

Hydroxycarbonylation of Isobutylene in the Presence of the Palladium Acetylacetonate–Triphenylphosphine–*p*-Toluenesulfonic Acid Catalyst System

Kh. A. Suerbaev^a, E. G. Chepaikin^b, G. Zh. Zhaksylykova^a, K. S. Kanybetov^a,
T. K. Turkbenov^a, and G. M. Abyzbekova^a

^a Al-Farabi Kazakh National University, ul. Al-Farabi 71, Almaty, 050038 Kazakhstan

^b Institute of Structural Macrokinetics and Materials Science, Russian Academy of Sciences, Chernogolovka, 142432 Russia

e-mail: echep@ism.ac.ru; grig@ism.ac.ru

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Abstract—The reaction of isobutylene hydroxycarbonylation with carbon monoxide and an alcohol (ethanol, 1-menthol) in the presence of the palladium acetylacetonate–triphenylphosphine–*p*-toluenesulfonic acid catalytic system was investigated. It was shown that the reaction proceeds regioselectively with the formation of linear products (ethyl isovalerate, 1-menthyl isovalerate). The optimum conditions for running the process were found, at which the yield of the main products is 67–79%.

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Hydroxycarbonylation of isobutylene, a product of oil refining, with carbon monoxide and an alcohol in the presence of homogeneous metal complex catalysts makes it possible to synthesize easily and conveniently in one step isovaleric acid esters, which possess biological activity and are components of pharmaceutical compositions or valuable intermediates for their synthesis. Some isovalerate esters possess a characteristic odor and are used as fragrance compounds in the manufacture of perfumes, cosmetics, and food essences [1].

The menthol ester of isovaleric acid (MIV) is an active principle of validol, a popular medicament [2]. It is synthesized in industry via esterification of isovaleric acid with menthol. The reactant isovaleric acid is obtained via the two-step oxidation of isoamyl alcohol isolated from fusel oils. The presence of the oxidation step, along with the use of feedstock of a plant origin (fusel oils), results in a high content of various undesirable impurities in isovaleric acid. It impairs the quality of MIV and, hence, the final medicine validol. Synthetic *d,l*-menthol contains an admixture of *d,l*-isomenthol (up to 25%) and, therefore, the use of phytogetic menthol (*l*-menthol) is more preferable, as only *l*-menthyl ester of isovaleric acid possesses biological activity [3]. One of the main active ingredients of the medicament corvalol is ethyl α -bromoisovalerate (EBIV) [2]. Commercially, the ester is obtained via a complex four-stage synthesis, in which the key stage is the bromination of isovaleryl chloride [4]. Isobutylene hydromenthoxycarbonylation with the synthesis gas in the presence of $(\text{PPh}_3)_2\text{PdCl}_2$ with an admixture of free triphenylphosphine was reported [5, 6]. An induction period was observed, which shortened as the ratio H_2/CO

increased. There are also patent data that describe the use of a synthesis gas as a source of carbon monoxide [7–9].

Earlier, we developed MIV and EBIV preparation methods that are more economical and environmentally friendly than the current industrial process, with the key steps of the methods being, respectively, the hydromenthoxycarbonylation and hydroethoxycarbonylation of isobutylene with carbon monoxide in the presence of the $\text{PdCl}_2(\text{PPh}_3)_2\text{-TsOH}$ and $\text{PdCl}_2\text{-PPh}_3\text{-TsOH}$ (TsOH is *p*-toluenesulfonic acid) catalytic systems [10–12].

In this work, we have investigated the reactions of isobutylene hydromenthoxycarbonylation and hydroethoxycarbonylation in the presence of the halogen-free palladium catalyst system $\text{Pd}(\text{acac})_2\text{-PPh}_3\text{-TsOH}$ with the purpose of the further development of the processes for manufacturing MIV and EBIV. The halogen-free catalytic system is much less corrosive and does not bring halogen in the final commercial product, thus making it possible to abandon testing the pharmaceutical for chlorine.

EXPERIMENTAL

The complex $\text{Pd}(\text{acac})_2$ was obtained according to the known procedure [13]. *p*-Toluenesulfonic acid (chemically pure grade) was recrystallized from 96% ethanol and dried until the composition $\text{TsOH} \cdot \text{H}_2\text{O}$. Triphenylphosphine (chemically pure grade, Chemapol) was recrystallized from an ether–ethanol mixture to a constant melting point. Absolute ethanol, isobutylene of 99.5% purity, carbon monoxide of

Table 1. Hydromenthoxycarbonylation of isobutylene with carbon monoxide and *l*-menthol in the presence of the Pd(acac)₂-PPh₃-TsOH system. Molar ratio [*l*-menthol] : [isobutylene] : [Pd(acac)₂] = 435 : 550 : 1. Amount of Pd(acac)₂ is 0.035 g (0.115 mmol)

| No. | Molar ratio of the catalyst components to Pd(acac) ₂ | | Reaction conditions | | | Unreacted <i>l</i> -menthol, % of initial quantity | Yield of <i>l</i> -menthylisovalerate, % | |
|-----|---|--------|---------------------|------------------------------|------------|--|--|------------------------------------|
| | [PPh ₃] | [TsOH] | <i>T</i> , °C | <i>p</i> _{CO} , MPa | τ , h | | on fed <i>l</i> -menthol basis | on reacted <i>l</i> -menthol basis |
| 1 | 2 | 12 | 100 | 2 | 4 | 79.8 | 13.2 | 65.3 |
| 2 | 3 | 12 | 100 | 2 | 4 | 74.2 | 19.3 | 74.8 |
| 3 | 5 | 12 | 100 | 2 | 4 | 75.1 | 21.5 | 90.1 |
| 4 | 7 | 12 | 100 | 2 | 4 | 28.3 | 67.6 | 94.3 |
| 5 | 9 | 12 | 100 | 2 | 4 | 44.2 | 48.2 | 86.4 |
| 6 | 7 | 8 | 100 | 2 | 4 | 56.6 | 35.3 | 80.5 |
| 7 | 7 | 10 | 100 | 2 | 4 | 26.6 | 61.9 | 84.1 |
| 8 | 7 | 13 | 100 | 2 | 4 | 53.5 | 36.7 | 80.1 |
| 9 | 7 | 12 | 90 | 2 | 4 | 40.6 | 54.8 | 91.8 |
| 10 | 7 | 12 | 110 | 2 | 4 | 40.1 | 52.1 | 87.3 |
| 11 | 7 | 12 | 100 | 1.5 | 4 | 46.5 | 46.9 | 87.2 |
| 12 | 7 | 12 | 100 | 2.5 | 4 | 57.9 | 39.7 | 97.1 |
| 13 | 7 | 12 | 100 | 2 | 2 | 54.2 | 39.2 | 85.6 |
| 14 | 7 | 12 | 100 | 2 | 5 | 62.0 | 30.2 | 79.8 |

99.8% purity, and *l*-menthol of 99.7% purity were used. The experiments were carried out in the solvent-free mode in a laboratory stainless steel autoclave unit. The components of the catalytic system and corresponding alcohols (ethanol, *l*-menthol) were loaded into an autoclave with a 100-ml capacity; the autoclave was sealed, purged with carbon monoxide, and charged with isobutylene and carbon monoxide; then, stirring and heating were switched on. After the completion of the reaction, the autoclave was cooled to ambient temperature, the pressure in the autoclave was reduced to atmospheric pressure, and the products were isolated by rectification according to the procedures described earlier [6, 10, 12]. The determination of the purity and the analysis of the products were carried out by means of a GLC technique on an LKhM-72 chromatograph with a thermal conductivity detector; stainless steel chromatographic columns 2-m-long and 3 mm in diameter packed with 5% Reoplex-400 on Chezasorb AW sorbent with a particle size of 0.15–0.25 mm. The temperature of the column oven was 110°C, that of the evaporator was 165–180°C, and the carrier gas (helium) flow rate was 30 ml/min.

RESULTS AND DISCUSSION

The influence of the various conditions of running the reaction of isobutylene hydromenthoxycarbonylation with carbon monoxide and *l*-menthol on the product yield was studied. The results are presented in Table 1. The carbonylation of isobutylene proceeds

regioselectively at the terminal carbon atom yielding the linear product *l*-menthyl isovalerate. The reaction was carried out at a molar ratio of [*l*-menthol] : [*iso*C₄H₈] : [Pd(acac)₂] = 435 : 550 : 1. As is seen from the data in Table 1, the reaction goes to completion in none of the runs: the recovery of unreacted *l*-menthol is 26.6–79.0% of the initial quantity.

The ratio of the components of the catalytic system has a strong effect on the yield of the product. An increase in the PPh₃/Pd(acac)₂ ratio from 2 up to 7 results in an increase in the yield of *l*-menthylisovalerate from 13.2 up to 67.6% (Table 1, entries 1–4). The further increase in the excess of PPh₃ reduces the yield of the product (Table 1, entry 5). The increase in the TsOH/Pd(acac)₂ ratio from 8 up to 12 increases the yield of the product from 35.3 up to 67.6% (Table 1; entries 4, 6, and 7). The optimum ratio of the components of the catalytic system turned out to be [Pd(acac)₂] : [PPh₃] : [TsOH] = 1 : 7 : 12. Such an effect of the increase in the excess of triphenylphosphine and *p*-toluenesulfonic acid in the system on the yield of the product may apparently be explained by their stabilizing effect on the catalyst. The temperature, carbon monoxide pressure, and the reaction time also strongly affect the yield of the product. With an increase in the reaction temperature from 90 up to 100°C, the yield of the product increases from 54.8 to 67.6% (Table 1; entries 4 and 9). With the further increase in the temperature (Table 1, entry 10), a decrease in the yield is observed because of the catalyst deactivation (appearance of palladium black). The dependence of the prod-

Table 2. Hydroethoxycarbonylation of isobutylene in the presence of the Pd(acac)₂-PPh₃-TsOH system. Amount of Pd(acac)₂ = 0.035 g (0.115 mmol). Molar ratio isobutylene : Pd(acac)₂ = 550

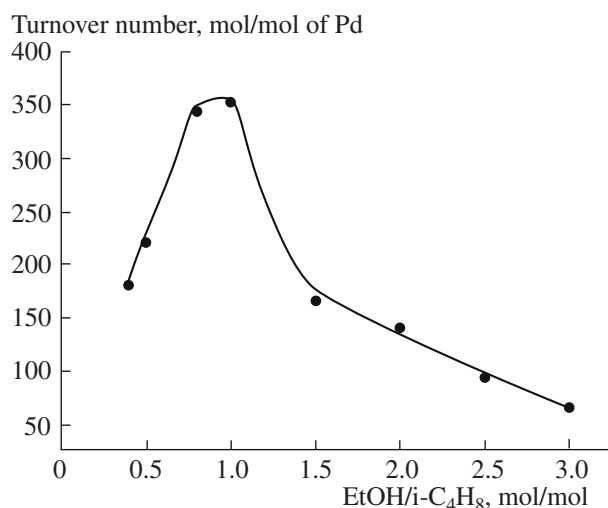
| No. | Molar ratio of the reactants and catalyst components to Pd(acac) ₂ | | | Reaction conditions | | | Ethyl isovalerate yield, % |
|-----|---|------------------|------|---------------------|-----------------------|------|----------------------------|
| | Ethanol | PPh ₃ | TsOH | T, °C | p _{co} , MPa | τ, h | |
| 1 | 435 | 7 | 12 | 100 | 2.0 | 6 | 68.0 |
| 2 | 435 | 5 | 12 | 100 | 2.0 | 6 | 72.0 |
| 3 | 435 | 4 | 12 | 100 | 2.0 | 6 | 73.5 |
| 4 | 435 | 3 | 12 | 100 | 2.0 | 6 | 74.5 |
| 5 | 435 | 2 | 12 | 100 | 2.0 | 6 | 46.0 |
| 6 | 435 | 9 | 12 | 100 | 2.0 | 6 | 66.0 |
| 7 | 435 | 3 | 13 | 100 | 2.0 | 6 | 63.0 |
| 8 | 435 | 3 | 10 | 100 | 2.0 | 6 | 71.0 |
| 9 | 435 | 3 | 8 | 100 | 2.0 | 6 | 64.0 |
| 10 | 435 | 3 | 12 | 110 | 2.0 | 6 | 58.0 |
| 11 | 435 | 3 | 12 | 90 | 2.0 | 6 | 60.0 |
| 12 | 435 | 3 | 12 | 100 | 1.5 | 6 | 52.0 |
| 13 | 435 | 3 | 12 | 100 | 2.2 | 6 | 75.0 |
| 14 | 435 | 3 | 12 | 100 | 2.5 | 6 | 76.0 |
| 15 | 435 | 3 | 12 | 100 | 2.8 | 6 | 77.0 |
| 16 | 435 | 3 | 12 | 100 | 3.0 | 6 | 78.0 |
| 17 | 435 | 3 | 12 | 100 | 3.2 | 6 | 68.0 |
| 18 | 435 | 3 | 12 | 100 | 3.5 | 6 | 37.0 |
| 19 | 435 | 3 | 12 | 100 | 3.0 | 4 | 77.0 |
| 20 | 275 | 3 | 12 | 100 | 3.0 | 5 | 79.0 |
| 21 | 435 | 3 | 12 | 100 | 3.0 | 5 | 79.0 |
| 22 | 550 | 3 | 12 | 100 | 3.0 | 5 | 64.0 |
| 23 | 1100 | 3 | 12 | 100 | 3.0 | 5 | 25.4 |

uct yield on the carbon monoxide pressure and the reaction time is likewise nonmonotonic in character: a carbon monoxide pressure of 2.0 MPa (Table 1; entries 4, 11, and 12) and a reaction time of 4 h (Table 1; entries 4, 13, and 14) are the optimum values. The further increase in the pressure of carbon monoxide to 2.5 MPa sharply reduces the yield of the product to 39.7% (Table 1, entry 12), a development that is obviously caused by the competition between the olefin and carbon monoxide for the place in the coordination sphere of palladium complexes.

The reaction of hydroethoxycarbonylation of isobutylene with carbon monoxide and ethanol also proceeds regioselectively to give the linear product. The influence of the reaction conditions on the yield of the main product ethyl isovalerate (Table 2) was studied. The optimum ratio of the components of the catalytic system is [Pd(acac)₂] : [PPh₃] : [TsOH] = 1 : 3 : 12 (Table 2, entries 1–9). Note that, unlike the case of hydromethoxycarbonylation of isobutylene, a smaller quantity of triphenylphosphine is required for isobutylene hydroethoxycarbonylation, a difference that is obvi-

ously due, first of all, to the nature of the alcohol reagent. The dependences of the yield of the product on temperature (Table 2; entries 4, 10, and 11) and reaction time (Table 2; entries 16, 19, and 21) are nonmonotonic with a maximum at 100°C and 5 h, respectively. The pressure (Table 2; entries 4, 12–18) strongly affects the yield of the product. The product yield increases from 52 to 74.5% with an increase in the pressure from 1.5 to 2.0 MPa. Furthermore, the yield continuously increases by 3.5% with an increase in pressure from 2.0 to 3.0 MPa and, then, sharply falls to 37% at 3.5 MPa. The reactant ratio has a substantial effect on the yield of the product. The increase in the [isobutylene] : [ethanol] molar ratio from 0.5 to 2 was found to increase the yield of the product from 25.4 to 79.0% (Table 2, entries 20–23). From the data presented in the figure, it follows that the optimum molar ratio of these compounds is 0.8–1.0; in this case, the productivity of the catalytic system is ca. 330 mol/mol of Pd.

Thus, a high catalytic activity of the halogen-free ternary homogeneous catalytic system Pd(acac)₂-PPh₃-TsOH in the reactions of isobutylene hydromen-



Dependence of the productivity of the Pd(acac)₂-PPh₃-TsOH catalytic system on the ethanol/isobutylene molar ratio. Amount of Pd(acac)₂ = 0.035 g (0.115 mmol). Isobutylene : PPh₃ : TsOH molar ratio = 550 : 3 : 12. *p*CO = 3.0 MPa, *T* = 100°C. Reaction time, 5 h.

thoxy- and hydroethoxycarbonylation with carbon monoxide and *l*-menthol or ethanol, respectively, was revealed. As expected, the reactions proceed regioselectively to give the linear products, *l*-menthyl isovalerate and ethyl isovalerate. The optimum conditions for the processes at which the yields of *l*-menthylisovalerate and ethyl isovalerate reach 67.6% (94.3% on a reacted *l*-menthol basis) and 79.0%, respectively, were found.

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