
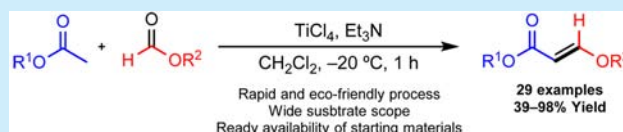


TiCl<sub>4</sub>/Et<sub>3</sub>N-Mediated Condensation of Acetate and Formate Esters: Direct Access to  $\beta$ -Alkoxy- and  $\beta$ -AryloxyacrylatesJosé María Álvarez-Calero, Zacarías D. Jorge, and Guillermo M. Massanet\*

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 Supporting Information

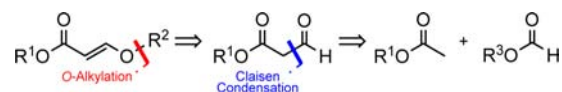
**ABSTRACT:** A methodology to build (*E*)- $\beta$ -alkoxy- and (*E*)- $\beta$ -aryloxyacrylate moieties from acetate and formate esters promoted by the TiCl<sub>4</sub>/Et<sub>3</sub>N system is presented. The reaction is compatible with a broad range of structural skeletons and elapses through an unusual condensation pathway. Taking into account the obtained results, we propose a plausible mechanism involving a bimetallic titanium intermediate for this type of transformation.



The  $\beta$ -alkoxyacrylate unit is a common structural motif present in biologically active natural and synthetic products, such as indole alkaloids,<sup>1</sup> strigolactones,<sup>2</sup> and  $\beta$ -methoxyacrylate fungicides (strobilurins, oudemansins, melithiazoles, haliangicins).<sup>3</sup> This  $\alpha,\beta$ -unsaturated moiety is a versatile synthon that allows building several heterocyclic structures and, recently, has served as an intermediate in natural products synthesis, such as ( $\pm$ )-gracilioether E (ene reaction),<sup>4a</sup> rocaglamide (metalation),<sup>4b</sup> ( $\pm$ )-hippolachnin A (ene reaction),<sup>4c</sup> ABC ring fragment of gymnocin A (radical cyclization),<sup>4d</sup> C'D'E'F' ring fragment of maitotoxin (radical cyclization),<sup>4e</sup> ( $\pm$ )-civet (Prins reaction),<sup>4f</sup> and (+)-vigulariol (radical cyclization).<sup>4g</sup>

Despite the synthetic applicability of  $\beta$ -alkoxyacrylates, they are mainly prepared by conjugate addition of alcohols/phenols to propiolate esters (Figure 1a).<sup>4b,d–g,5</sup> Other less employed

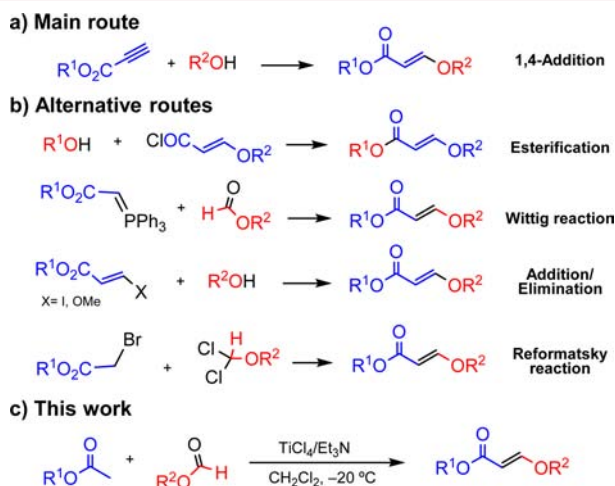
alternatives (Figure 1b) consist of esterification of alcohols with 3-alkoxyacryloyl chloride,<sup>6</sup> Wittig reaction between (phosphanylidene)acetates and alkyl formates,<sup>7</sup> addition/elimination of alcohols to  $\beta$ -iodo- or  $\beta$ -methoxyacrylates,<sup>4c,5g,h,8</sup> and Reformatsky reaction with bromoacetates.<sup>9</sup> The existence of a single methodology for obtaining this synthon has led us to search for a new possible route via a retrosynthetic analysis with two disconnections (Scheme 1): the first based on O-alkylation

Scheme 1. Retrosynthetic Analysis for  $\beta$ -Alkoxyacrylates

of a formylacetate derivative followed by a Claisen condensation. Herein, we describe an efficient method to introduce a  $\beta$ -alkoxy- or  $\beta$ -aryloxyacrylate unit in different acetate esters using alkyl/aryl formates combined with a TiCl<sub>4</sub>/Et<sub>3</sub>N system through an unusual condensation pathway (Figure 1c).

Claisen and Dieckmann condensations mediated by titanium enolates generated by TiCl<sub>4</sub> and a tertiary amine<sup>10</sup> have gained great importance over traditional methods (enolates generated by strong bases, such as LDA and LHMDs) due to the following advantages: high reaction velocities, good yields, a ready available low-toxic metal (TiCl<sub>4</sub>), use of practical amines (Et<sub>3</sub>N or Bu<sub>3</sub>N), and toleration of basic labile functionalities. The  $\alpha$ -formylation of diverse esters employing the TiCl<sub>4</sub>/Et<sub>3</sub>N system combined with methyl formate was reported by Tanabe et al.,<sup>10c</sup> but to our knowledge, acetate esters have not been assayed.

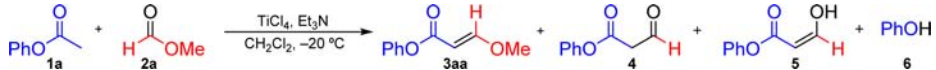
Phenyl acetate (1a) was chosen as a model substrate and was subjected to a preliminary condensation conditions using methyl formate (2a) (1.2 equiv), TiCl<sub>4</sub> (1.3 equiv), and Et<sub>3</sub>N (3.0 equiv) (entry 1, Table 1). The reaction was followed by TLC, and after an hour, a slightly more polar product had formed. The <sup>1</sup>H NMR analysis of the reaction crude showed unreacted 1a, the desired



**Figure 1.** (a) Main route for synthesizing  $\beta$ -alkoxyacrylates by conjugate addition; (b) reported alternative routes; (c) novel building of  $\beta$ -alkoxy- and  $\beta$ -aryloxyacrylate units from acetate and formate esters promoted by TiCl<sub>4</sub>/Et<sub>3</sub>N.

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Table 1. Optimization of Reaction Conditions<sup>a</sup>


entry	2a (equiv)	TiCl <sub>4</sub> (equiv)	Et <sub>3</sub> N (equiv)	CH <sub>2</sub> Cl <sub>2</sub> (mL)	ratio <sup>b</sup> 1a/3aa/4/5/6	yield of 3aa (%) <sup>c</sup>
1	1.2	1.3	3.0	3.0	50:39:2:1:8	37
2	1.2	2.6	3.0	3.0	0:60:3:1:36	35
3	3.3	1.3	3.0	3.0	45:49:3:2:1	46
4	3.3	1.3	3.0	1.5	41:52:3:3:1	49
5 <sup>d</sup>	3.3	1.3	3.0	1.5	34:57:4:4:1	54
6	3.3	2.3	3.0	1.5	0:88:6:5:1	80
7	3.3	2.3	5.3	1.5	13:77:4:2:4	69
8	3.3	2.3	3.0	3.0	3:89:4:3:1	80
9	3.3	2.6	3.4	3.0	0:88:6:5:1	81
10 <sup>e</sup>	3.3	2.6	3.4	3.0	0:88:6:5:1	79

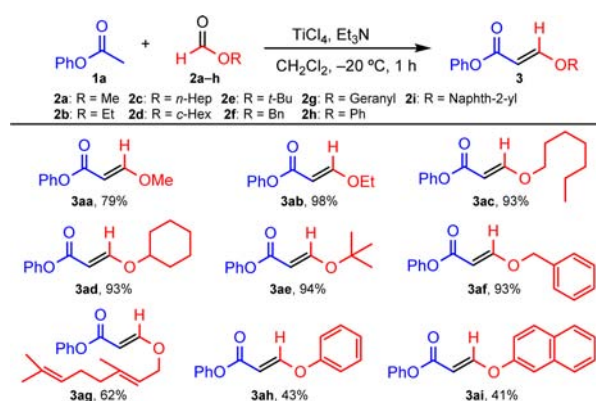
<sup>a</sup>TiCl<sub>4</sub> was added to a -20 °C solution of **1a** (1.0 mmol), **2a**, and Et<sub>3</sub>N under inert atmosphere. The mixture was stirred for 1 h at the same temperature. <sup>b</sup>The ratio was established from <sup>1</sup>H NMR (400 MHz) analysis of reaction crude. <sup>c</sup>Isolated yield. <sup>d</sup>Reaction stirred for 2 h at -20 °C.

<sup>e</sup>Workup using half of the volume of the solvents.

formylacetate **4** as minor product, along with the enol form **5** and, unexpectedly, phenyl (*E*)-β-methoxyacrylate (**3aa**). The last compound could be derived from a formal dehydration during a Claisen condensation. Three related reactions that involve 3-substituted pent-2-enedioates<sup>11</sup> or thioesters<sup>12</sup> as starting materials have been described. The increase of metal source produced a similar yield of **3aa** (entry 2, Table 1), but an increase of the hydrolysis of **1a** was observed. A greater proportion of the formyl source not only improved the yield but also prevented the hydrolysis of the acetate ester (entry 3, Table 1). Factors such as concentration (entry 4, Table 1) or reaction time (entry 5, Table 1) did not significantly affect neither the product ratio nor the yield of **3aa**. Better results were obtained by increasing the amount of TiCl<sub>4</sub> (entry 6, Table 1). Instead, when the amine load was increased, the yield was lower (entry 7, Table 1). As concentration could affect the solubility of other acetate esters in further assays, an experiment under more dilute conditions was tested (entry 8, Table 1). The dilution did not affect the yield of **3aa** but showed unreacted starting material. The above problem was solved with a slight increase of both TiCl<sub>4</sub> and Et<sub>3</sub>N (entry 9, Table 1). Finally, the use of one-half of the volume of solvents in the workup produced the same result (entry 10, Table 1).

Once the optimal conditions for the synthesis of phenyl (*E*)-β-methoxyacrylate (**3aa**) were established (Table 1), the scope of the condensation was studied using formate esters **2b–2i** (Scheme 2). Ethyl (**2b**), *n*-heptyl (**2c**), cyclohexyl (**2d**), *t*-butyl (**2e**), and benzyl (**2f**) substituents in the formyl source produced the β-alkoxyacrylates **3ab–3af** with high yields, and unlike the reaction crude from the **2a** assay, the formylacetate derivative with its enol form appeared as traces. The decrease of yield of **3ag** could be explained by the decomposition experienced by geranyl derivatives. Aromatic formates **2h** and **2i** led to low yields, and <sup>1</sup>H NMR spectra of the reaction crudes showed a minor ratio of the desired β-acrylate with respect to the formylacetate with the enol form, 64:16:20 and 61:31:8, respectively.

Analysis of the scope was continued by choosing different acetate esters with a wide structural diversity and, in some cases, derived from natural products for their potential biological implications. Non-heterocyclic acetates **1b–1p** were treated with formate **2b** as the formyl source (Scheme 3) due to its efficiency and ease of removal under reduced pressure. Linear saturated aliphatic acetates **1b,1c** produced acrylate derivatives with high yield, and even the reaction was effective with hindered starting

Scheme 2. Scope of Formate Esters<sup>a,b</sup>

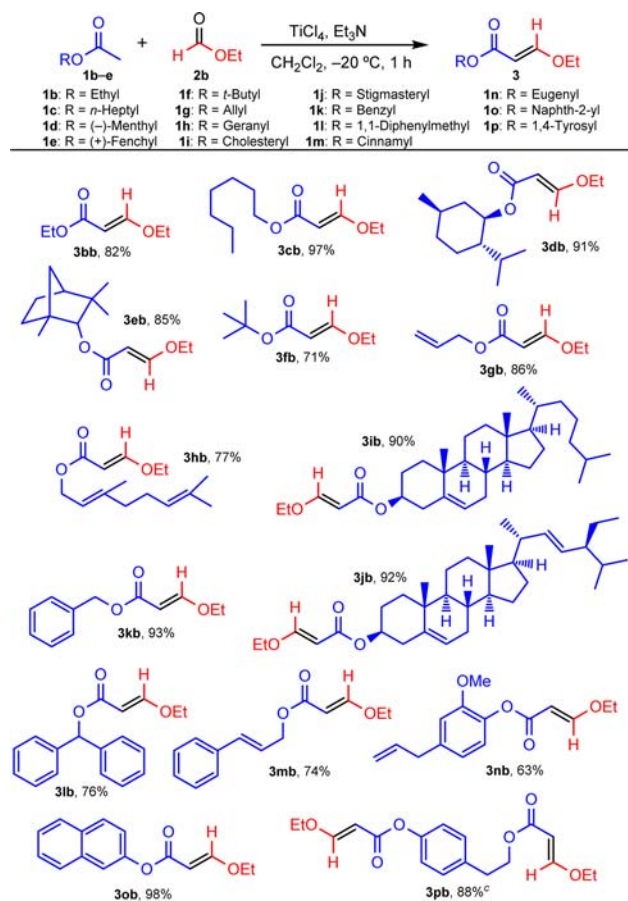
<sup>a</sup>All reactions were carried out using **1a** (1.0 mmol), formate esters **2a–2i** (3.3 mmol), Et<sub>3</sub>N (3.4 mmol), TiCl<sub>4</sub> (2.6 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), -20 °C, 1 h. <sup>b</sup>Isolated yield.

materials such as *t*-butyl acetate (**1f**), (–)-menthyl acetate (**1d**), or (1*R*)-endo-(+)-fenchyl acetate (**1e**). Acetates in both allylic (**1g, 1h**, and **1m**) and benzylic (**1k,1l**) positions were also compatible under the same reaction conditions with moderated yields. Complex esters such as cholesteryl acetate (**1i**) or stigmasteryl acetate (**1j**) and aromatic compounds such as naphth-2-yl acetate (**1o**) gave good yields, although with eugenyl acetate (**1n**), the yield decreased. The presence of more than one ester group, as is the case of 1,4-tyrosyl acetate (**1p**), does not affect the good yield of the corresponding bisacrylate **3pb**.

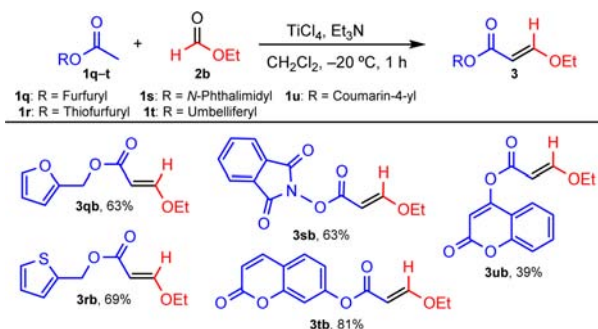
Heterocyclic acetates **1q–1u** (Scheme 4) constituted a second set of tested substrates. Furan and thiophene rings, **1q** and **1r**, were compatible with the reaction conditions and produced **3qb** and **3rb** in moderated yields.

*N*-Acetoxypthalimide (**1s**), 7-acetoxycoumarin (**1t**), and 4-acetoxycoumarin (**1u**) were found to be labile acetates because, in addition to the desired products, hydroxyl compounds derived from the hydrolysis were observed in the crude reaction mixture. The low yield obtained from acetate **1u** can be explained by considering its enol–acetate nature.

Finally, the study of the reaction scope was expanded to esters other than acetates, such as γ-butyrolactone (**1v**), ethyl propionate (**1w**), and methyl phenylacetate (**1y**) (Figure 2). The aim was to study the behavior of esters that have been

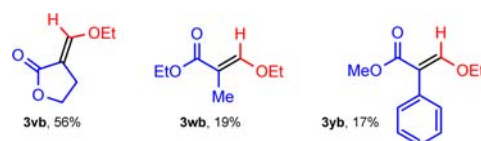
Scheme 3. Scope of Non-heterocyclic Acetate Esters<sup>a,b</sup>

<sup>a</sup>All reactions were carried out using the acetate esters **1b–1o** (1.0 mmol), **2b** (3.3 mmol), Et<sub>3</sub>N (3.4 mmol), TiCl<sub>4</sub> (2.6 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), -20 °C, 1 h. <sup>b</sup>Isolated yield. <sup>c</sup>Reaction using **2b** (9.9 mmol), Et<sub>3</sub>N (10.2 mmol), and TiCl<sub>4</sub> (5.2 mmol).

Scheme 4. Scope of Heterocyclic Acetates<sup>a,b</sup>

<sup>a</sup>All reactions were carried out using the acetate esters **1q–1u** (1.0 mmol), **2b** (3.3 mmol), Et<sub>3</sub>N (3.4 mmol), TiCl<sub>4</sub> (2.6 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), -20 °C, 1 h. <sup>b</sup>Isolated yield.

employed in  $\alpha$ -formylations using methyl or ethyl formate combined with TiCl<sub>4</sub> and Et<sub>3</sub>N.<sup>10c,h</sup> Surprisingly, lactone **1v** exclusively produced the expected  $\beta$ -ethoxyacrylate **3vb**, while the other esters gave a 1:1 mixture of the  $\alpha$ -formyl derivative and (*E*)- $\beta$ -ethoxyacrylate. These results are different than those reported for Claisen condensations using TiCl<sub>4</sub>/Et<sub>3</sub>N, in which the only product described was the 1,3-dicarbonyl derivative. This behavior can be explained by differences in the reaction conditions (larger reaction times, room temperature, and higher

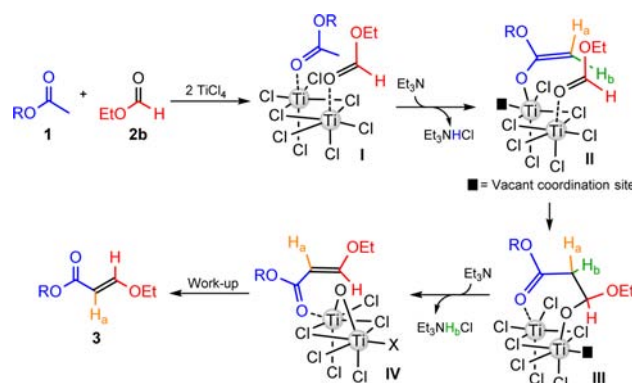


**Figure 2.** Assays with esters other than acetates. All reactions were carried out using  $\gamma$ -butyrolactone (**1v**), methyl propionate (**1w**), or methyl phenylacetate (**1y**) (1.0 mmol); **2b** (3.3 mmol), Et<sub>3</sub>N (3.4 mmol), TiCl<sub>4</sub> (2.6 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), -20 °C, 1 h. Isolated yield.

acidity of the reaction media derived from TiCl<sub>4</sub> hydrolysis in the aqueous workup).

A plausible mechanism for this condensation is outlined in Scheme 5. The need for a minimum of 2 equiv of TiCl<sub>4</sub> involves the formulation of a bimetallic intermediate, a hypothesis that has been proposed by other authors.<sup>13</sup>

**Scheme 5.** Plausible Mechanism for the Condensation between Acetate Esters and Ethyl Formate (**2b**) Promoted by TiCl<sub>4</sub>/Et<sub>3</sub>N



The mechanism begins by the formation of a 2:2 adduct between TiCl<sub>4</sub> with formate and acetate esters (intermediate **I**). This intermediate exhibits two octahedral titanium cores with two chlorine bridges and the alkoxide groups from the esters away from the bimetallic plane, according to reported crystallographic structures for this type of metallic complex with ethyl formate (**2b**) and ethyl acetate (**1b**).<sup>14</sup> One equivalent of Et<sub>3</sub>N would generate the bimetallic enolate **II**, which attacks the carbonyl of ethyl formate to form the eight-membered intermediate **III**. In a process favored by the high avidity of titanium for oxygen, the removal of H<sub>b</sub> by the amine and the cleavage of the C–O bond give the bridged intermediate **IV**. The *anti*-disposition of H<sub>b</sub> with respect to the leaving group explains its removal instead H<sub>a</sub>. Finally, the coordinated (*E*)- $\beta$ -ethoxyacrylate ester is released upon workup. This mechanism can explain the optimum yields when the amount of alkyl formate was increased to 3.3 equiv because these conditions increase the probability that acetate and formate are facing each other. The reaction with  $\gamma$ -butyrolactone (**1v**) may be better explained by intermediate **III** than the six-membered Zimmerman–Traxler model because of lesser strain produced by the lactone. The formation of formyl derivatives from **1w** and **1y** can also be explained by this mechanism because only the (*E*)-enolate can form intermediate **III** while the (*Z*)-isomer evolves through the mechanism of the Claisen condensation to give the corresponding 1,3-dicarbonyl derivatives. The absence of  $\alpha$ -formylation with  $\gamma$ -butyrolactone (**1v**) can be justified because it only produces the (*E*)-enolate.

In summary, we have studied an unusual condensation reaction between formate and acetate esters promoted by the  $\text{TiCl}_4/\text{Et}_3\text{N}$  system. This methodology has been optimized and lets one introduce a  $\beta$ -alkoxy- or  $\beta$ -aryloxyacrylate moiety into acetate esters of different nature. Based on the results, a mechanism involving a bimetallic intermediate has been proposed. This reaction increases the knowledge about the titanium reactivity and could be a basis for future research. The possible biological activity of these newly synthesized  $\beta$ -alkoxy- and  $\beta$ -aryloxyacrylates is currently under study.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b03233](https://doi.org/10.1021/acs.orglett.6b03233).

Experimental details, compound data, and  $^1\text{H}/^{13}\text{C}$  NMR copies (PDF)

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### Notes

The authors declare no competing financial interest.

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