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Condensation of orthoacetates with aldehydes: a new strategy for the preparation of α,β-unsaturated esters☆

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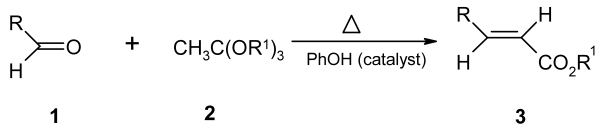
Abstract—α,β-Unsaturated esters are formed in good yields when aldehydes are heated with orthoacetates in the presence of a catalytic amount of phenol. © 2003 Elsevier Science Ltd. All rights reserved.

α,β-Unsaturated esters are useful chemical entities which are accessible through condensation reactions involving aldehydes, viz. (i) Knoevenagel condensations of active methylene esters with aldehydes,[1] (ii) condensations of alkyl acetates with aldehydes followed by dehydration,[2] (iii) Reformatsky reactions with aldehydes followed by β-elimination of the ensuing hydroxy esters,[3] (iv) Wadsworth–Emmons olefination of carbonyl compounds.[4] Even though some of the above methods have advantages, the Knoevenagel condensation route, particularly for cinnamic esters, involves two separate steps, i.e. the preparation of the cinnamic acid followed by its esterification and the Reformatsky reaction has the limitation[2] of not being suitable for the preparation of cinnamic acids with halo, phenoxy or nitro substituents on the aromatic moiety.

Reactions of orthoesters with various carbonyl compounds are well documented in the literature.[5] Aldehydes and ketones form acetals when heated with orthoformates and an acidic catalyst, whereas esters are formed when acids react with orthoacetates or formates. Recently we reported an *O*-alkylation reaction of benzylic and allylic alcohols using orthoesters which has been applied to the total synthesis of various natural products.[6] In continuation of our interest in exploring new synthetic uses of orthoesters, we herein report a new application which describes the condensation of orthoacetates with aldehydes to generate α,β-unsaturated esters in high yields.

Various aldehydes and ketones were heated with orthoacetates at elevated temperatures in the presence of a catalytic quantity of phenol. The reactions were conducted in the absence of any solvent by simply heating (120–130°C) the reactants under an inert atmosphere (see Table 1). The progress of the reaction could be monitored by thin layer chromatography (TLC) and after the appropriate time, the reaction was cooled to room temperature and treated with dilute HCl to remove excess orthoacetate and the residual crude α,β-unsaturated ester was purified by column chromatography (purity >90%, GC). This reaction is general with regard to various aldehydes such as aliphatic, aromatic, heterocyclic and α,β-unsaturated aldehydes.[7] However, in the case of ketones, cyclohexanone gave only trace amounts of the corresponding unsaturated ester, whereas acetophenone failed to react under identical reaction conditions. Aromatic aldehydes generally required 12 h or more heating whereas heterocyclic aldehydes such as furfural required only 6 h for complete conversion. This reaction was also found to be general with regard to different orthoesters, e.g. both trimethyl and triethyl orthoacetates gave comparable yields of the corresponding α,β-unsaturated esters under identical experimental conditions (Scheme 1).



R= aryl, alkyl, heterocyclic and α,β-unsaturated

$R^1 = CH_3, C_2H_5$

Scheme 1.

Keywords: orthoesters; aldehydes; α,β-unsaturated esters.

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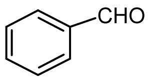
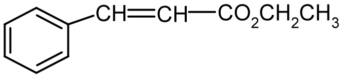
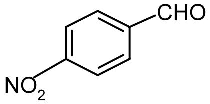
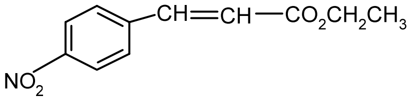
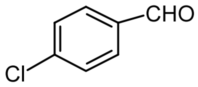
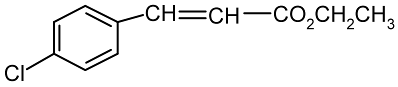
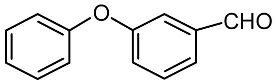
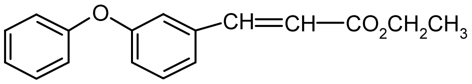
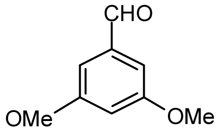
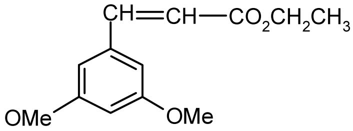
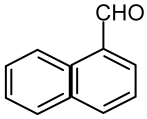
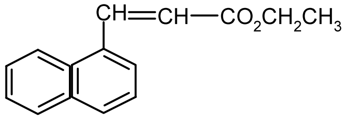
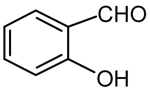
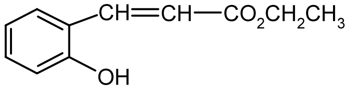
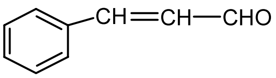
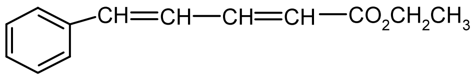
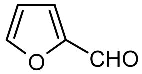
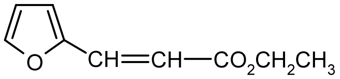
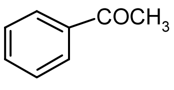
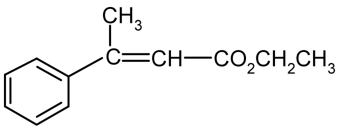
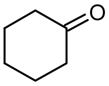
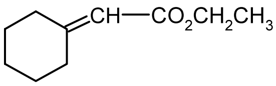
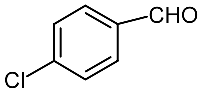
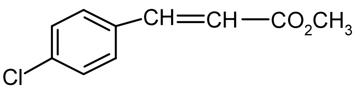
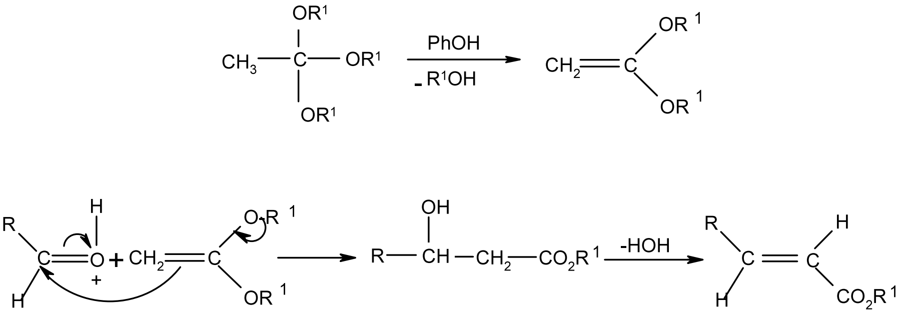
Table 1. Preparation of α,β-unsaturated esters

Entry	Carbonyl Compounds (**1**)	Product (**3**)	Reaction Time (h)	Yield[a] (Purity,GC)[b]
1			16	85 (95%)
2			12	90 (96%)
3			18	88 (92%)
4			12	87 (94%)
5			20	88 (95%)
6			26	82 (97%)
7			12	91 (95%)
8			14	82 (94%)
9			6	92 (97%)
10	$CH_3 (CH_2)_8 CHO$	$CH_3 (CH_2)_8$—CH=CH—$CO_2CH_2CH_3$	12	64 (90%)
11			20	-
12			20	8 (90%)
13			8	80 (96%)

a). Isolated yields after column chromatography b).Purity based on GC analysis : column OV-1 carrier gas flow H_2/N_2 : 20 ml/min, sample size 0.2 ml.



Scheme 2.

This condensation may proceed through the attack of an enol ether, generated by acid catalyzed degradation of the orthoacetate, on the oxonium ionfollowed by β-elimination to afford the *trans* α,β-unsaturated ester. Finally, when we attempted the direct condensation of ethyl acetate with aldehydes in the presence of a catalytic quantity of phenol under analogous experimental conditions, i.e. heating at 130°C for 12 h (a sealed tube was used on this occasion in order to prevent evaporation of ethyl acetate) no α,β-unsaturated ester could be detected in the reaction mixture. Thus, the reaction is unlikely to proceed through the direct condensation of the acetic acid ester generated in situ as the by-product of acid catalyzed degradation of the orthoacetate. This augments our proposed mechanism for the formation of α,β-unsaturated esters from the interaction of orthoacetates and aldehydes (Scheme 2, Table 1).

In conclusion, we have presented in this paper, a novel and efficient acid catalyzed condensation of orthoacetates with various aldehydes to generate α,β-unsaturated esters in good yields. The above method may find utility as an alternative to the currently available procedures for the preparation of these compounds.

Acknowledgements

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7. *Experimental: Typical procedure for the preparation of α,β-unsaturated esters*: A mixture of furfural (0.968 g, 10 mmol) and triethyl orthoacetate (3.24 g, 20 mmol) and phenol (0.2 g, 20% w/w of aldehyde) was heated at 130°C under a nitrogen atmosphere for 6 h at the end of which time the complete conversion could be ascertained by the total disappearance of aldehyde on TLC. The reaction mass was cooled to rt and washed with portions of cold dilute hydrochloric acid to remove any excess orthoacetate. This was followed by extraction with ether (2×25 ml) and the combined organic extracts washed with brine (10 ml) and dried (Na_2SO_4). Evaporation of the ether afforded a crude residue, which after column chromatography (silica gel, EtOAc–hexane, gradient) gave 1.59 g (92%) of product (entry 9, GC purity, 97%) as a viscous liquid;[8] bp 230°C; IR ($CHCl_3$): 1712 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3 (t, 3H, $J=7.4$ Hz), 4.2 (q, 2H, $J=7.4$ Hz), 6.3 (d, 1H, $J=15.7$ Hz), 6.43 (m, 1H), 6.56 (d, 1H, $J=3.4$ Hz), 7.39 (d, 1H, $J=15.7$ Hz), 7.45 (d, 1H, $J=1.6$ Hz).
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