**TiCl₄/Et₃N-Mediated Condensation of Acetate and Formate Esters: Direct Access to β-Alkoxy- and β-Aryloxyacrylates**

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Supporting Information

**ABSTRACT:** A methodology to build (E)-β-alkoxy- and (E)-β-aryloxyacrylate moieties from acetate and formate esters promoted by the TiCl₄/Et₃N 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 β-alkoxyacrylate unit is a common structural motif present in biologically active natural and synthetic products, such as indole alkaloids, strigolactones and β-methoxyacrylate fungicides (strobilurins, oudemansins, melithiazoles, halilangins). This α,β-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 (+)-gracilioether E (ene reaction), rocaglamide (metalation), ABC ring fragment of gymnocin A (radical cyclization), (+)-civet (Prins reaction), and (+)-vigulariol (radical cyclization).

Despite the synthetic applicability of β-alkoxyacrylates, they are mainly prepared by conjugate addition of alcohols/phenols to propiolate esters (Figure 1a). Other less employed alternatives (Figure 1b) consist of esterification of alcohols with 3-alkoxyacryloyl chlorides, Wittig reaction between (phosphanylidene)acetates and alkyl formates, addition/elimination of alcohols to β-iodo- or β-methoxyacrylates, and Reformatsky reaction with bromoacetates. 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 of a formylacetate derivative followed by a Claisen condensation. Herein, we describe an efficient method to introduce a β-alkoxy- or β-aryloxyacrylate unit in different acetate esters using alkyl/aryl formates combined with a TiCl₄/Et₃N system through an unusual condensation pathway (Figure 1c).

Claisen and Dieckmann condensations mediated by titanium enolates generated by TiCl₄ and a tertiary amine 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 (TiCl₄), use of practical amines (Et₃N or Bu₃N), and toleration of basic labile functionalities. The α-formylation of diverse esters employing the TiCl₄/Et₃N system combined with methyl formate was reported by Tanabe et al., 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), TiCl₄ (1.3 equiv), and Et₃N (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 ¹H NMR analysis of the reaction crude showed unreacted 1a, the desired...
and ease of removal under reduced pressure. Linear saturated implications. Non-heterocyclic acetates derived from natural products for their potential biological yield, and even the reaction was e-formate

2b

form, 64:16:20 and 61:31:8, respectively.

desired NMR spectra of the reaction crudes showed a minor ratio of the condensation was studied using formate esters the workup produced the same result (entry 10, Table 1). Factors such as concentration could a ect the solubility of other acetate esters in the hydrolysis of the acetate ester (entry 3, Table 1). Factors such as concentration could a ect neither the product ratio nor the yield of 3aa. Better results were obtained by increasing the amount of TiCl4 (entry 6, Table 1). Instead, when the amine load was increased, the yield was lower (entry 7, Table 1). As concentration could a ect the yield of 3aa was solved with a slight increase of both TiCl4 and Et3N (entry 9, 3aa but showed unreacted starting material. The above problem further assays, an experiment under more dilute conditions was tested (entry 4, Table 1). The dilution did not a ect the yield of 3aa but showed unreacted starting material. The above problem was solved with a slight increase of both TiCl4 and Et3N (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-buty1 (2e), and benzyl (2f) substituents in the formyl source produced the β-alkoxyacrylates 3ab—3ai with high yields, and unlike the reaction crude from the 2a assay, the formylacrylate 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 1H NMR spectra of the reaction crudes showed a minor ratio of the desired β-acrylate with respect to the formylacrylate 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 materials such as t-butyl acetate (1f), (−)-menthol acetate (1d), or (1R)-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 napth-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-Acetoxyphthalimide (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

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"TiCl4 was added to a −20 °C solution of 1a (1.0 mmol), 2a, and Et3N under inert atmosphere. The mixture was stirred for 1 h at the same temperature. The ratio was established from 1H NMR (400 MHz) analysis of reaction crude. Isolated yield. Reaction stirred for 2 h at −20 °C. Workup using half of the volume of the solvents."
employed in α-formylations using methyl or ethyl formate combined with TiCl4 and Et3N.10c,h Surprisingly, lactone 1v exclusively produced the expected β-ethoxyacrylate 3vb, while the other esters gave a 1:1 mixture of the α-formyl derivative and (E)-β-ethoxyacrylate. These results are different than those reported for Claisen condensations using TiCl4/Et3N, 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 acidity of the reaction media derived from TiCl4 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 TiCl4 involves the formulation of a bimetallic intermediate, a hypothesis that has been proposed by other authors.13

The mechanism begins by the formation of a 2:2 adduct between TiCl4 with formate and acetate esters (intermediate I). This intermediate exhibits two octahedral titanium cores, according to structural corroborations for this type of complex with ethyl formate (2b) and ethyl acetate (1b).14 One equivalent of Et3N 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 Hb by the amine and the cleavage of the C−O bond gives the bridged intermediate IV. The anti-disposition of Hb with respect to the leaving group explains its removal instead Ha. Finally, the coordinated (E)-β-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 γ-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-dicarboxyl derivatives. The absence of α-formylation with γ-butyrolactone (1v) can be justified because it only produces the (E)-enolate.

The mechanism begins by the formation of a 2:2 adduct between TiCl4 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 complex with ethyl formate (2b) and ethyl acetate (1b). One equivalent of Et3N 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 Hb by the amine and the cleavage of the C−O bond gives the bridged intermediate IV. The anti-disposition of Hb with respect to the leaving group explains its removal instead Hα. Finally, the coordinated (E)-β-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 γ-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-dicarboxyl derivatives. The absence of α-formylation with γ-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 TiCl4/Et3N system. This methodology has been optimized and lets one introduce a β-alkoxy- or β-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 β-alkoxy- and β-aryloxyacrylates is currently under study.

## acknowledgments
We are grateful to the Ministry of Economy and Competitiveness of Spain (Project AGL2013-42238-R) and the Junta de Andalucía (FQM-169) for the financial support. J.M.A.-C. acknowledges the Spanish Ministry of Education, Culture and Sport for a fellowship. The authors are thankful to the Servicios Centrales de Investigación Científica y Tecnológica (SC-ICYT) of the University of Cádiz.

## references