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PII: S0040-4020(16)30174-0

DOI: 10.1016/j.tet.2016.03.043

Reference: TET 27583

To appear in: *Tetrahedron*

Received Date: 8 February 2016

Revised Date: 2 March 2016

Accepted Date: 13 March 2016

Please cite this article as: Singjunla Y, Colombano S, Baudoux J, Rouden J, Stereoselective synthesis of dehydroamino acids using malonic acid half oxyester and aromatic aldehydes, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.03.043.

## Graphical Abstract

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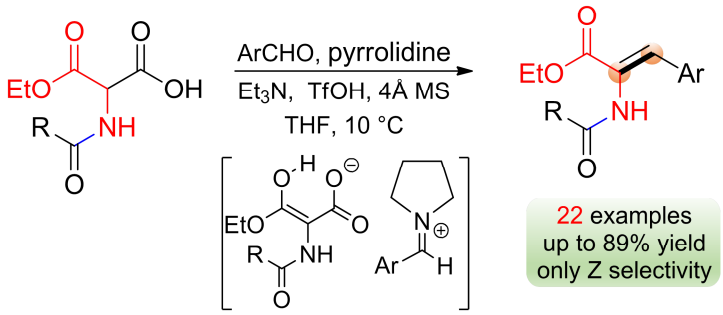

Tetrahedron
journal homepage: www.elsevier.com

# Stereoselective synthesis of dehydroamino acids using malonic acid half oxyester and aromatic aldehydes

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Amino acid
Doebner condensation
Malonic half oxyester
Organocatalysis
Decarboxylation

ABSTRACT

An efficient and direct approach was developed for the synthesis of α,β-dehydroamino acid derivatives with a broad range of substrates. Amido-substituted Malonic Acid Half Oxyesters (MAHOs) have proven to be excellent partners of various aromatic aldehydes in the presence of secondary amine, trifluoromethanesulfonic acid to perform a Knoevenagel-Doebner condensation under mild conditions with good to excellent yields. A mechanistic study revealed that the sequence involved the formation of an iminium intermediate to provide stereoselectively Z-α,β-unsaturated amino acids.



## 1. Introduction

*α,β*-Dehydroamino acids (ΔAAs) are a new class of non-proteinogenic amino acids occurring in recently characterized natural peptides.[1] Several bioactive products are composed of trisubstituted dehydroamino acids derived from valine (ΔVal), isoleucine (ΔIle), leucine (ΔLeu) and phenylalanine (ΔPhe) such as Tentoxin.[1,2] The incorporation of ΔAAs into a peptide could modify the backbone geometry of the chain by increasing its rigidity. Moreover, *α,β*-dehydroamino acids may be involved in biological processes as biochemical intermediates to bring better stability in biological media.[3] As a result, the development of new approaches for the synthesis of α,β-dehydroamino acid derivatives is essential to evaluate their biological reactivity and to facilitate the preparation of new synthetic peptides. In synthetic chemistry, dehydroamino acids have been used as starting materials for several reactions, mainly in asymmetric hydrogenations[4] but also epoxidations,[5] conjugated additions,[6] cyclopropanations[7] and Diels-Alder reactions.[8]

The most commonly used strategy for the one-pot synthesis of *α,β*-dehydroamino acids involves Wittig reaction[9] and alternative methods.[10] Ito et al. used the Schöllkopf method, isolating an oxazoline intermediate which was opened in the presence of Pd(0).[11] Alvarez-Ibarra et al. used a Schiff base in the presence of ethyl propynoate and potassium tert-butoxide to induce a [1.3]-hydride shift followed by a double bond migration to the *α,β*-position of the amino acid moiety.[12] Alternatively, Henry's reaction followed by dehydration was used to access *α*-nitroesters-*α,β*-unsaturated esters from nitroacetate.[13] Other transformations reported for the synthesis of *α,β*-dehydroamino acids involve the elimination of *β*-hydroxy-*α*-amino ester derivatives.[14] Although the synthesis of *β*-hydroxy-*α*-amino esters is well described, easy access to these compounds is still challenging. Furthermore, the dehydration step sometimes requires restrictive conditions with the use of EDC/Cu(OTf)$_2$,[15] TsCl/DCC/CuCl$_2$, EDC/CuCl$_2$,[16] Ts$_2$O/DABCO[17] or PPh$_3$/DEAD[18] and very recently an interesting study has been realized by Ess and Castle to selectively generate *Z* or *E*-ΔIle by using Martin sulfurane.[19] In recent years, malonic acid half oxyesters (MAHOs) have been utilized with aliphatic aldehyde to perform decarboxylative aldol reactions followed by a subsequent dehydration step but very low overall yields of *α,β*-dehydroamino esters were observed in all cases.[20]

In this context, the Knoevenagel-Doebner condensation[21] represents a convenient and mild method to create a double bond from unsubstituted malonic acid or malonic acid half oxyesters (MAHOs) and aldehydes *via* a one-pot domino decarboxylative aldol-elimination process. The recent report by List and co-workers who developed a set of mild conditions for this transformation is particularly attractive, but only unsubstituted malonates were used (scheme 1a).[21d] To the best of our knowledge, only one example reported by Xu and co-workers involves this methodology starting from a substituted 2-amido MAHO with an alkyl aldehyde to synthesize a ΔAA derivative in moderate yield and as a mixture of stereoisomers (*Z*-dehydroamino acid as the major).[22]

With the aim of developing a short and flexible methodology to synthesize *α,β*-dehydroamino esters of various structural and electronic properties and with our experience in the use of 2-amido MAHO,[23] we report hereafter a straightforward synthesis of ΔAAs under mild conditions using the Doebner reaction (scheme 1b).

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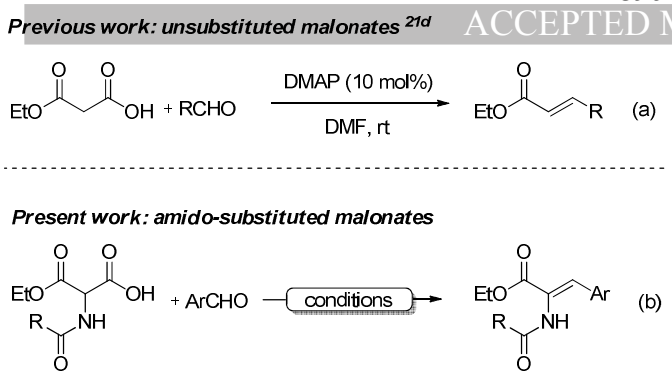


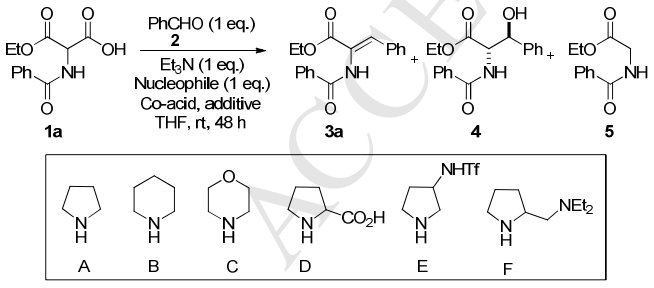

**Scheme 1:** Previous work and our strategy using MAOHs in the Doebner reaction.

## 2. Results and discussion

Our first attempt to transform 2-benzamido MAHO **1a** into a ΔAA derivative was carried out by using the efficient conditions developed by List and co-worker with unsubstituted malonates.[21d] The reaction led quantitatively to decarboxylative aldol product **4** and no traces of Doebner compound **3a** was detected even after a prolonged reaction time (entry 1, table 1). Compared to unsubstituted malonates, amido-substituted MAHO appeared to behave quite differently and the Doebner reaction with these starting materials therefore represent an interesting synthetic challenge.

Reassessment of these conditions started using a secondary amine such as pyrrolidine to transform benzaldehyde **2** into a more reactive iminium intermediate as Xu recently developed with an alkyl aldehyde.[22] Again, the reaction led to a mixture of three different compounds, the expected *Z*-dehydroamino ester **3a**,[24] the decarboxylative-aldol ester **4** and the decarboxylative-protonated ester **5**, all in very poor yields (entry 2, table 1). Based on previous works including ours, we envisaged a double activation of the substrates, basic for MAHO and nucleophilic for the aldehyde. We attempted the reaction by adding triethylamine to deprotonate MAHO but also a strong acid as co-catalyst with pyrrolidine to facilitate the iminium formation from benzaldehyde **2**. Compared to alkyl aldehyde, a careful optimization had to be performed in order to determine the best catalyst combination working for all types of aromatic aldehydes.

**Table 1**
Optimization of the Knoevenagel-Doebner condensation



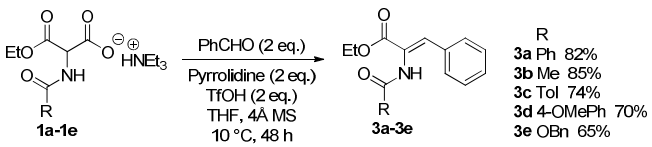

| Entry[a] | Nu | Co-acid | Additive | 3a[b] | 4[b] | 5[b] |
|---|---|---|---|---|---|---|
| 1 | | List's conditions [21d] | | - | >95%[c] | - |
| 2[d] | A | - | - | 26% | 12% | 23% |
| 3 | A | TFA | - | 42% | 6% | 21% |
| 4 | A | TfOH | - | 61% | 16% | 20% |
| 5 | A | 4-nitrobenzoic acid | - | 55% | 7% | 27% |
| 6 | B | TfOH | - | trace | 21% | 38% |
| 7 | C | TfOH | - | 27% | trace | 68% |
| 8 | D | - | - | trace | 19% | 53% |
| 9 | E | - | - | 19% | 35% | 34% |
| 10 | A | TfOH | 4 Å MS[e] | 70% | <2% | 11% |
| 11[f] | A | TfOH | 4 Å MS[e] | 74% | <2% | <2% |
| 12[d,g] | A | TfOH | 4 Å MS[e] | 59% | trace | trace |
| 13[d] | F | TfOH | 4 Å MS[e] | 49% | trace | trace |
| 14[h] | A | TfOH | 4 Å MS[e] | 82% | 8% | 8% |

[a] Reactions performed on 0.2 mmol scale at 0.33 M **1a**. [b] Isolated yields. [c] $^1$H NMR conversion. [d] Without $Et_3N$. [e] Molecular sieves. [f] Performed at 10 °C. [g] Performed at 10 °C with 1 eq. of benzaldehyde, 1 eq. of TfOH and 2 eq. of pyrrolidine. [h] Performed at 10 °C with 2 eq. of benzaldehyde, pyrrolidine and TfOH.

Three strong acids, trifluoroacetic acid (TFA), trifluoromethane sulfonic acid (TfOH) and 4-nitrobenzoic acid, were tested in stoichiometric amounts (entries 3-5). TfOH initially provided the best improvement allowing the isolation of Doebner product **3a** in 61% yield along with **4** and **5**. With TfOH, the use of piperidine or morpholine, two amines with similar nucleophilicity to pyrrolidine,[25] afforded product **3a** in low yield (entries 6-7).

To enhance cooperation between the acid and the pyrrolidine in order to increase the concentration of iminium in the reaction mixture, we selected proline **D** and pyrrolidine-NHTf **E** as bifunctionnal catalysts. In the case of proline, only trace of **3a** was observed, probably due to the poor solubility of this catalyst in THF (entry 8). It is noteworthy that proline in ethanol as solvent afforded 8% yield of **3a** while the use of proline-Boc in THF with *in-situ* deprotection by TfOH gave 18% yield of **3a** (data not shown). Pyrrolidine *N*-triflimide **E** gave only a slight improvement (entry 9) compared to proline with 19% yield. In all cases when changing the nucleophilic catalyst, glycine was observed as a major product (product of protodecarboxylation).

To shift the equilibrium toward the formation of iminium, we added molecular sieves and a significant enhancement was observed to afford **3a** in 70% yield (entry 10)**.** Performing the reaction at 10 °C, a 74% yield of Doebner product was achieved with very low amounts of side products **4** and **5** (entry 11). The selected combination of acid, tertiary and secondary amines to simultaneously activate MAHO **1a** and aldehyde **2** was confirmed during additional experiments. Without deprotonation of MAHO (no $Et_3N$) but with optimal iminium formation, the reaction lead to **3a** in only 59% yield (entry 12). Diamine **F** containing the base and the nucleophile on the same molecule afforded 49% yield (entry 13). Finally, the yield of **3a** was improved to 82% with a stoichiometric amount of $Et_3N$, two equivalents of pyrrolidine, TfOH and aldehyde (entry 14). All these experiments afforded the same stereoisomer and exclusively the *Z*-dehydroamino ester **3a**.



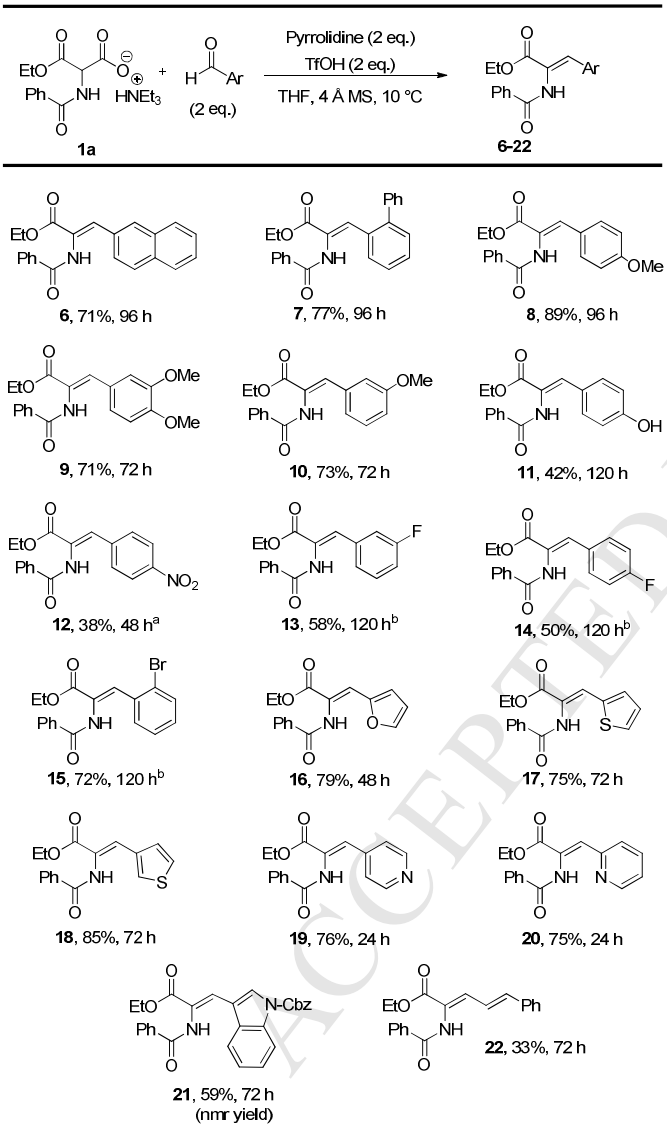

**Scheme 2**: Assessment of various protecting groups.

With these optimized conditions in hand, the effect on the reaction of various protecting groups at the nitrogen of MAHO was investigated (Scheme 2). *N*-acetyl **1b** afforded a similar yield of 85%. The reaction with *N*-(4-methylbenzoyl) **1c** and *N*-(4-methoxybenzoyl) **1d** gave slightly lower yields, **3c** in 74% and **3d** in 70% yield respectively. Benzyl carbamate *N*-Cbz **1e** generated Doebner product **3e** in 65% yield.

The scope of the reaction with various aromatic aldehydes was then evaluated (table 2). We started with 2-naphthyl-carboxaldehyde and the hindered 2-phenylbenzaldehyde. The corresponding dehydroamino esters **6** and **7** were obtained in 71% and 77% yields, respectively. With benzaldehydes bearing an electron donating group (4-MeO, 3,4-diMeO and 3-OMe), the reaction afforded products **8**, **9**

and **10** in very good yields (up to 89%). In the presence of a hydroxyl group, 4-hydroxybenzaldehyde reacted slowly to provide the compound **11** in 42% yield. Even with 4-nitrobenzaldehyde (one equivalent) which is difficult to transform into an iminium intermediate, the desired compound **12** was isolated, albeit in moderate yield (38%). This low yield was due to a competitive decarboxylative aldol reaction.[26] Halogen-substituted benzaldehydes were successfully tested with MAHO **1a** at 0 °C. At this temperature, Doebner condensation prevails to provide the compounds **13** (58%), **14** (50%) and **15** (72%). Furthermore, we extended our study to heterocyclic aldehydes such as furfural, 2- and 3-thiophenecarboxaldehyde, 2- and 4-pyridinecarboxaldehyde. Electron-rich or -poor aromatic aldehydes reacted similarly in our conditions and the π-conjugated heterocyclic products **16-20** were obtained in very good yields between 75% and 85%.

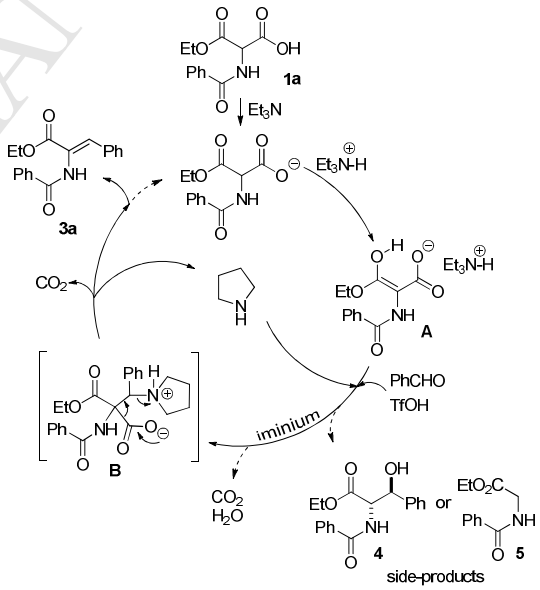
**Table 2**
Synthesis of various substituted *Z*-dehydroamino esters




[a] performed with 1 eq. of aldehyde, TfOH, and pyrrolidine.[26b] Performed at 0 °C.

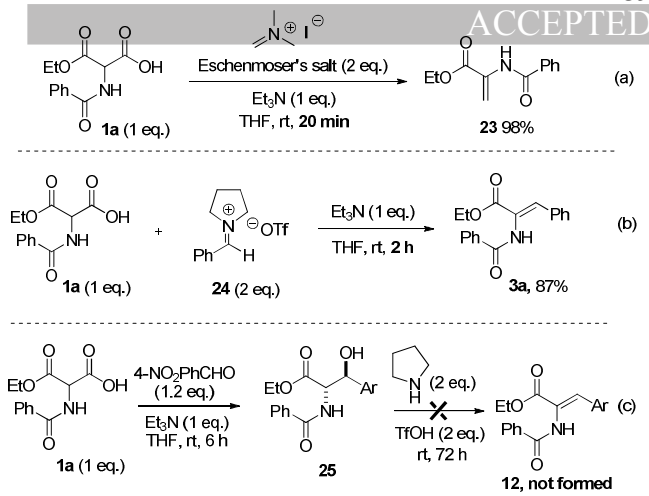
Indole carboxaldehyde proposed a significant challenge. In our first attempts, indole-3-carboxaldehyde or 1-methylindole-3-carboxaldehyde were unreactive substrates (data not shown). However, with a Cbz group the reaction led to the product **21** in 59% NMR yield.[27] Finally the Doebner condensation with cinnamaldehyde afforded diene-amino ester **22** in 33% yield. Enolizable aldehydes such as crotonaldehyde or butyraldehyde did not lead to the desired products, only glycine **5** was observed after 72 h of reaction (data not shown). However, the conditions developed by Xu and co-workers should provide the Doebner products with these aliphatic aldehydes.[22]

Next, we investigated the mechanism operating under our conditions by performing a few additional experiments. Our initial strategy was based on a nucleophilic addition of an amine to aldehyde forming an iminium species. After the addition of the α-amido MAHO **1a**, a spontaneous decarboxylative β-elimination reaction would occur from the intermediate β-ammonium carboxylate **B** to generate the double bond under mild conditions. Thus, the reaction begins simultaneously by deprotonation of MAHO with triethylamine (activated MAHO **A**) and by the iminium formation in presence of TfOH (scheme 3). The key step could be the addition of the secondary amine to the aldehyde in order to generate the highly electrophilic iminium species. To confirm this hypothesis, we tested Eschenmoser's salt with MAHO **1a** and $Et_3N$, the reaction was complete in less than 20 minutes to give product **23** in a quantitative yield (scheme 4a). Similarly, the isolated iminium triflate **24**[25] reacted completely with **1a** after only 2 h and compound **3a** was obtained in an excellent yield without side products (Scheme 4b). These experiments prove a rapid addition of the activated MAHO **1a** to the electrophilic iminium followed by the spontaneous decarboxylative β-elimination to afford the Doebner product. Therefore, the limiting step of this overall process is the slow condensation of the aldehyde with pyrrolidine to form the highly electrophilic iminium which was confirmed by the reaction of **1a** and 4-nitrobenzaldehyde affording the expected dehydroamino esters **12** in a low yield (table 2).




**Scheme 3:** Plausible mechanism for the Doebner condensation.

Moreover, adding pyrrolidine and trifluoromethanesulfonic acid to β-hydroxy-α-amino ester **25** did not generate the dehydrated product **12** even after 72 h (scheme 4c). This result completes the previous experiments insofar as, during the Doebner condensation, dehydroamino esters are not formed by dehydration of putative hydroxyl amino ester intermediates such as **25** or **4**.




**Scheme 4:** Additional experiments for mechanistic studies.

According to the literature, the reaction between unsubstituted hemimalonates and aldehydes in presence of pyridine (or DMAP) and $Ac_2O$ gives a mixture of *E*- and *Z*-alkenes. With $\alpha$-amido MAHOs, Xu et al. have observed a significant evolution of the ratio in favor of the *Z*-alkene (a ratio similar to Horner-Wadsworth-Emmons condensation) but the *E*-isomer is always present in small amounts and contaminates the crude reaction.[22] Hengartner et al. were able to convert *E*-alkene into the more stable *Z*-isomer by treatment with NaOEt.[28] Under our conditions, the Doebner condensation of α-amido MAHOs gives exclusively the thermodynamically more stable *Z*-dehydroamino esters and the minor diastereomers were not observed during the process ($^1$H NMR monitoring).

## 3. Conclusion

In summary, we have developed an efficient and direct approach to prepare *Z*-dehydroamino acid derivatives according to the Knoevenagel-Doebner reaction. A variety of $\alpha$-amido MAHOs and aromatic aldehydes in the presence of pyrrolidine, triethylamine and trifluoromethanesulfonic acid afforded various dehydroamino esters in moderate to excellent yields. The developed Doebner reaction using 2-amido MAHOs with aromatic aldehydes complements well the already known conditions. The methodology displays interesting features such as readily available starting materials and a simple experimental procedure which could be useful for large-scale applications. It is therefore a practical tool to access new scaffolds for making synthetic peptides.

## 4. Experimental section

### 4.1. General

All reagents were purchased from Acros Organics, Sigma Aldrich, Alfa Aesar, TCI or Fluka and were used without further purification and used as received. Solvents were used in RPE grade without further purification. Anhydrous solvents were obtained from a PURESOLV SPS400 apparatus developed by Innovative Technology Inc. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX 400 MHz or a Bruker DRX 500 MHz spectrometer. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$, acetone-d6, $D_2O$). The chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane for $^1$H and $^{13}$C nuclei, and coupling constants are indicated in Hz. Abbreviations for signal coupling are as follows: s = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet; quin = quintet; m = multiplet; br = broad signal. To assign the signals to the different proton and carbon atoms, as well as the relative stereochemistry of the cycloadducts, additional 2D NMR experiments (COSY, HSQC, HMBC) and NOESY experiments were performed. Mass spectra were obtained on a GC/MS Saturn 2000 spectrometer. High-resolution mass spectra (HRMS) were performed on Q-TOF Micro WATERS by electrospray ionisation (ESI). Infrared (IR) spectra were recorded with a Perkin Elmer 16 PC FT-IR ATR spectrometer, using the pure product (oil or solid). Thin Layer Chromatography (TLC) was run on pre-coated aluminum plates of silica gel 60 F-254 (Merck). Flash chromatography was performed on silica gel column (Merck silica gel, 40-63 µm) using air pressure. Compounds **1b**[29], **1e**[30] were known in literature and synthesized as described below.

### 4.2. General procedure for the preparation of malonic half oxyesters (MAOHs)

Diethylmalonate (1 eq.) was diluted in EtOH. A KOH solution (1 eq.) in 10:1 EtOH/water was added dropwise at 0 °C. The mixture was stirred 15 h. A 1M HCl solution was added dropwise until pH = 1, then the mixture was saturated with NaCl and extracted twice with ethyl acetate. The organic layer was dried over $MgSO_4$ and solvents removed under reduced pressure. All malonic half oxyesters were easily detected by TLC (Rf = 0 in 60/40 cyclohexane/EtOAc)

### 4.3. General procedure for Doebner reaction

**Procedure I**: With aldehyde

Under inert atmosphere, triethylamine (0.2 mmol) was added to a solution of malonic acid half ester (0.2 mmol) in dry THF (0.6 ml) in the presence of molecular sieve (50 mg). At 0 °C, pyrrolidine (0.4 mmol) was added dropwise followed by trifluoromethanesulfonic acid (0.4 mmol) and aldehyde (0.4 mmol). The mixture was stirred at 10 °C for 24-120 h. The solution was concentrated under reduced pressure. The residue was directly purified by flash chromatography.

**Procedure II**: With iminium

Triethylamine (0.2 mmol) was added to a solution of malonic acid half ester **2** (0.2 mmol) in dry THF (0.6 ml). Iminium (0.4 mmol) was added to the solution and the reaction mixture was stirred at room temperature for 0.3-2 h. The solution was concentrated under reduced pressure. The residue was directly purified by flash chromatography.

*4.3.1. 3-Ethoxy-2-benzamido-3-oxopropanoic acid (**1a**).* White solid, mp 105-106 °C, 95% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, t, *J* = 7.2 Hz), 7.51-7.55 (1H, m), 7.39-7.45 (3H, m), 5.37 (d, *J* = 6.8 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.3, 166.6, 132.8, 132.6, 129.0, 127.7, 63.5, 57.2, 14.2. IR (neat) 3299, 2926, 1748, 1709, 1639, 1520, 1248, 1197, 1172, 711, 691 cm$^{-1}$. HRMS *m/z* (ESI): calcd. for $C_{12}H_{13}NO_5Na$ $[M+Na]^+$: 274.0691, found: 274.0703.

*4.3.2. 3-Ethoxy-2-(4-methylbenzamido)-3-oxopropanoic acid (**1c**).* White solid, mp 114-115 °C, 61% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.26 (b, 1 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 5.81 (b, 1H), 5.33 (d, *J* = 6.4 Hz, 1H), 3.04 (s, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.5, 166.6, 162.9, 129.4, 124.5, 113.9, 63.1, 57.0, 55.5, 13.9. IR (neat) 3397, 2982, 1738, 1605, 1497, 1257, 1183, 1024, 767 cm$^{-1}$. HRMS *m/z* (ESI) calcd for $C_{13}H_{14}NO_6$ $[M-H]^-$: 280.0821, found: 280.0814.

*4.3.3. 3-Ethoxy-2-(4-methoxybenzamido)-3-oxopropanoic acid (**1d**).* White solid, mp 109-112 °C. 52% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2 H), 6.71 (b, 1H), 5.35 (d, *J* = 6.4 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.4, 168.0, 166.3, 143.2, 129.5, 129.4, 127.4, 63.1, 56.9, 21.5, 13.9. IR (neat) 3305, 3131, 1749, 1726, 1634, 1523, 1499, 1238, 1185, 1164, 759, 669 cm$^{-1}$. HRMS *m/z* (ESI) calcd for $C_{13}H_{16}NO_5$ $[M+H]^+$: 266.1028, found: 266.1035.

*4.3.4. (Z)-Ethyl 2-benzamido-3-phenylacrylate (**3a**).* White solid, mp 128-130 °C, 48.6 mg, 82% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.77 (b, 1H), 7.56 (t, *J* = 8.4 Hz, 1H), 7.47-7.51 (m, 5H), 7.30-7.36 (m, 3H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.9, 165.7, 134.2, 133.9, 132.4, 131.6, 129.9, 129.6, 129.0, 128.8, 127.7, 124.7, 62.2, 14.5. IR (neat) 3262, 2924, 1709, 1644, 1635, 1518, 1486, 1239, 1141, 1090, 712 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1287; found 296.1274.

*4.3.5. (Z)-Ethyl 2-acetamido-3-phenylacrylate (**3b**).* Solid, mp 92-93 °C, 39.5 mg, 85% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.8 Hz, 2H), 7.35-7.38 (m, 4H), 6.97 (b, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.1, 165.6, 134.1, 132.1, 129.9, 129.6, 128.8, 124.8, 62.1, 23.7, 14.5. IR (neat) 3242, 2983, 1716, 1665, 1642, 1513, 1490, 1371, 1251, 1203, 691 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$: 256.0950; found 256.0943.

*4.3.6. (Z)-Ethyl 2-(4-methylbenzamido)-3-phenylacrylate (**3c**).* Solid, mp 120-123 °C, 45.8 mg, 74% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.39 (s, 1H), 7.23-7.30 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.5 (2C), 142.8, 134.1, 130.9, 130.8, 129.6, 129.4, 129.3, 128.6, 127.5, 124.5, 61.9, 21.5, 14.3. IR (neat) 3304, 2981,1724, 1636, 1525, 1497, 1490, 1250, 1189, 752, 667 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1443; found 310.1451.

*4.3.7. (Z)-Ethyl 2-(4-methoxybenzamido)-3-phenylacrylate (**3d**).* Solid, mp 117-119 °C, 45.5 mg, 70% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.69 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.43 (s, 1H), 7.29-7.34 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.5, 165.1, 162.8, 134.1, 130.6, 129.6, 129.4, 129.3, 128.6, 126.0, 124.6, 113.9, 61.9, 55.5, 14.3. IR (neat) 3286, 2972, 1709, 1643, 1603, 1479, 1246, 1175, 1026, 761, 690 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$: 348.1212; found 348.1214.

*4.3.8. (Z)-Ethyl 2-(((benzyloxy)carbonyl)amino)-3-phenylacrylate (**3e**).* Colorless oil, 42.3 mg, 65% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43-7.53 (m, 2H), 7.25-7.27 (m, 8H), 6.29 (b, 1H), 5.04 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.3, 153.9, 136.0, 133.8, 136.0, 133.8, 131.4, 129.8, 129.4, 128.6, 128.5, 128.3, 128.2, 124.5, 67.5, 61.8, 14.2. IR (neat) 3296, 2977, 1699, 1498, 1312, 1254, 1221, 1201, 1039, 1024, 734, 690 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$: 348.1212; found 348.120.

*4.3.9. (Z)-Ethyl 2-benzamido-3-(naphthalen-2-yl)acrylate (**6**).* White solid, mp 99-102 °C, 49.1 mg, 71% yield. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.03 (d, *J* = 8.2 Hz, 1H), 7.78-7.89 (m, 3H), 7.68-7.71 (m, 3H), 7.46-7.61 (m, 4H), 7.36-7.43 (m, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) *δ* 165.6, 165.0, 133.0, 133.5, 132.1, 131.2, 131.1, 129.5, 128.8, 128.7, 127.5, 127.4, 127.3, 126.7, 126.3, 126.2, 125.3, 124.3, 62.0, 14.3. IR (neat) 3229, 2977, 1636, 1509, 1481, 1292, 1241, 768, 689 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{22}H_{20}NO_3$ $[M+H]^+$: 346.1443; found: 346.1437.

*4.3.10. (Z)-Ethyl 3-([1,1'-biphenyl]-2-yl)-2-benzamidoacrylate (**7**).* White solid, mp 138-140 °C, 57.2 mg, 77% yield. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.58-7.63 (m, 3H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.33-7.37 (m, 3H), 7.06-7.28 (m, 9H), 4.07 (q, *J* = 7.2 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) *δ* 165.3, 165.2, 141.9, 140.4, 133.9, 132.7, 132.0, 130.6, 130.2, 129.9, 129.0, 128.7, 128.3, 128.1, 128.0, 127.5, 127.4, 127.1, 124.8, 61.7, 14.2. IR (neat) 3281, 2967, 1709, 1651, 1509, 1476, 1266, 1244, 730, 705 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{24}H_{22}NO_3$ $[M+H]^+$: 372.1600; found: 372.1594.

*4.3.11. (Z)-Ethyl 2-benzamido-3-(4-methoxyphenyl)acrylate (**8**).* Solid, mp 136-137 °C, 58.0 mg, 89% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.77 (s, 1H), 7.54-7.58 (m, 1H), 7.47-7.50 (m, 5H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.7, 165.6, 160.5, 133.9, 132.2, 131.8, 131.7, 128.8, 127.5, 126.5, 121.9, 114.1, 61.7, 55.3, 14.3. IR (neat) 3289, 2927, 1713, 1649, 1603, 1509, 1477, 1244, 1173, 728, 706 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1392; found 326.1386.

*4.3.12. (Z)-Ethyl 2-benzamido-3-(3,4-dimethoxyphenyl)acrylate (**9**).* White solid, mp 112-114 °C, 50.5 mg, 71% yield. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.90 (d, *J* = 7.4 Hz, 2H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.46-7.50 (m, 3H), 7.10-7.14 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 1H), 3.68 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) *δ* 165.6 (2C), 150.2, 148.6, 133.8, 132.2, 132.1, 128.8, 127.4, 127.0, 126.7, 124.1, 112.2, 110.8, 61.8, 55.8, 55.6, 14.3. IR (neat) 3309, 2980, 1713, 1649, 1513, 1480, 1246, 1140, 1023, 721 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{20}H_{21}NO_5Na$ $[M+Na]^+$: 378.1317; found: 378.1318.

*4.3.13. (Z)-Ethyl 2-benzamido-3-(3-methoxyphenyl)acrylate (**10**).* White solid, mp 82-84 °C, 47.5 mg, 73% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.4 Hz, 2H), 7.59 (s, 1H), 7.37-7.40 (m, 1H), 7.28-7.32 (m, 2H), 7.05-7.09 (m, 2H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 6.69 (dd, *J* = 2.2, 8.2 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.53 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.6, 165.3, 135.2, 133.6, 132.2, 131.1, 129.6, 128.8, 127.4, 124.7, 122.2, 115.5, 114.4, 61.9, 55.1, 14.3. IR (neat) 3279, 2982, 1716, 1651, 1511, 1478, 1295, 1271, 1236, 709, 689 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$: 348.1212; found 348.1219.

*4.3.14. (Z)-Ethyl 2-benzamido-3-(4-hydroxyphenyl)acrylate (**11**).* White solid, mp 100-103 °C, 26.2 mg, 42% yield. $^1$H NMR (400 MHz, $CD_3OD$) *δ* 7.97 (d, *J* = 7.4 Hz, 2H), 7.53-7.56 (m, 6H), 7.79 (d, *J* = 8.6 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) *δ* 165.5, 165.7, 159.2, 135.7, 133.6, 131.8, 128.3, 127.3, 124.7, 122.4, 115.2, 61.8, 13.2. IR (neat) 3264, 2928, 1695, 1644, 1602, 1508, 1478, 1202, 1251, 1165, 708 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{18}H_{18}NO_4$ $[M+H]^+$: 312.1236; found: 312.1225.

*4.3.15. (Z)-Ethyl 2-benzamido-3-(4-nitrophenyl)acrylate (**12**).* White solid, mp 165-166 °C, 25.9 mg, 38% yield. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.21 (br, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.56-7.59 (m, 3H), 7.47-7.51 (m, 3H), 4.38 (q, *J* = 8.0 Hz, 2H), 1.40 (t, *J* = 8.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 165.1, 164.8, 147.3, 141.6, 133.4, 132.8, 130.0, 129.1, 127.6, 126.4, 126.1, 123.7, 62.8, 14.4. IR (neat) 3273, 2984, 1719, 1660, 1517, 1478, 1343, 1305, 1253 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{18}H_{16}N_2O_5Na$ $[M+Na]^+$: 363.0957; found: 363.0947.

*4.3.16. (Z)-Ethyl 2-benzamido-3-(3-fluorophenyl)acrylate (**13**).* The experiment was performed at 0 °C.White solid, mp 135-136 °C, 36.4 mg, 58% yield. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.86 (d, *J* = 7.6 Hz, 3H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.43 (s, 1H), 7.27-7.32 (m, 2H), 7.19 (d, *J* = 9.9 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) *δ* 165.4, 165.2, 162.2 (d, *J* = 246.4 Hz), 136.3 (d, *J* = 8.2 Hz), 133.5, 132.3, 130.0 (d, *J* = 8.3 Hz), 129.4, 128.8, 127.4, 125.4 (d, *J* = 2.8 Hz), 124.9, 116.2 (d, *J* = 21.3 Hz), 116.1 (d, *J* = 22.4 Hz), 62.2, 14.2. $^{19}$F NMR (376 MHz, $CDCl_3$) *δ* -112.7. IR (neat) 3272, 2985, 1719, 1652, 1509, 1479, 1291, 1230, 1153, 709, 686 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{18}H_{16}NO_3FNa$ $[M+Na]^+$: 336.1012; found: 336.1004.

*4.3.17. (Z)-Ethyl 2-benzamido-3-(4-fluorophenyl)acrylate (**14**).* The experiment was performed at 0 °C. White solid, mp 120-121 °C, 31.4 mg, 50% yield. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.62-6.66 (m, 3H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.27-7.29 (m, 4H), 7.04 (s, 1H), 6.80 (t,

*J* = 8.6 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 165.4 (2C), 162.6 (d, *J* = 250.0 Hz), 133.6, 132.3, 131.7 (d, *J* = 8.4 Hz), 130.3 (d, *J* = 3.3 Hz), 130.2, 128.8, 127.5, 123.6, 115.6 (d, *J* = 21.8 Hz), 62.0, 14.3. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ -110.2. IR (neat) 3273, 2986, 1717, 1652, 1601, 1507, 1479, 1251, 1230, 708 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{18}H_{16}NO_3FNa$ $[M+Na]^+$: 336.1012; found: 336.1013.

*4.3.18. (Z)-Ethyl 2-benzamido-3-(2-bromophenyl)acrylate (**15**).* The experiment was performed at 0 °C. White solid, mp 106-107 °C, 53.9 mg, 72% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, *J* = 7.1 Hz, 3H), 7.62 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.51-7.55 (m, 2H), 7.42-7.47 (m, 3H), 7.21 (td, *J* = 0.8, 7.6 Hz, 1H), 7.14 (td, *J* = 1.6, 7.6 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 165.1, 165.0, 135.1, 133.6, 132.9, 132.2, 130.1, 129.3, 128.8, 128.5, 127.4, 127.2, 126.0, 124.4, 62.2, 14.2. IR (neat) 3286, 2977, 1714, 1648, 1509, 1479, 1287, 1249, 1024, 705 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{18}H_{16}NO_3BrNa$ $[M+Na]^+$: 396.0211; found: 396.0208.

*4.3.19. (Z)-Ethyl 2-benzamido-3-(furan-2-yl)acrylate (**16**).* White solid, mp 124-125 °C, 45.1 mg, 79% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (s, 1H), 7.93 (d, *J* = 6.8 Hz, 2H), 7.56-7.59 (m, 1H), 7.48-7.52 (m, 3H), 7.08 (s, 1H), 6.57 (d, *J* = 3.4 Hz, 1H), 6.47 (dd, *J* = 1.8, 3.4 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.6, 164.9, 150.1, 144.4, 133.7, 132.2, 128.8, 127.6, 123.2, 115.9, 115.3, 112.3, 61.7, 14.2. IR (neat) 3292, 2982, 1715, 1650, 1509, 1480, 1286, 1259, 1210, 1182, 1022, 716 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{16}H_{15}NO_4Na$ $[M+Na]^+$: 308.0899; found: 308.0907.

*4.3.20. (Z)-Ethyl 2-benzamido-3-(thiophen-2-yl)acrylate (**17**).* White solid, mp 170-173 °C, 45.2 mg, 75% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, *J* = 7.2 Hz, 2H), 7.87 (s, 1H), 7.42-7.60 (m, 5H), 7.35 (d, *J* = 3.4 Hz, 1H), 7.07 (dd, *J* = 3.4, 4.9 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.7, 164.9, 136.5, 133.9, 133.2, 132.2, 130.7, 128.8, 128.7, 127.6, 127.2, 121.6, 61.7, 14.3. IR (neat) 3281, 2972, 1714, 1648, 1628, 1512, 1471, 1261, 1198, 705 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{16}H_{15}NO_3SNa$ $[M+Na]^+$: 324.0670; found: 324.0679.

*4.3.21. (Z)-Ethyl 2-benzamido-3-(thiophen-3-yl)acrylate (**18**).* White solid, mp 177-179 °C, 51.3 mg, 85% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, *J* = 7.4 Hz, 2H), 7.68 (s, 1H), 7.46-7.57 (m, 5H), 7.26-7.28 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 165.9, 165.5, 135.1, 133.7, 132.4, 129.3, 128.8, 127.9, 127.5, 126.9, 126.1, 122.6, 61.8, 14.3. IR (neat) 3260, 2987, 1699, 1630, 1514, 1476, 1256, 1203, 1140, 1087, 705, 690 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{16}H_{15}NO_3SNa$ $[M+Na]^+$: 324.0670; found: 324.0685.

*4.3.22. (Z)-Ethyl 2-benzamido-3-(pyridin-4-yl)acrylate (**19**).* White solid, mp 117-120 °C, 45.0 mg, 76% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.57 (d, *J* = 3.7 Hz, 2H), 8.17 (s, 1H), 7.83-7.85 (m, 2H), 6.57 (d, *J* = 3.4 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.32-7.34 (m, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.7, 164.6, 148.8, 143.6, 133.2, 132.7, 128.9, 127.5, 127.2, 125.5, 123.4, 62.7, 14.2. IR (neat) 3265, 2967, 1721, 1633, 1514, 1476, 1287, 1249, 1016, 710, 685 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1239; found: 297.1245.

*4.3.23. (Z)-Ethyl 2-benzamido-3-(pyridin-2-yl)acrylate (**20**).* Colorless oil, 44.5 mg, 75% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 12.9 (s, 1H), 8.05 (d, *J* = 4.6 Hz, 1H), 7.71 (td, *J* = 1.8, 7.8 Hz, 1H), 7.50-7.60 (m, 3H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 4.6, 7.8 Hz, 1H), 6.34 (s, 1H) 4.40 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.4, 165.1, 155.3, 148.2, 137.2, 135.0, 133.4, 132.3, 128.7, 127.9, 125.4, 121.9, 113.3, 61.8, 14.1. IR (neat) 3063, 1724, 1673, 1635, 1469, 1421, 1309, 1279, 1254, 1208, 1145, 698 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{17}H_{16}N_2O_3Na$ $[M+Na]^+$: 319.1059; found: 319.1073.

*4.3.24. (Z)-Benzyl 3-(2-benzamido-3-ethoxy-3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylate (**21**).* Yellow solid, mp 122-124 °C, 54.2 mg, 59% NMR yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (d, *J* = 7.5 Hz, 1H), 7.68-7.83 (m, 6H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.22-7.34 (m, 7H), 5.31 (s, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 165.2 (2C), 150.3, 134.9, 134.5, 133.8, 132.1, 129.5, 128.8, 128.74, 128.72, 128.3, 127.4, 127.3, 125.4, 123.6, 122.3, 119.0, 115.3, 115.1, 69.0, 61.9, 14.3. IR (neat) 3255, 2977, 1742, 1711, 1666, 1481, 1453, 1339, 1233, 1216, 1082, 753, 698 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{28}H_{24}N_2O_5Na$ $[M+Na]^+$: 491.1583; found: 491.1591.

*4.3.25. (2Z,4E)-Ethyl 2-benzamido-5-phenylpenta-2,4-dienoate (**22**).* Yellow solid, mp 95-96 °C, 21.2 mg, 33% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, *J* = 7.2 Hz, 2H), 7.82 (br s, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.42-7.53 (m, 4H), 7.23-7.29 (m, 4H), 6.87-7.01 (m, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).$^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 165.9, 165.4, 140.1, 136.7, 134.3, 132.3, 131.7, 129.1, 129.0, 128.9, 127.7, 127.6, 124.5, 123.3, 62.0, 14.5 IR (neat) 3288, 2924, 1713, 1647, 1508, 1478, 1276, 1230, 967, 705 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{20}H_{20}NO_3$ $[M+H]^+$: 322.1443; found: 322.1440.

*4.3.26. Ethyl 2-benzamidoacrylate (**23**).* Colorless oil, 43.0 mg, 98% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.55 (br s, 1H), 7.83 (d, *J* = 8.0 Hz 2H), 7.45-7.56 (m, 3H), 6.78 (s, 1H), 5.99 (s, 1H), 4.33 (q, *J* = 8.0 Hz, 2H), 1.37 (t, *J* = 8.0 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.1, 164.6, 134.6, 132.3, 131.5, 129.1, 127.2, 108.9, 62.7, 14.4. IR (neat) 3355, 2983, 1730, 1651, 1604, 1244, 1095, 1024, 710, 691 cm$^{-1}$. HRMS *m/z* (ESI) calcd. for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0974; found: 220.0974.

**Acknowledgements**

The Ministery of Higher Education and Research, the "Region Basse Normandie" (fellowships to Y.S.), CNRS, and the European Union (FEDER) are gratefully acknowledged for funding this work. We thank the LABEX SynOrg (ANR-11-LABX-0029) for financial support.

**Supplementary data**

Supplementary data associated with this article can be found in the online version, at

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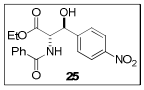
26. The following hydroxyamino ester **25** was isolated in 50% yield as the major product.




**25**

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