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Effect of phase transfer chemistry, segmented fluid flow, and sonication on the synthesis of cinnamic esters

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ABSTRACT

Wittig reaction under Phase Transfer conditions was performed in a flow reaction system. Different bases, aldehydes, phosphonium salts, and flow reaction parameters were investigated, in absence of a phase transfert catalyst. An improvement of the reaction outcome (yield and reaction time) was achieved through the immersion of the reactor into an ultrasound bath.

1. Introduction

Phase-transfer catalyst (PTC) technology is used in the commercial manufacture of more than $10 billion per year of chemicals, including pharmaceuticals, flavors & fragrances, dyes, additives, and polymers.[1] PTC technology is used in these applications because it provides many compelling benefits, primarily related to reducing the cost of manufacture of organic chemicals and pollution prevention. Among the synthetic advantages that phase transfer chemistry offers there are the ease of the procedure, the reduced formation of by-products and the improved selectivity and reactivity if compared to the same reaction in homogeneous phase.[2,3] Additionally, under the phase transfer conditions the inorganic bases (NaOH, KOH or K_2CO_3) can be used in place of more expensive and dangerous organic bases (*t*-BuOK, NaH or R_2NLi) and the dipolar aprotic solvents, such as DMF can be avoided.[4] However, in a bi-phasic system the width of the contact surface plays a crucial role because the reaction either occurs at the interface or the phase transfer catalyst has a catalytic cycle between the two phases.[5,6] For this reason, the scale-up of the reaction could be difficult and reaction time could grow longer because of the inefficiency of the mixing. Moreover, phase transfer catalysts (tetra-alkylammonium halides or crown ethers, for example) usually employed in PTC to speed up the reaction, are often toxic,[7] expensive and are eliminated with difficulty from the reaction mixture in the work-up and purification phases.

In this context, flow chemistry can be an alternative choice. In fact, among the advantages that continuous flow organic syntheses offer over the conventional batch techniques (e.g., precise control of variables, such as temperature, pressure, concentration, residence time, and heat transfer),[8,9] there is the possibility of reaching a high surface-to-volume ratio in reactions involving a fluidic biphasic system. In particular, as reported by Wirth et al.,[10] working with a T-shaped geometry of the inlet junction, a series of organic-aqueous segments are generated as shown in Figure 1 (figure on the left). As in a flow reaction system the reactant solutions flow into very long channels, the total contact surface is enormously increased if compared to a traditional bi-phasic batch reaction. In addition, the interaction of the fluids with the channel wall generates an internal vortex that leads to a continuous refreshing of the interface.

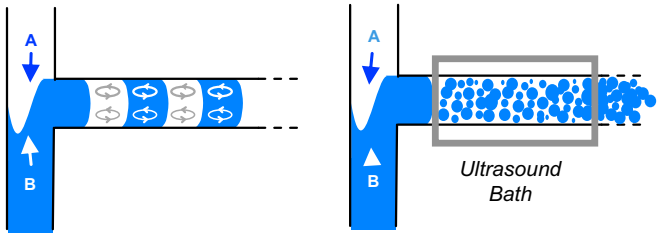

Figure 1. Segmented flow (on the left) and effect of sonication on segmented flow (on the right).

A further increase of the interface area can be achieved by the combination of flow chemistry and sonochemistry. Indeed, immersing the flow reactor in an ultrasound bath, irregular sized segments, and emulsion are formed (Fig. 1, on the right). In addition, the propagation and the consequent effects of the sonic waves are significantly improved when the reaction is performed into really small channels (diameter: 10–100 μm) than in a standard flask.

To prove such hypothesis, we employed a model Wittig olefin-forming reaction. The cinnamic esters and close analogs are broadly employed in the chemical industries, in particular for the

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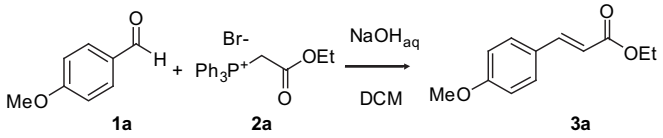
production of flavors, synthetic dye, and perfumes.[11] Moreover, the cinnamic moiety occurs in several molecules with a wide spectrum of biological activities, for example, the 4-methoxy ethyl cinnamate **3a** (Scheme 1) is reported to be a monoamine oxidase inhibitor.[12] Several methods for the synthesis of this class of compounds have been published so far.[13] However, due to the importance of cinnamic esters and derivatives, the development of new methodologies for their multi-gram synthesis is still of great interest.

2. Results and discussion

In particular, we focused our attention on the reaction between anisaldehyde **1a** and (ethoxycarbonylmethyl)-triphenylphosphonium bromide **2a** to obtain ethyl 4-methoxy cinnamate **3a** (Scheme 1).



Scheme 1. Synthesis of 4-methoxy ethyl cinnamate.

This reaction is broadly reported in the literature; for instance, Avery et al. claimed a quantitative yield by treating **2a** with potassium *tert*-butoxide in anhydrous diethyl ether under an inert atmosphere, followed by reaction with **1a** (room temperature for 48 h).[14] In another example, Frattini et al. achieved 54% conversion heating **1a** and **2a** under microwave irradiation at 280 W in DMSO for 5 min, whereas the same reaction refluxed for 1 h in THF afforded just 28% conversion.[15] El-Batta et al. proved that water is an effective medium for Wittig reaction over a wide range of stabilized ylides and aldehydes.[16] They reported that *p*-anisaldehyde reacts slowly with ylides to give 66% of cinnamic ester after 4 h at 20 °C, even though a little formation of undesired *Z*-regiosomer was observed (*E*/*Z*-ratio: 92:8). At the same time, heating the reaction to 90 °C for 30 min increased the yield of cinnamic ester to 90% without affecting the *E*/*Z*-ratio. The efficiency of water as a reaction medium compared to the organic solvents is evident in view of the fact that the same reaction has been reported in refluxing DCM (4 h, 8%),[17] in refluxing benzene (2 days, 73% yield)[17] or in ionic liquid at 60 °C (3 days, 82% yield).[18] Nevertheless, the poor solubility of reagents and products in water can be considered as a relevant limit of this procedure. Indeed different protocols have to be set up depending on the particular nature of the aldehydes (e.g., solid or liquid). Moreover, the poor solubility of the reagents makes the scaling-up process complicated.

In this paper we report a protocol that allows achieving stereoselectively compound **3a** in 96% yield in five minutes, without using thermal or microwave heating, anhydrous conditions and phase transfer catalyst. Moreover, this protocol can be also readily scaled up with no need of any further optimization or set-up process.

We first conducted a comparison study between the reaction in a standard batch process and in a flow system, to evaluate the effect of the interfacial area on the yield (Table 1). A solution of **1a** and **2a** in DCM and a solution of NaOH in water were vigorously stirred in presence of a catalytic amount (0.5%) of tetra-butylammonium bromide (TBAB) at room temperature for 24 h.[19] This reaction (entry 1) afforded, after chromatography purification, compound **3a** in 55% yield. The same reaction was then run in a flow system (Vapourtec® R2–R4 series flow reactor system) using the same amount of reagents, concentration and temperature. Thus, the organic solution of **1a** and **2a** and the aqueous solution of NaOH were simultaneously pumped into the flow reactor (Reactor volume 10 mL; reagents flow rate of 1 mL min^{-1}) using a T-inlet junction. As a result, we obtained an improved yield (78%, entry 2), in a shorter reaction time (total: 30 min; residence time: 5 min) and without formation of *Z*-stereoisomer. Encouraged by the surprising impact of flow chemistry, we repeated the reaction in the flow system without the phase transfer catalyst (TBAB). In this case we obtained a result comparable to the flask system (63% yield, entry 3) but in a considerably shorter time (total: 30 min; residence time: 5 min) and avoiding PTC.

Table 1
Comparison of reaction carried out in batch and using the flow-reactor

Entry	System	Isolated yield[a] (%)
1	Flask reaction[b]	55
2	Flow system[c]	78
3	Flow system without PTC[c]	63

[a] Product purified by flash chromatography on silica gel.
[b] Reaction carried out as described in Ref. 19.
[c] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/1/1.1 (with or without 0.5% of TBAB).

Given these encouraging results, we further investigated the reaction reported as entry 3 in Table 1; we tried to optimize the reaction conditions and studied the influence of different parameters on the outcome of the reaction. In a first set of experiments, we studied the influence of temperature, flow rate, and solvent on the reaction yield (Table 2).

Table 2
Optimization of experimental parameters

Entry[a]	Temperature (°C)	Reagent flow rate (mL/min)	Solvent	Isolated yield[b] (%)
1	rt	1	DCM	63
2	50	1	DCM	58
3	100	1	DCM	0
4	rt	2	DCM	40
5	rt	1	Toluene [c]	44
6	rt	1	EtOAc[c]	33
7	rt	1	THF[c]	49

[a] Reactor volume: 10 mL; Molar ratio: aldehyde/phosponium salt/NaOH=1/1/1.1 (without PTC).
[b] Product purified by flash chromatography on silica gel.
[c] Presence of 20% of CH_3CN is needed to completely dissolve the phosponium salt.

The ambient temperature (63% yield, entry 1) turned out to be the best compromise of a good yield without degradation of reagents and products. In fact, the yield slightly decreased when the reaction was conducted at 50 °C (58%, entry 2) and completely dropped at 100 °C (entry 3).

The reaction yield also decreased when the flow rate was increased. In fact, compound **3a** was collected in 40% yield conducting the same reaction as entry 1 with a flow rate of 2 mL min^{-1} (entry 4). On the other hand, lowering the flow rate led to the formation of particulate matter in the microchannel of the flow system that might plug the reactor.

As far as the solvent is concerned, the reaction was repeated replacing DCM with the typical solvents used in the phase transfer chemistry, namely Toluene, EtOAc, and THF (entries 5–7). As the solubility of the phosphonium salt in these solvents is lower than in DCM, a little amount of acetonitrile had to be added to get clear solutions. Nevertheless, DCM proved to be the best solvent for this reaction.

Then, the reaction was further studied varying the stoichiometric ratio of the reagents, as summarized in Table 3.

Table 3
Optimization of stoichiometric ratio

Entry[a]	Aldehyde (equiv)	Phosphonium salt (equiv)	NaOH (equiv)	Isolated yield[b] (%)
1	1	1	1	63
2	1	1	10	56
3	2	1	2	43
4	1	2	2	85
5	1	5	5	88

[a] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; No PTC was used.
[b] Product purified by flash chromatography on silica gel.

The best result was obtained working with an excess of phosponium salt and base, as reported in entry 4 (85% yield; aldehyde: phosponium salt: NaOH=1:2:2) or in entry 5 (88% yield; aldehyde: phosponium salt: NaOH=1:5:5). Nevertheless, this last protocol entails both a greater waste of reagents and a more complicated final purification, without a significant improvement in the reaction yield compared to the conditions of entry 4.

At last we studied the effect of sonication on the reaction carried out both in batch and in the flow system (Table 4).

Table 4
Effect of sonication on reaction carried out in batch or in the flow-reactor without using PTC

Entry	System	Time	Sonication	Isolated Yield[a] (%)
1	Flask[b]	1 h	No	—
2	Flask[b]	1 h	Yes	70
3	Flow[c]	5 min[d]	No	63
4	Flow[c]	5 min[d]	Yes	96

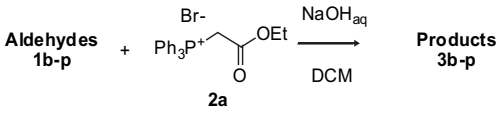
[a] Product purified by flash chromatography on silica gel.
[b] Reaction carried out as described in Ref. 19 but without any phase transfer catalyst.
[c] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/2/2 (without PTC).
[d] Residence time.

As expected, no product was formed after one hour when the reaction was conducted in a flask without sonication (entry 1). Conversely, the same reaction carried out in an ultrasound bath (entry 2) led to the desired product in 70% yield, clearly showing the positive effect of sonication on the reaction rate. As already reported, the reaction conducted in flow instrument, without PTC and sonication gave desired product in 63% yield. Finally, with the aim of verifying if the combination of segmented flow and sonochemistry could positively affect the yield, we ran the same reaction in a flow system, immersing the PTFE tubing reactor in an ultrasound bath maintained at 25 °C. In this case we achieved a complete conversion of aldehyde **1a** into the desired *E*-cinnamic ester **3a** (*Z*-stereoisomer was not formed), which was collected in 96% yield after chromatographic purification. The combination of flow chemistry and sonochemistry allowed the desired compound to be formed in excellent yield, in high *E*-selectivity, without any phase transfer catalyst and using a continuous process.

As a next step, the effectiveness and reproducibility of the optimized reaction conditions (Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/2/2; without PTC) were evaluated varying the reagents reported in Scheme 1.

In the first instance, reaction was performed replacing aldehyde **1a** with the other aldehydes listed in Table 5.

Table 5
Aldehydes investigation



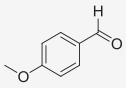
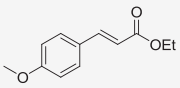
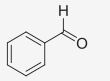
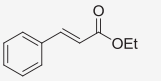
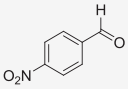
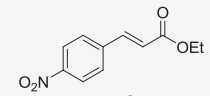
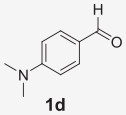
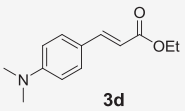
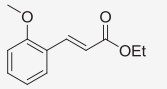
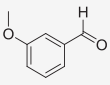
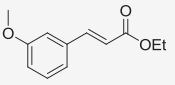
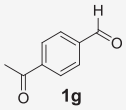
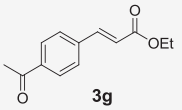
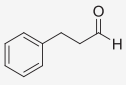
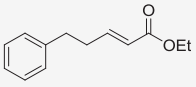
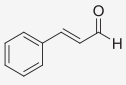
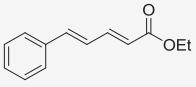
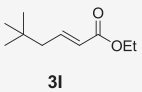
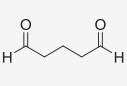
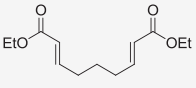
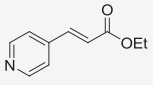
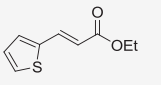
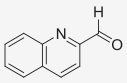
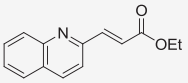
Entry[a]	Aldehydes	Products[b]	Isolated yield[c] (%)
1	 1a	 3a	96
2	 1b	 3b	98
3	 1c	 3c	98
4	 1d	 3d	55
5	 1e	 3e	83[d]
6	 1f	 3f	86
7	 1g	 3g	37
8	 1h	 3h	63
8	 1i	 3i	89
9	 1l	 3l	53
10	 1m	 3m	41[e]
11	 1n	 3n	75
12	 1o	 3o	100

Table 5 (*continued*)

Entry[a]	Aldehydes	Products[b]	Isolated yield[c] (%)
13	 1p	 3p	48

[a] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/2/2 (without PTC).
[b] The *Z*-stereoisomer was not revealed in UPLC-MS analysis.
[c] Product purified by flash chromatography on silica gel.
[d] E/Z stereoisomers in 6:1 ratio as determined by ^{1}H NMR.
[e] Molar ratio: aldehyde/phosponium salt/NaOH=1/4/4.

An almost quantitative yield (98%, entry 2) was obtained using benzaldehyde **1b** as the starting material, proving the presence of an electron-releasing group is not strictly required to have a complete conversion. The same yield was also achieved replacing the methoxy group with the electron-withdrawing nitro group (entry 3). When aldehyde **1d** was used, the corresponding product was collected in 55% yield (entry 4). It is worth noting that the literature reports that the *p*-Me$_2$-*N*-substituted benzaldehyde does not react with ylide in water at 20 °C or in refluxing DCM (4 h), whereas it affords desired product in 78% yield when conducted in MeOH, but the *E*/*Z*-ratio is significantly diminished to 3:1.[16] In order to assess to what extent the steric hindrance affects the yield, the reaction was performed using the 2-methoxybenzaldehyde **1e** (entry 5) and the product was collected again in a good yield (83% yield), even if a mixture of *E* and *Z* stereoisomers was obtained (*E*/*Z*-ratio: 6/1). On the other hand, using 3-methoxy benzaldehyde **1f** (entry 6) as the staring material, desired compound **3f** was achieved in comparable yield (86%) but without the formation of undesired *Z*-stereoisomer, suggesting the *ortho* substitution affects the regiochemistry of the reaction. As expected, the Wittig reaction conducted on 4-acetylbenzaldehyde **1g** occurred only on aldehyde moiety, even if the yield was rather modest (37%). Then we extended our study to aliphatic aldehydes (entries 8–10) and heteroaromatic aldehydes (entries 11–13). Compound **3h** was achieved in 63% yield while compound **3i** in 89%, likely thanks to the more extended conjugation. The double Wittig reaction on glutaraldehyde **1m** afforded desired compound **3m** in 41% yield. As far as the heteroaromatic aldehydes are concerned, the reaction yield was modest employing quinoline-2-carbaldehyde **1p** (48%) and isonicotinaldehyde **1n** (75%) but exceptional when using thiophene-2-carbaldehyde (quantitative), may be because of the different solubility in water of these aldehydes. It is noteworthy that in all the examples reported in Table 5 (with the only exception of entry 5) the *Z*-stereoisomer was not formed, even using cinnamaldehyde **1i**, which is known to give modest to low *E*/*Z* ratios upon exposure to stabilized ylides.[16]

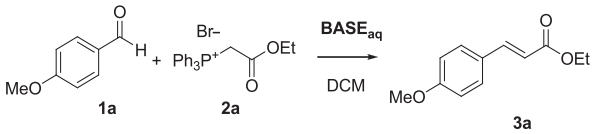
Then, the influence of different bases on reaction outcome was evaluated as reported in Table 6.

The Wittig reaction did not occur using lithium hydroxide as the base. Conversely, the reaction can be conducted using potassium carbonate without affecting the reaction yield (98%, entry 2). The use of a milder base, such as sodium bicarbonate or an organic base, such as DMAP turned out to be well tolerated too (78% yield in both cases).

In order to understand if K_2CO_3 could be a valuable alternative to NaOH, the reactions reported Table 7 were carried out.

We found that when 3,3-dimethylbutanal **1l** was used as the aldehyde (entries 1 and 2), the reaction yield was slightly decreased using potassium carbonate (41%) instead of sodium hydroxide (53%). In significant contrast, using quinoline-2-carbaldehyde **1p** (entries 3 and 4), the reaction yield was considerably improved replacing sodium hydroxide (48%) with potassium carbonate (100%).

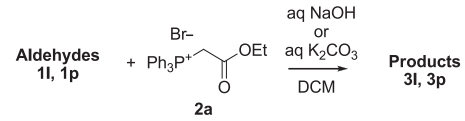
Table 6
Bases investigation

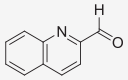
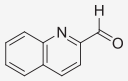


Entry[a]	Base	Isolated yield[b,c] (%)
1	NaOH	96
2	LiOH	—
3	K_2CO_3	98
4	$NaHCO_3$	78
5	DMAP	78

[a] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/2/2 (without PTC).
[b] The *Z*-stereoisomer was not revealed in UPLC-MS analysis.
[c] Product purified by flash chromatography on silica gel.

Table 7
NaOH and K_2CO_3 comparison



Entry[a]	Base	Aldehydes	Isolated yield[b,c] (%)
1	NaOH	 1l	53
2	K_2CO_3	 1l	41
3	NaOH	 1p	48
4	K_2CO_3	 1p	100

[a] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/2/2 (without PTC).
[b] The *Z*-stereoisomer was not revealed in UPLC-MS analysis.
[c] Product purified by flash chromatography on silica gel.

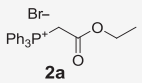
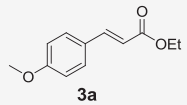
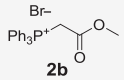
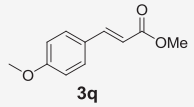
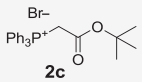
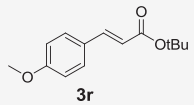
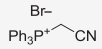
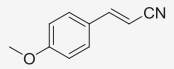
The possibility of using alternative phosphonium salts was finally investigated, as reported in Table 8.

We observed that *p*-anisaldehyde reacts with phosphonium salt **2a** and **2b** (entry 1 and 2) to give the corresponding compounds in comparable yields (96% and 95%, respectively). On the contrary, reaction between *p*-anisaldehyde and **2c** and **2d** afforded desired compounds in lower yields (42% and 48%). This result can be explained considering that traces of 3-(4-methoxyphenyl)acrylic acid (entry 3) and 3-(4-methoxyphenyl)acrylamide (entry 4) were detected in the aqueous phase of these reactions.

At last, we considered the possibility of preparing phosporanes in situ during the Wittig process, by mixing a DCM solution of Ph_3P, ethyl 2-bromoacetate, and aldehyde with aqueous NaOH (Table 9).

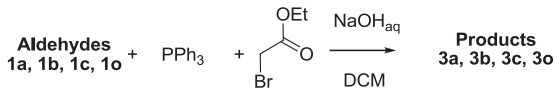
The one-pot protocol afforded compound **3a** (entry 1) in lower yield than the standard protocol (63% and 96%, respectively). In this

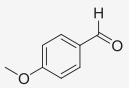
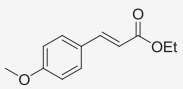
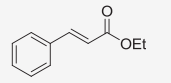
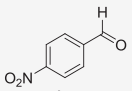
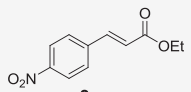
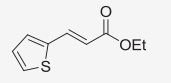
Table 8
Phosphonium salts investigation

Entry[a]	Phosphonium Salt	Product[b]	Isolated yield[c] (%)
1	 2a	 3a	96
2	 2b	 3q	95
3	 2c	 3r	42[d]
4	 2d	 3s	48[e]

[a] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/phosponium salt/NaOH=1/2/2 (without PTC).
[b] The *Z*-stereoisomer was not revealed in UPLC-MS analysis.
[c] Product purified by flash chromatography on silica gel.
[d] *E*/*Z* stereoisomers in 6:1 ratio, as determined by ^{1}H NMR.
[e] *E*/*Z* stereoisomers in 1.4:1 ratio, as determined by ^{1}H NMR.

Table 9
Phosphonium Salts generated in situ



Entry[a]	Aldehydes	Product[b]	Isolated yield[c] (%)
1	 1a	 3a	63[d]
2	 1b	 3b	93
3	 1c	 3c	100
4	 1o	 3o	66[e]

[a] Reactor volume: 10 mL; reagents flow rate: 1 mL min^{-1}; temperature: room temperature; organic solvent: DCM; molar ratio: aldehyde/triphenylphosphine/ethyl 2-bromoacetate/NaOH=1/1.5/1.5/5 (without PTC).
[b] The *Z*-stereoisomer was not revealed in UPLC-MS analysis.
[c] Product purified by flash chromatography on silica gel.
[d] The same reaction carried out without sonication afforded the product in 38% yield after chromatography purification.
[e] *E*/*Z* stereoisomers in 5:1 ratio, as determined by ^{1}H NMR.

case too, the positive effect of sonication was assessed (the one-pot reaction conducted without sonication afforded compound **3a** in 38% yield). As for aldehyde **1o**, the one-pot protocol gave compound **3o** in lower yield (66% vs 100%) and *E*/*Z*-ratio (5:1). On the other hand, the one-pot procedure provided compounds **3b** (entry 2) and **3c** (entry 3) in excellent yield (93% and 100%, respectively), without formation of *Z*-stereoisomer. The results reported in Table 9 proved that Ph_3P, ethyl 2-bromoacetate can be used instead of the corresponding phosphonium salt. Yet, a deeper optimization of the one-pot reaction conditions could lead to better results.

3. Conclusions

In conclusion, we developed a simple, mild, and fast protocol for the synthesis of cinnamic ester derivatives by means of Wittig reaction, combining segmented flow chemistry and sonication. It was proved that the protocol can be applied to different aldehydes, alkyl phosponium salts, and bases affording stereoselectively *E*-cinnamic esters in moderate to excellent yields, in the absence of any phase transfer catalyst and in a really short reaction time (5 min residence time). Moreover, as the flow system works in a continuous way, the reaction can be easily scaled up to provide virtually any amount of product, simply running the system for the required time.

The possibility of applying the developed protocol to not stabilized ylides is presently under investigation. In addition, the effect of combination of flow chemistry and sonochemistry is going to be studied using other model reactions.

4. Experimental section

4.1. General

Commercially available reagents were used throughout without any further purification unless otherwise stated. Wittig reactions under Segmented Flow Condition were performed on commercially available Vapourtec® R2−R4 series flow reactor system. The reaction outcome was supported by TLC and UPLC-MS analysis. Analytical thin layer chromatography was carried out using aluminum-backed plates coated with Merk Kieselgel 60 F_{254}. Plates were visualized under UV light (at 254 and/or 360 nM). UPLC-MS were recorded on Waters Alliance, Micromass ZQ and Waters 2996 photodiode array. The product was purified by flash chromatography using Merck Geduran Si 60 and the products were characterized by ^{1}H NMR spectra recorded on a Bruker ARX300 Spectrometer at 300.13 MHz (1H) using deuterated solvents, such as DMSO-d_6 or $CDCl_3$. The instrument was equipped with a multinuclear inverse probe and temperature controller. Chemical shifts are expressed in parts of million (ppm, δ units) and coupling constants *J* in units of hertz (Hz).

4.2. General procedure for Wittig reactions under segmented flow condition (method A)

In the reagent stock bottle 'A', aldehyde (1 equiv) and triphenylphosphonium bromide (2 equiv) were dissolved in DCM (0.01 M). In the stock bottle 'B', the base (2 equiv) was dissolved in water (0.02 M). The automated injection system combined the two solutions through a T-inlet junction and pumped them at the same flow rate (1 ml/min) into a 10 ml reactor, immersed in an ultrasonic bath maintained at 25 °C. The output was collected into a separation funnel, regulated to continuously remove the organic phase that was filtered through a phase separator (Isolute® Varian). The solvent was evaporated under reduced pressure and crude was purified by flash chromatography on silica gel.

*4.2.1. 3-(4-Methoxy-phenyl) acrylic acid ethyl ester (**3a**).* Obtained from 4-methoxy-benzaldheyde (0.25 mmol, 30.3 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 214.6 mg) dissolved in DCM (25 mL) and aqueous NaOH (0.02 M, 25 mL). Chromatography eluent: petroleum ether/diethyl ether

(95/5) to obtain the title compound as clear oil (49.8 mg; 96.5% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (d, 1H, J=15); 7.5 (d, 2H, J=7.5); 6.9 (d, 2H, J=7.5); 6.35 (d, 1H, J=15); 4.27 (q, 2H, J=7.5); 3.85 (s, 3H); 1.35 (t, 3H, J=7.5).

*4.2.2. 3-Phenyl-acrilic acid ethyl ester (**3b**).* Obtained from benzaldheyde (0.25 mmol, 25.4 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 214.6 mg). Chromatography eluent: petroleum ether/diethyl ether (98/2). The title compound was collected as a colorless oil (43.1 mg; yield 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.7 (d, 1H, J=15); 7.55 (m, 2H); 7.4 (m, 3H); 6.45 (d, 1H, J=15); 4.27 (q, 2H, J=7.5); 1.35 (t, 3H, J=7.5).

*4.2.3. 3-(4-Nitro-phenyl)-acrylic acid ethyl ester (**3c**).* Obtained from 4-nitrobenzaldheyde (0.25 mmol, 37.7 mg) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 214.6 mg). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was collected as a white solid (54 mg; 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.26 (d, 2H, J=7.5); 7.68 (m, 3H); 6.55 (d, 1H, J=15); 4.3 (q, 2H, J=7.5); 1.35 (t, 3H, J=7.5).

*4.2.4. 3-(4-Dimethylammino-phenyl) acrilic acid ethyl ester (**3d**).* Obtained from 4-dimethylamino-benzaldheyde (0.25 mmol, 37.2 mg) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 214.6 mg). Chromatography eluent: DCM. The title compound was collected as a white solid (30.3 mg; 55.2% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.68 (d, 1H, J=15); 7.61 (m, 1H); 7.27 (d, 2H); 6.60 (d, 2H, J=15); 6.47 (d, 1H, J=7.5); 6.39 (d, 1H, J=7.5); 4.26 (q, 2H); 3.03 (s, 6H); 1.34 (t, 3H).

*4.2.5. 3-(2-Methoxy-phenyl)-acrylic acid ethyl ester (**3e**).* Obtained from 2-methoxy-benzaldheyde (0.25 mmol, 30.3 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.50 mmol, 215 mg). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was collected as colorless oil (43 mg; 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.05 (m, 1H); 7.56 (m, 1H); 7.07 (m, 1H); 6.89 (m, 1H); 4.39 (d, 1H); 4.24 (q, 2H); 3.84 (s, 3H); 1.23 (t, 3H).

*4.2.6. (E)-Ethyl 3-(3-methoxyphenyl)acrylate (**3f**).* Obtained from 3-methoxy-benzaldheyde (0.1 mmol, 12 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.2 mmol, 86 mg) dissolved in 10 mL of dichloromethane and aqueous NaOH (0.02 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (9/1). The title compound was collected as an oil (17.7 mg, 86.1% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.62 (d, J=16.1, 1H); 7.33 (t, J=7.6, 1H); 7.23–7.31 (m, 2H); 6.99 (ddd, J=7.8, 2.6, 1.3, 1H); 6.66 (d, J=15.8, 1H); 4.20 (q, J=7.0, 2H); 3.80 (s, 3H); 1.27 (t, J=7.0, 3H).

*4.2.7. (E)-Ethyl 3-(4-acetylphenyl)acrylate (**3g**).* Obtained from 4-acetylbenzaldehyde (0.2 mmol, 29.6 mg) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.80 mmol, 344 mg) dissolved in 20 mL of DCM and aqueous NaOH (0.04 M, 20 mL). Chromatography eluent: DCM/MeOH (95/5). Desired compound was collected as pale yellow oil (16 mg; 37% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.93–8.07 (m, 2H); 7.81–7.93 (m, 2H); 7.71 (d, J=15.8, 1H); 6.77 (d, J=16.1, 1H); 4.22 (q, J=7.0, 2H); 2.60 (s, 3H); 1.27 (t, J=7.0, 3H).

*4.2.8. 5-Phenyl-2-pent-enoic acid ethyl ester (**3h**).* Obtained from 3-phenyl-propionaldheyde (0.25 mmol, 30.2 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 215 mg). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was obtained as an oil (32.8 mg; 63.4% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.28–727 (m, 2H); 7.14–7.27 (m, 3H); 7.02 (dt, 1H); 5.87 (dt, 1H); 4.20 (q, 2H); 2.70–2.92 (m, 2H); 1.30 (t, 3H).

*4.2.9. (2E,4E)-Ethyl 5-phenylpenta-2,4-dienoate (**3i**).* Obtained from of cinnamaldehyde (0.1 mmol, 13 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.2 mmol, 86 mg) dissolved in 10 mL of DCM and aqueous NaOH (0.02 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (9/1). The title compound was obtained as pale yellow oil (18 mg; 89% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.49–7.66 (m, 2H); 7.27–7.48 (m, 4H); 7.02–7.23 (m, 2H); 6.09 (d, J=15.3, 1H); 4.16 (q, J=7.2, 2H); 1.24 (t, J=7.0, 3H).

*4.2.10. (E)-Ethyl 5,5-dimethylhex-2-enoate (**3l**).* Obtained from 3,3-dimethylbutanal (0.2 mmol, 26 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (172 mg, 0.40 mmol) dissolved in 20 mL of DCM and aqueous NaOH hydroxide (0.02 M, 20 mL). Chromatography eluent: petroleum ether/diethyl ether (9/1). The final compound was obtained as a colorless oil (14 mg; 52.9% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.00 (dt, J=15.5, 7.92, 1H); 5.82 (dt, J=15.5, 1.5, 1H); 4.21 (q, J=7.0, 2H); 2.10 (dd, J=7.9, 1.2, 2H); 1.31 (t, J=7.0, 3H); 0.96 (s, 9H).

*4.2.11. (2E,7E)-Diethyl nona-2,7-dienedioate (**3m**).* Obtained from glutaraldehyde (0.1 mmol, 10.0 mg) and (2-ethoxy-2-oxoethyl)triphenylphosphonium bromide (0.40 mmol, 172 mg) dissolved in 10 mL of DCM and aqueous NaOH (0.04 M, 10 mL). Chromatography eluent: DCM/MeOH (95/5). The title compound was obtained as a colorless oil (9.8 mg; yield 41.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.95 (dt, J=15.6, 7.0, 2H); 5.85 (dt, J=15.6, 1.6, 2H); 4.21 (q, J=7.1, 4H); 2.25 (m, J=7.3, 7.3, 7.1, 1.5, 4H); 1.66 (quin, J=7.4, 2H); 1.31 (t, J=7.0, 6H).

*4.2.12. 3-Pyridin-4-yl-acrylic-acid ethyl ester (**3n**).* Obtained from pyridine-4-carbaldheyde (0.25 mmol, 23.8 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.50 mmol, 215 mg). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was collected as a white solid (33.3 mg; 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.59–8.86 (m, 2H); 7.66 (d, 1H); 7.57–7.67 (m, 2H); 6.71 (d, 1H); 4.34 (q, 2H); 1.38 (t, 3H).

*4.2.13. (E)-Ethyl 3-(thiophen-2yl) acrylate (**3o**).* Obtained from thiophene-2-carbaldehyde (0.1 mmol, 9.17 μL), ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.2 mmol, 86 mg), and aqueous NaOH (0.02 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was collected as yellow oil (18 mg; quantitative yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.80 (dt, J=15.5, 0.6, 1H); 7.73 (dt, J=5, 0.9, 1H); 7.56 (d, 1H); 7.15 (dd, J=5, 3.5, 1H); 6.26 (d, J=15.5, 1H); 4.18 (q, J=7.2, 2H); 1.25 (t, J=7.0, 3H).

*4.2.14. (E)-Ethyl 3-(quinolin-2-yl)acrylate (**3p**).* Obtained from quinoline-2-carbaldehyde (0.10 mmol, 15.7 mg) and (2-ethoxy-2-oxoethyl)triphenylphosphonium bromide (0.20 mmol, 86 mg). Chromatography eluent: dichloromethane/diethyl ether (7/3). The title compound was obtained as a brown solid (11 mg; 48.4% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.44 (d, J=8.5, 1H); 8.05 (dd, J=8.5, 0.9, 1H); 8.01 (dd, J=8.2, 1.2, 1H); 8.00 (d, J=8.5, 1H); 7.81 (ddd, J=8.5, 7.0, 1.7, 1H); 7.79 (d, J=16.1, 1H); 7.65 (ddd, J=8.2, 7.0, 1.2, 1H); 7.09 (d, J=16.1, 1H); 4.25 (q, J=7.0, 2H); 1.30 (t, J=7.0, 3H).

*4.2.15. 3-(4-Methoxy-phenyl) acrylic acid ethyl ester (**3a**) using K_2CO_3 as the base.* Obtained from 4-methoxy-benzaldheyde (0.25 mmol, 30.3 μL), ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 215 mg) dissolved in DCM (25 mL) and

aqueous K_2CO_3 (0.02 M, 25 mL). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was obtained as colorless oil (49.8 mg; 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (d, 1H, J=15); 7.5 (d, 2H, J=7.5); 6.9 (d, 2H, J=7.5); 6.35 (d, 1H, J=15); 4.27 (q, 2H, J=7.5); 3.85 (s, 3H); 1.35 (t, 3H, J=7.5).

*4.2.16. (E)-3-(4-Methoxy-phenyl) acrylic acid ethyl ester (**3a**) using $NaHCO_3$ as the base.* Obtained from 4-methoxy-benzaldheyde (0.1 mmol, 12 μL), ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.2 mmol, 86 mg) dissolved in DCM (10 mL) and aqueous $NaHCO_3$ (0.02 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (8/2). The title compound was obtained as colorless oil (16 mg; 78% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.64–7.74 (m, 2H), 7.60 (d, J=16.1, 1H); 6.80–7.08 (m, 2H); 6.47 (d, J=15.8, 1H); 4.18 (q, J=7.2, 2H); 3.80 (s, 3H); 1.26 (t, J=7.2, 3H).

*4.2.17. (E)-3-(4-Methoxy-phenyl) acrylic acid ethyl ester (**3a**) using DMAP as the base.* Obtained from 4-methoxy-benzaldheyde (0.25 mmol, 30.3 μL) and ethoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 214.6 mg) dissolved in DCM (25 mL) and aqueous DMAP (0.02 M, 25 mL). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was obtained as colorless oil (49.8 mg 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (d, 1H, J=15); 7.5 (d, 2H, J=7.5); 6.9 (d, 2H, J=7.5); 6.35 (d, 1H, J=15); 4.27 (q, 2H, J=7.5); 3.85 (s, 3H); 1.35 (t, 3H, J=7.5).

*4.2.18. (E)-Ethyl 5,5-dimethylhex-2-enoate (**3l**) using K_2CO_3 as base.* The procedure is the same as described for (**3a**) but using potassium carbonate (0.40 mmol, 56 mg) dissolved in 20 mL of H_2O. Chromatography eluent: petroleum ether/diethyl ether (9/1). The title compound was collected as colorless oil (14 mg; 41.1% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.00 (dt, J=15.5, 7.9, 1H); 5.82 (dt, J=15.5, 1.5, 1H); 4.21 (q, J=7.2, 2H); 2.10 (dd, J=7.9, 1.5, 2H); 1.31 (t, J=7.0, 3H); 0.96 (s, 9H).

*4.2.19. (E)-Ethyl 3-(quinolin-2-yl)acrylate (**3p**) using K_2CO_3 as base.* The procedure is the same as described for (**3a**) but using quinoline-2-carbaldehyde (0.1 mmol, 15.7 mg), (2-ethoxy-2-oxoethyl) triphenylphosphonium bromide (0.2 mmol, 86 mg) and of potassium carbonate (27.6 mg, 0.20 mmol). Chromatography eluent: dichloromethane/diethyl ether (7/3). The title compound was obtained as a brown solid (22.7 mg; quantitative yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.44 (d, J=8.5, 1H); 7.96–8.11 (m, 3H); 7.78–7.86 (m, 1H); 7.80 (d, J=16.1, 1H); 7.65 (ddd, J=8.1, 6.9, 1.2, 1H); 7.09 (d, J=16.1, 1H); 4.25 (q, J=7.0, 2H); 1.30 (t, J=7.0, 3H).

*4.2.20. (E)-Methyl 3-(4-methoxyphenyl)acrylate (**3q**).* Obtained from 4-methoxy-benzaldheyde (0.25 mmol, 25.4 μL) and methoxycarbonylmethyl-triphenyl-phosphonium bromide (0.5 mmol, 215 mg). Chromatography eluent: petroleum ether/diethyl ether (98/2). The title compound was collected as colorless oil (45.6 mg; yield 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (d, 1H, J=15); 7.5 (d, 2H, J=7.5); 6.9 (d, 2H, J=7.5); 6.35 (d, 1H, J=15); 3.88 (t, 3H); 3.84 (s, 3H).

*4.2.21. (E), (Z)-tert-Butyl 3-(4-methoxyphenyl) acrylate (**3r**).* Obtained from 4-methoxy-benzaldheyde (0.1 mmol, 12 μL), (2-*tert*-butoxy-2-oxoethyl) triphenylphosphonium chloride (0.2 mmol, 83 mg) and aqueous NaOH (0.02 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (9/1). (*E*)-*tert*-Butyl 3-(4methoxyphenyl) acrylate was collected as a colorless oil (10 mg; 42.7% yield) and (*Z*)-*tert*-butyl 3-(4methoxyphenyl) acrylate was collected as a colorless oil (1.7 mg; 7% yield). *E*-regiosiomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.57–7.70 (m, 2H); 7.50 (d, J=16.1, 1H); 6.76–7.09 (m, 2H); 6.36 (d, J=16.1,1H); 3.80 (s, 3H); 1.48 (s, 9H). *Z*-regioisomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.64 (m, 2H); 6.95 (m, 2H); 6.82 (d, J=12.9, 1H); 5.76 (d, J=12.9, 1H); 3.79 (s, 3H); 1.43 (s, 9H).

*4.2.22. 3-(4-Methoxy-phenyl)-acrylonitril (**3s**).* Obtained from 4-methoxy-benzaldheyde (0.2 mmol, 24 μL), cyanomethyl-triphenyl-phosphonium bromide (0.4 mmol, 152 mg) and aquoeus NaOH (0.02 M, 20 mL). Chromatography eluent: petroleum ether/diethyl ether (95/5). The title compound was collected as white solid of were obtained as final product (15.3 mg; 48.5% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.42 (m, 2H); 7.36 (d, J=16.4, 1H); 6.96 (m, 2H); 5.73 (d, J=16.4, 1H); 3.87 (s, 3H).

4.3. General procedure for one-pot Wittig reactions under segmented flow condition (method B)

In the reagent stock bottle 'A', aldehyde (1 equiv), triphenylphosphine (1.5 equiv) and α-bromoester (1.5 equiv) were dissolved in DCM (0.1 M). In the stock bottle 'B', the base (5 equiv) was dissolved in water (0.5 M). The automated injection system combined the two solutions through a T-inlet junction and pumped them at the same flow rate (1 ml/min) into a 10 ml reactor, immersed in an ultrasonic bath maintained at 25 °C. The outcome was collected into a separation funnel, regulated to continuously remove the organic phase that was filtered through a phase separator (Isolute® Varian). The solvent was evaporated under reduced pressure and crude was purified by flash chromatography on silica gel.

*4.3.1. 3-(4-Methoxy-phenyl) acrylic acid ethyl ester (**3a**).* Obtained from 4-methoxybenzaldehyde (1 mmol, 121 μL), triphenylphosphine (1.50 mmol, 393 mg), and ethyl 2-bromoacetate (1.50 mmol, 166 μL) dissolved in DCM (10 mL) and aqueous NaOH (0.5 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (85/15 to 8/2) to obtain the title compound as pale yellow oil (78.6 mg, 38.1% yield).

The same reaction carried out putting the reactor in a sonic bath at room temperature afforded 130 mg (63.1% yield) of the title compound after chromatography purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.64–7.72 (m, 2H); 7.60 (d, J=16.1, 1H); 6.87–7.08 (m, 2H); 6.47 (d, J=16.1, 1H); 4.18 (q, J=7.0, 2H); 3.80 (s, 3H); 1.25 (t, J=7.0, 3H).

*4.3.2. (E)-Ethyl cinnamate (**3b**).* Obtained from benzaldehyde (0.1 mmol, 10 μL), triphenylphosphine (0.15 mmol, 39.3 mg) and ethyl 2-bromoacetate (0.15 mmol, 17.0 μL) dissolved in DCM (10 mL) and aqueous NaOH (0.5 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (8/2). The title compound was collected as colorless oil (16.3 mg, 93% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.69–7.76 (m, 2H); 7.65 (d, J=16.1, 1H); 7.34–7.48 (m, 3H); 6.63 (d, J=16.1, 1H); 4.20 (q, J=7.2, 2H); 1.27 (t, J=7.2, 3H).

*4.3.3. (E)-Ethyl 3-(4-nitrophenyl)acrylate (**3c**).* Obtained from 4-nitrobenzaldehyde (1 mmol, 151 mg), triphenylphosphine (1.5 mmol, 393 mg), and ethyl 2-bromoacetate (1.5 mmol, 166 μL) dissolved in DCM (1 mL) and aqueous NaOH (0.5 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (8/2). The title compound was collected as colorless oil (113 mg; 51% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.16–8.34 (m, 2H), 7.98–8.09 (m, 2H); 7.77 (d, J=16.1, 1H); 6.86 (d, J=15.8, 1H); 4.23 (q, J=7.1, 2H); 1.28 (t, J=7.0, 3H).

*4.3.4. (E), (Z)-Ethyl 3-(thiophen-2-yl)acrylate (**3o**).* Obtained from thiophene-2-carbaldehyde (0.1 mmol, 9.2 μL), triphenylphosphine (39.3 mg, 0.15 mmol), and ethyl 2-bromoacetate (0.150 mmol,

17 μL) dissolved in DCM (10 mL) and aqueous NaOH (0.5 M, 10 mL). Chromatography eluent: petroleum ether/diethyl ether (8/2).

(*E*)-Ethyl 3-(thiophen-2-yl)acrylate (yield 65, 8%, 12 mg) and 2.7 mg of (*Z*)-ethyl 3-(thiophen-2-yl)acrylate (yield 14.82%) were obtained as final compounds.

E-regioisomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.80 (d, J=15.8, 1H); 7.70–7.76 (m, 1H); 7.47–7.59 (m, 1H); 7.15 (dd, J=5, 3.5, 1H), 6.26 (d, J=15.8, 1H), 4.18 (q, J=7.1, 2H); 1.25 (t, J=7.0, 3H). *Z*-regioisomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.44–7.81 (m, 2H); 7.29 (d, J=12.3, 1H); 7.13 (dd, J=5.1, 3.7, 1H); 5.77 (d, J=12.6, 1H); 4.18 (q, J=7.0, 2H); 1.25 (t, J=7.0, 3H).

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