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 3.86 (s, 3 H), 4.98 (s, 2 H), 6.44 (d, J = 16.1 Hz, 1 H), 7.06–7.18 (m, 2 H), 7.28–7.40 (m, 4 H), 7.40–7.46 (m, 2 H), 7.81 (dd, J = 16.3, 1.4 Hz, 1 H), 12.31 ppm (s, 1 H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ = 55.9, 74.6, 114.5, 118.8, 120.1, 124.5, 128.1, 128.2, 128.3 (2 C), 128.3 (2 C), 137.0, 138.3, 146.1, 152.8, 167.6 ppm; ESI-MS: m/z = 285.1 ($[M + H]^+$, calcd for $C_{17}H_{17}O_4^+$: 285.1)

Final process after streamlining

In a double jacketed reactor equipped with a Dean-Stark trap, aldehyde **4** (20 g, 1.0 eq.) and malonic acid (**5**) (10.31 g, 1.2 eq.) were suspended in toluene (55 mL) and

heated to JT = 110 °C with a gradient of 0.5 K/min. At IT = 55 °C, a solution of morpholine (1.19 mL, 0.165 eq.) in toluene (5 mL) was added dropwise. The mixture was stirred for 3 h at JT = 110 °C (IPC showed <1a% of aldehyde **4**), the Dean-Stark trap was removed and the mixture cooled to IT = 80 °C with a gradient of 0.5 K/min. EtOH (2 mL) was added, followed by the addition of heptane (80 mL) over 30 min, maintaining an IT of 70–80 °C. After around 1/3 of the heptane volume, precipitation was observed. The suspension was then cooled to 20 °C with 0.5 K/min, stirred for 30 min, and filtered. The filter cake was washed with heptane (40 mL) to afford the product **3** as a white solid (23 g, 98%), containing approx. 4mol% morpholine.

Conclusion

In summary, we developed conditions for the Knoevenagel-Doebner condensation in toluene with morpholine as the organocatalyst, avoiding the undesired pyridine and piperidine. To our knowledge, these conditions have not been used for a Knoevenagel-Doebner condensation. These novel conditions were successfully scaled to 2 batches of

12.5 kg each. Cinnamic acid **3** could be obtained meeting all specifications. After additional process development, the conditions were further improved to yield cinnamic acid **3** in a 98% yield. The optimized conditions in toluene, with morpholine as organocatalyst appear to be generally applicable for a broad range of substrates, as shown in a screening with various aromatic aldehydes.

ASSOCIATED CONTENT

The following files are available free of charge.

Solubility data and NMR spectra of cinnamic acid **3**, HPLC or LCMS data for the screening of various aromatic compounds (PDF)

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Author Contributions

The manuscript was written by L.A.H. through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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ABBREVIATIONS

CPME, cyclopentylmethyl ether; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA, diisopropylethylamine; DMSO, dimethylsulfoxide; DSC, differential scanning calorimetry; HPLC, high pressure liquid chromatography; IPC, in-process control; LCMS, liquid chromatography – mass spectrometry; MeTHF, 2-methyl tetrahydrofuran; PAL, phenylalanine ammonia lyase; SI, supporting information; TEA, triethylamine; THF, tetrahydrofuran; wrt, with respect to

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schedule VI, e) JP Narcotics and Psychotropic control Act, Article 2 (vii) sparate Table 4, and f) CH Swiss controlled substances act (BetmVV-EDI) Narcotics List F.

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