

SHORT
COMMUNICATIONS

Synthesis of L-Menthyl Isovalerate by Esterification of Isovaleric Acid with L-Menthol under Microwave Irradiation

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Isovaleric acid esters have found a wide range of practical applications. Many compounds of this series exhibit biological activity and are used as components of widely used drugs such as validol, corvalol, etc. [1, 2]. Ethyl, isopentyl, 2-phenylethyl, and cinnamyl isovalerates are components of food additives and perfumes [3]. L-Menthyl isovalerate is the main active component of the spasmolytic validol [2] (25–30% solution of menthol in menthyl isovalerate).

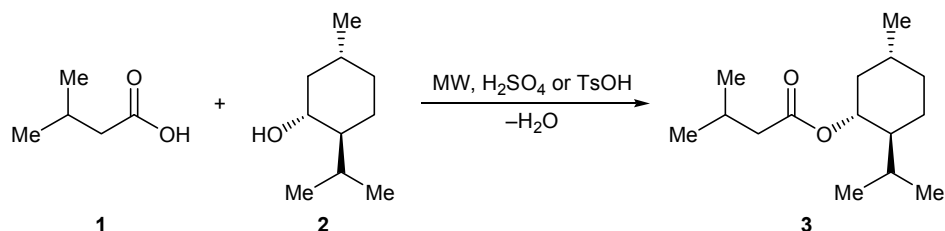
The existing technology for the large-scale production of validol is based on the esterification of isovaleric acid (**1**) with menthol (**2**) in the presence of concentrated sulfuric acid as catalyst. Ester **3** can also be obtained by reaction of isobutylene with synthesis gas and menthol in the presence of PdCl₂(PPh₃)₂-PPh₃ in dioxane or *p*-xylene [4]. We have developed a convenient procedure for the synthesis of L-menthyl isovalerate by reaction of isobutylene with carbon(II) oxide and L-menthol using Pd(PPh₃)₄-PPh₃-TsOH as catalytic system [5].

In this communication we report esterification of isovaleric acid with L-menthol in the presence of acid catalysts under microwave irradiation. Microwave-assisted syntheses of organic compounds constitute now a rapidly progressing field of chemistry [6–9]. Microwave (MW) irradiation accelerates chemical

reactions by several orders of magnitude and ensures fast heating of both liquid and solid materials. Microwave-assisted reactions generally conform to the green chemistry principles, i.e., are environmentally benign [8]. Wide prospects in using MW radiation have aroused great interest in studying its effects and their practical applications. Syntheses of esters by esterification of carboxylic acids with alcohols under microwave irradiation have been reported [6, 9].

With the goal of finding optimal conditions for the esterification of isovaleric acid with L-menthol in the presence of concd. H₂SO₄ under MW irradiation, we examined the effects of different factors (irradiation power, reaction time, reactant and catalyst ratio) on the yield of ester **3**. It was found that the optimal irradiation power is 560 W at a 1–2–H₂SO₄ molar ratio of 1:1:4.8×10⁻⁵ and irradiation time of 2 min. No reaction was observed at a power of 450 W, at 560 W the yield was 17.4%, while increase of the irradiation power to 900 W led to sharply reduced yield (2.2%). Therefore, further experiments were carried out at a power of 560 W.

Increase of the irradiation duration from 2 to 12 min (the power and reactant ratio being the same as indicated above) increased the yield of **3** from 18 to 55%, but the yield decreased to 52% after 14 min. The



Esterification of isovaleric acid with L-menthol in the presence of *p*-toluenesulfonic acid under microwave irradiation

Ratio 1–2–TsOH (mol %)	Reaction time, min	Yield of 3 , wt %
1:1:5.45 × 10 ⁻⁵	10	55.2
1:1:5.45 × 10 ⁻⁵	11	63.9
1:1:5.45 × 10 ⁻⁵	12	65.7
1:1:5.45 × 10 ⁻⁵	13	60.6
1:1:4.1 × 10 ⁻⁵	12	55.8
1:1:6.81 × 10 ⁻⁵	12	77.7
1:1:8.51 × 10 ⁻⁵	12	78.8
1:0.9:8.51 × 10 ⁻⁵	12	81.4
1:1.1:8.51 × 10 ⁻⁵	12	82.5
1:1.2:8.51 × 10 ⁻⁵	12	88.7
1:1.3:8.51 × 10 ⁻⁵	12	81.7

optimal 1–2–H₂SO₄ ratio was 1:1:9.6 × 10⁻⁵ (irradiation time 12 min). Thus the yield of **3** is strongly determined by the MW power and irradiation duration, whereas the ratio of the reactants and catalyst is less significant. The yield of **3** under the optimal conditions was 59%.

When the reaction was carried out in the presence of another acid catalyst, *p*-toluenesulfonic acid, the optimal conditions were MW power 560 W, irradiation time 12 min, and ratio 1–2–TsOH 1:1.2:8.51 × 10⁻⁵. These conditions ensured 89% yield of **3**.

The structure of **3** was confirmed by IR and ¹H NMR spectra. The IR spectrum of **3** showed a strong ester carbonyl stretching band at 1731 cm⁻¹, and absorption bands at 1050–1300 (C–O–C) and 2870–3543 cm⁻¹ (C–H). The ¹H NMR spectrum of **3** was fully consistent with published data [5].

L-Menthyl isovalerate (3). A glass beaker was charged with required amounts of isovaleric acid, L-menthol, and catalyst, and the mixture was subjected to microwave irradiation in a Samsung MB 39449G household microwave furnace (2.45 GHz). The mixture was analyzed by GC/MS. Fractional distillation gave ester **3** with bp 123°C (6 mm), *n*_D²⁰ = 1.4480; published data [10]: bp 129°C (10 mm), *n*_D²⁰ = 1.4486.

Gas chromatographic–mass spectrometric analysis was performed on an Agilent Technologies 7890A gas

chromatograph coupled with an HP 5975C mass-selective detector; HP-FFAP capillary column (30 m × 0.25 mm), stationary phase poly(ethylene glycol)-modified nitroterephthalic acid; carrier gas helium; injector temperature 300°C, oven temperature programming from 40°C (1 min) at a rate of 5 deg/min to 250°C (1 min); total time 44 min; split ratio 1000:1; electron impact ionization; retention time of **3** 20.4 min. The IR spectra were recorded in KBr on a UR-20 spectrometer. The ¹H NMR spectrum was measured on a Bruker DPX 400 instrument (300 MHz) using chloroform-*d* as solvent and tetramethylsilane as internal standard.

Commercial isovaleric acid and *p*-toluenesulfonic acid (Sigma–Aldrich) and reagent grade L-menthol and concentrated sulfuric acid were used without additional purification.

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