ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 10, pp. 1596–1597. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © N.O. Appazov, S.S. Seitzhanov, A.T. Zhunissov, R.A. Narmanova, 2017, published in Zhurnal Organicheskoi Khimii, 2017, Vol. 53, No. 10, pp. 1560–1561.

SHORT COMMUNICATIONS

Synthesis of Cyclohexyl Isovalerate by Carbonylation of Isobutylene with Carbon Monoxide and Cyclohexanol in the Presence of $Pd(PPh_3)_4$–PPh_3–TsOH and Its Antimicrobial Activity

N. O. Appazov,* S. S. Seitzhanov, A. T. Zhunissov, and R. A. Narmanova

Korkyt Ata Kyzylorda State University, ul. Aiteke bi 29A, Kyzylorda, 120014 Kazakhstan
**e-mail: nurasar.82@mail.ru*

Received October 28, 2016

Abstract—A procedure has been developed for the synthesis of cyclohexyl isovalerate by reaction of isobutylene with carbon monoxide and cyclohexanol in the presence of the three-component catalytic system $Pd(PPh_3)_4$–PPh_3–TsOH. Cyclohexyl isovalerate showed a pronounced antibacterial activity.

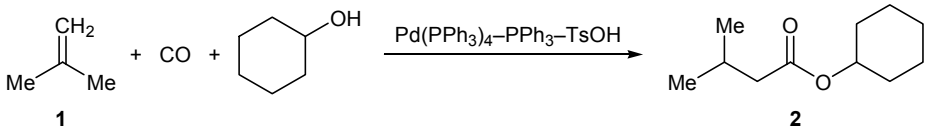
DOI: 10.1134/S1070428017100189

Isovaleric acid esters are used as components of medicines (valerian root, corvalol, validol), perfumes, and food flavoring agents (ethyl, propyl, isoamyl, hexyl, decadienyl, geranyl, and 2-phenylethyl isovalerates) [1–3]. Industrial methods for the synthesis of carboxylic acid esters are based on esterification of carboxylic acids with the corresponding alcohols. The technology is complicated and is environmentally unsafe because of a number of secondary operations (neutralization, washing, etc.), producing large amounts of industrial wastes.

A promising method for the manufacture of carboxylic acid esters is alkoxycarbonylation of alkenes with carbon monoxide and alcohols in the presence of catalysts based on Group VIII transition metal complexes [4–14]. Ethyl carboxylates can be obtained by reaction of alkenes with carbon monoxide and ethanol in the presence of the two-component catalytic system $Pd(PPh_3)_4$–TsOH (1 : 3 to 1 : 12) at 60–100°C and a pressure of 0.5–3.0 MPa (reaction time 0.5–4 h). A significant drawback of this procedure is that it is hardly suitable for the preparation of esters from alicyclic alcohols. Cyclohexyl isovalerate (**2**) was obtained in a low yield (46.6%) by hydroalkoxycarbonylation of isobutylene (**1**) with CO and cyclohexanol in the presence of $Pd(PPh_3)_4$–TsOH (1 : 12) at 100°C and a pressure of 2.0 MPa for 4 h [15].

We have developed a procedure for the synthesis of ester **2** by reaction of alkene **1** with carbon monoxide and cyclohexanol under catalysis by the three-component system $Pd(PPh_3)_4$–PPh_3–TsOH (1 : 3 : 12) at 100°C (CO pressure 2.0 MPa, 4 h). Under these conditions, ester **2** was formed in quantitative yield and was isolated in up to 71% yield. The product structure was confirmed by IR and mass spectra. The IR spectrum of **2** contained absorption bands at 3000–2872 (C–H) and 1294–1095 cm^{-1} (C–O–C) and a strong band at 1736 cm^{-1} (C=O).

Preliminary tests revealed considerable antimicrobial and antifungal activity of compound **2** against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*. The antimicrobial and antifungal activity of **2** was assayed by the agar diffusion method [16]. Ester **2** was dissolved in 96% ethanol to a concentration of 1 mg/mL. The bacterial and fungal cultures were grown by incubation for 18–24 h at 37°C, dispersed in a 0.9% solution of sodium chloride, and applied in 1-mL portions to Petri



1 **2**

dished filled with beef extract agar to obtain a "continuous lawn." Wells with a diameter of 6 mm were made by pressing out, and samples of **2** and 96% ethanol (as control) were placed therein. The antimicrobial activity was evaluated by the inhibition zone diameter (mm). An inhibition zone of smaller than 10 mm was assumed to indicate the absence of antimicrobial activity, 10–15 mm, weak activity, 15–20 mm, moderate activity, and 20 mm and larger, pronounced activity.

Cyclohexyl isovalerate (**2**) showed pronounced antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (inhibition zone diameter 20–22 mm) and moderate antifungal activity against *Candida albicans* (16± 0.1 mm); therefore, it may be used in medicine as antibacterial and antifungal agent.

Cyclohexyl 3-methylbutanoate (2). A 100-mL steel high-pressure reactor equipped with a stirrer and adapter for the introduction of carbon monoxide and isobutylene was charged with 0.133 g (6.35×10^{-4} mol) of $Pd(PPh_3)_4$, 0.091 g (3.46×10^{-4} mol) of PPh_3, 0.263 g (1.38×10^{-3} mol) of TsOH, and 5.03 g (5.02×10^{-2} mol) of cyclohexanol (the ratio of isobutylene, cyclohexanol, and catalytic system components was 550 : 435 : 1 : 3 : 12). The reactor was hermetically closed, purged twice with carbon monoxide to expel air, and filled with carbon monoxide to a pressure of 1.0 MPa. Isobutylene, 3.562 g (6.35×10^{-2} mol), was then loaded with stirring, the CO pressure was raised to 1.7–1.8 MPa, the reactor was heated to 100°C over a period of 1 h, and the mixture was stirred for 4 h at that temperature and a pressure of 2.0 MPa. The stirring was turned off, the reactor was cooled to room temperature and kept for at least 1 h, and the product was isolated by fractional distillation. Yield 6.55 g (71%), bp 223°C, $n_D^{20} = 1.442$.

Gas chromatographic–mass spectrometric analysis was performed using an Agilent Technologies 7890A chromatograph coupled with a 5975C mass-selective detector; HP-5MS capillary column, 30 m×0.25 mm, carrier gas helium; injector temperature 250°C; oven temperature programming from 40°C (1 min) at a rate of 5 deg/min to 200°C (1 min); total time 34 min; split ratio 1000 : 1; electron impact; retention time of **2** 19.4 min. The IR spectra were recorded on a Shimadzu IR-Prestige 21 spectrometer equipped with a Smiths DuraSamplIR II diamond ATR accessory.

REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Medicines), Moscow: Novaya Volna, 2012, 16th ed.
2. Voitkevich, S.A., *865 dushistykh veshchestv dlya parfyumerii i bytovoi khimii* (865 Fragrant Substances for Perfumery and Household Chemicals), Moscow: Pishchevaya Promyshlennost', 1994.
3. Kheifits, L.A. and Dashunin, V.M., *Dushistye veshchestva i drugie produkty dlya parfyumerii: Spravochnoe izdanie* (Fragrant Substances and Other Compounds for Perfumery. Reference Book), Moscow: Khimiya, 1994.
4. Suerbaev, Kh.A., Zhaksylykova, G.Z., and Appazov, N.O., *J. Pet. Environ. Biotechnol*., 2014, vol. 4, p. 164. doi 10.4172/2157-7463.1000164
5. Suerbaev, Kh.A., Chepaikin, E.G., Appazov, N.O., and Dzhiembaev, B.Zh., *Pet. Chem*., 2012, vol. 52, p. 189.
6. Suerbaev, Kh.A., Zhaksylykova, G.Zh., and Appazov, N.O., *Eur. Chem. Tecnol. J*., 2014, vol. 16, p. 299.
7. Boulanger, J., Seingeot, A., Leger, B., Pruvost, R., Ibert, M., Mortreux, A., Chenal, T., Sauthier, M., Ponchel, A., and Monflier, E., *Catal. Commun*., 2015, vol. 69, p. 143.
8. Liu, J., Heaton, B.T., Iggo, J.A., Whyman, R., Bickley, J.F., and Steiner, A., *Chem. Eur. J*., 2006, vol. 12, p. 4417.
9. Rangits, G. and Kollár, L., *J. Mol. Catal. A: Chem*., 2006, vol. 246, p. 59.
10. Aver'yanov, V.A., Nosova, N.M., and Batashev, S.A., *Pet. Chem*., 2006, vol. 46, p. 99.
11. Keglevich, G., Kégl, T., Odinets, I.L., Vinogradova, N.M., and Kollár, L., *C. R. Chim*., 2004, vol. 7, p. 779.
12. Nobbs, J.D., Low, C.H., Stubbs, L.P., Wang, C., Drent, E., and van Meurs, M., *Organometallics*, 2017, vol. 36, p. 391.
13. Dong, K., Fang, X., Gülak, S., Franke, R., Spannenberg, A., Neumann, H., Jackstell, R., and Beller, M., *Nat. Commun*., 2017, vol. 8, article no. 14117. doi 10.1038/ncomms14117
14. Maffei, M., Giacoia, G., Mancuso, R., Bartolo, G., Motti, E., Costa, M., and Della, Ca'N., *J. Mol. Catal. A: Chem*., 2017, vol. 426, p. 435.
15. Suerbaev, Kh.A., Shalmagambetov, K.M., Abyzbekova, G.M., Turkbenov, T.K., and Zhaksylykova, G.Zh., KZ Patent no. 16185, 2005; *Promyshl. Sobstv. Ofits. Byull. Nats. Inst. Intell. Sobstv. MYu RK*, 2005, no. 9.
16. Pokrovskii, V.I. and Pozdeev, O.K., *Meditsinskaya mikrobiologiya* (Medical Microbiology), Moscow: GEOTAR Meditsina, 1999.