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Efficient transesterification of ethyl acetoacetate with higher alcohols without catalysts

L. I. Koval *, V. I. Dzyuba, O. L. Ilnitska, V. I. Pekhnyo

V.I. Vernadskii Institute of General and Inorganic Chemistry, Ukrainian National Academy of Sciences, Prospect Palladina 32-34, 03680 Kyiv 142, Ukraine

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Abstract

The transesterification of ethyl acetoacetate (EtOAcac) without the use of catalysts is shown for primary, secondary and tertiary alcohols. The use of molecular sieves, which are used to shift the equilibrium, allows the synthesis of products in high yields and acceptable reaction times, which are on a par with those for transesterification processes using catalysts. The kinetics of the transesterification of EtOAcac with *tert*-amyl alcohol is studied.

Keywords: Transesterification; β-Ketoesters; Alcohols; Molecular sieves

The sphere of our scientific interests is in coordination chemistry of biometals[1] with organic compounds as ligands, which contain functional coordinating groups typical of biochemical systems. The use of such coordination compounds in various fields of science and engineering has promise in the development of modern environmentally acceptable technologies.

Among the above organic compounds, β-ketoesters are of interest since their chelate complexes with metals can find application as multifunctional additives in various lubricating compositions, including those based on oils of biological origin,[2] as potential antiviral drugs[3] and catalysts for various stereoselective reactions.[4] Moreover, β-ketoesters are of practical importance in preparative organic synthesis and can be used in lubricants as efficient friction modifiers.[5]

It is known[3] that metal chelates of β-diketones suppress the activity of some pathogenic viruses through the formation of a coordinate bond to metal ions at the active site of the virus enzyme responsible for virus replication. It may be assumed that β-ketoester derivatives, as the closest structural analogs of β-diketones, also have antiviral activity. In view of this, compounds, which contain bulky alicyclic fragments of alcohols such as menthol, borneol and adamantanol in addition to a β-dicarbonyl group, are of interest. These compounds are bioactive substances that occur in Nature, and efficient antiviral drugs have been developed based on adamantane.[6]

The aim of our work was to obtain a number of β-ketoesters by the simple and commonly used method of transesterification from readily available ethyl acetoacetate. The latter can be synthesized by Claisen condensation from ethyl acetate, which can be produced commercially from renewable raw materials of vegetable origin, viz. by esterification of acetic acid with ethanol. In addition to menthol, borneol and 1-adamantanol, we also used 1-hexanol, 1-dodecanol, cyclohexanol and 2-methyl-2-butanol as substrates. The presence of bulky alkyl substituents will impart high solubility in organic media of the coordination compounds.

For the transesterification of β-ketoesters, a large number of catalysts have been proposed and investigated,[7] many of which are expensive (e.g., Nb_2O_5)[8] and rather dangerous to the environment and health (tin derivatives).[9] Different catalysts give different results: the transesterification time, reactant ratio and end product yields differ greatly for the

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* Corresponding author. Tel.: +380 44 424 3461; fax: +380 44 424 3070.
E-mail address: l_koval@ionc.kiev.ua (L. I. Koval).

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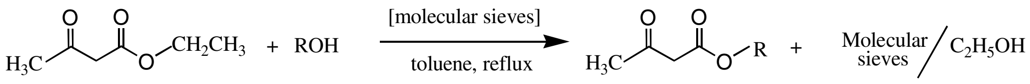
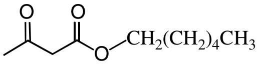
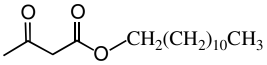
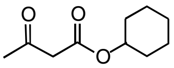
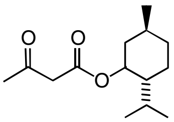
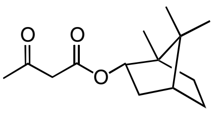
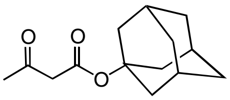
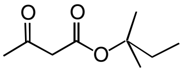


same starting compounds. According to Le Chatelier's principle, effective removal of one of the products from the reaction is required to shift the equilibrium of reversible processes, for example, transesterification. Bader et al.[10] synthesized a number of β-ketoesters of higher alcohols, including 1-dodecanol, cyclohexanol and menthol, in high yields without the use of catalysts, by continuously distilling the lower alcohol formed from the reaction mixtures. A simple and more convenient method for the removal of the lower alcohol is azeotropic distillation, which allows the use of stoichiometric reactants.[11] An alternative method, involving adsorption of the alcohol formed with molecular sieves,[12] is more efficient. The use of molecular sieves has been reported for the transesterification of carboxylic esters,[13] sugar orthoesters,[14] and methyl or ethyl β-ketoesters with allyl alcohol derivatives.[15] At the same time, all the above reactions were carried out in the presence of catalysts. Studying the transesterification of dimethyl terephthalate with *tert*-butanol, which is catalyzed by potassium *tert*-butylate in the presence of molecular sieves, Roelofsen et al.[16] showed that the time for almost complete transesterification of the original ester into the end product was much shorter in cases where molecular sieves form part of the reaction medium. However, the interpretation of this result was not correct since molecular sieves themselves can be transesterification reaction catalysts.[17]

In our experiments, we used molecular sieves with a pore size of 0.4 nm (4 Å) (ethyl alcohol molecules penetrate easily into pores of this size and are selectively bound by the active adsorbent), placed in a Sohxlet apparatus, to obtain primary, secondary and tertiary β-ketoesters from ethyl acetoacetate using equimolar reactant ratios (with the exception of reaction with 2-methyl-2-butanol) in the absence of catalysts.[18] Under such conditions, the transesterification process was carried out successfully with special preparation of the molecular sieves (which increased greatly their adsorption capacity) and exclusion of atmospheric moisture. The molecular sieves were first activated at 300 °C at atmospheric pressure for 8 h and then further dried for 3 h at the same temperature under 12 Pa vacuum using a trap placed in liquid nitrogen to freeze out water vapor.[19] The results of our investigations are listed in Table 1.

Analysis of the tabulated data shows that the reaction time increases as expected, in going from primary to

Table 1
Transesterification of ethyl acetoacetate using various alcohols and molecular sieves

Entry	Alcohol	Time (h)		Product	Boiling point of product, (°C)	Yield (%)	
		A	B			A	B
1	1-Hexanol	4	—		127–128 (25 hPa)	95	—
2	1-Dodecanol	5	8[17]		115–116 (12 Pa)	93	86[17]
3	Cyclohexanol	9.5	24[9a]		132–134 (25 hPa)	87	91[9a]
4	Menthol	12	8[17], 24[9a]		92–93 (12 Pa)	92	95[17], 93[9a]
5	Borneol	16	42[9a]		90–91 (12 Pa)	78	95[9a]
6	1-Adamantanol	24	—		94–95 (12 Pa)	25	—
7	2-Methyl-2-butanol	9	—		99–101 (25 hPa)	90	—

(A) Experimental data; (B) literature data.

secondary alcohols and on complication of the hydrocarbon skeleton of secondary alcohols. The yields of the desired β-ketoester decreased in the same order. Both the reaction time and the end product yield were on a par with the literature data for transesterifications carried out in the presence of a catalyst.

The rate of transesterification is greatly affected by steric factors, thus tertiary alcohols are less active. However, we obtained 1-adamantanyl acetoacetate; the yield of the purified product (a colorless labile liquid, which crystallizes with time) was 25% after boiling the reaction mixture for 24 h. The identity of the product was confirmed by liquid chromatography (TLC and HPLC); ^{1}H, ^{13}C NMR and IR spectroscopic data agreed with the literature data.[20]

Thermodynamic and kinetic investigations of β-ketoester transesterification reactions in the absence of catalysts have been reported. Witzeman has asserted that it is impossible to obtain tertiary β-ketoesters from methyl acetoacetate or ethyl acetoacetate because of the high thermodynamic stability of the latter and high rate of product decomposition in the reverse reaction.[21] We decided to verify this assertion by studying the kinetics of the reaction of ethyl acetoacetate with *tert*-amyl alcohol. Taking into account that displacement of the equilibrium of reversible reactions is easily attained by using an excess of one of the reactants, the synthesis was carried out in *tert*-amyl alcohol pre-dried over molecular sieves; the bp of this alcohol (102 °C) is much higher than that of ethanol, which makes it possible to remove effectively the latter from the reaction medium. The rate of the reaction was checked by following the increase in concentration of *tert*-amyl acetoacetate and by the consumption of the starting β-ketoester using GC. The results showed that the original β-ketoester was almost converted completely to the desired product within 9 h (Fig. 1).

Thus the use of specially prepared molecular sieves for the removal of ethanol formed during the transesterification of ethyl acetoacetate with various alcohols makes is possible to obtain β-ketoesters of primary, secondary and tertiary alcohols in high yields, including those with bulky alicyclic fragments. The simple experimental set-up, possibility of regeneration of molecular sieves, and the use of raw materials of vegetable origin make the proposed method acceptable for the development of environmentally friendly industrial technology.

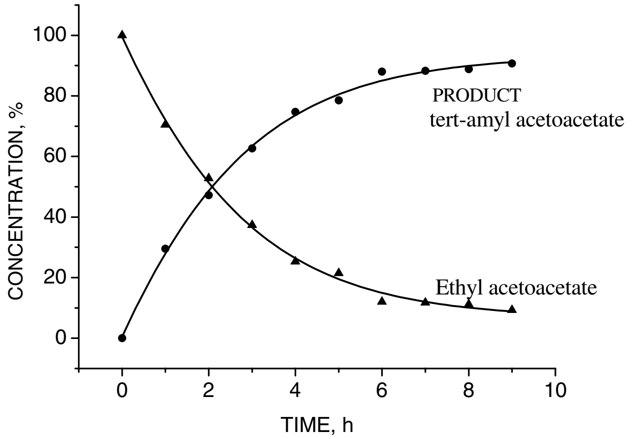


Fig. 1. Kinetic curves for the transesterification of ethyl acetoacetate with *tert*-amyl alcohol at 102 °C.

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18. General procedure for the transesterification: freshly distilled (or sublimated) dry alcohol (1 equiv) and ethyl acetoacetate (1 equiv) were refluxed (Table 1) in dry toluene under an inert-gas atmosphere in a system provided with Soxhlet extractor body (filled with molecular sieves) to remove the ethanol formed. Toluene was chosen as a solvent since it forms an azeotropic mixture with an ethanol content of 70%, owing to which the effectiveness of ethanol removal increases (unlike benzene, in which the reaction does not go to completion under the same conditions). The inert atmosphere was produced by passing argon through a capillary; gas bubbles created boiling centers on the one hand and prevented superfluous resinification of the reaction medium on the other hand. The extent of the reaction was checked by TLC. The solvent was removed using a rotary evaporator. The residues were distilled in vacuo to yield the products. All products were analyzed by bp, NMR, IR, GC and HPLC, and the spectra were consistent with the structures of the desired products.
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