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SHORT COMMUNICATIONS

One-Pot Ozonolytic Synthesis of Isoniazid Derivatives from (–)-α-Pinene and Δ^3-Carene

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Abstract—Optically active isoniazid derivatives containing a cyclopropane or cyclobutane fragment have been synthesized by ozonolysis of (+)-Δ^3-carene and (–)-α-pinene, followed by treatment of the ozonolysis products with isonicotinic acid hydrazide.

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An important approach to the design of new medicines is based on the introduction of a pharmacophoric group into the target molecule. Isoniazid (**1**, isonicotinic acid hydrazide) is utilized in almost all schemes for the prophylactics and treatment of tuberculosis. However, this drug is toxic (LD_{50} 178 mg/kg) [1]; therefore, a topical problem is search for new compounds possessing a high tuberculostatic activity in combination with low toxicity [2]. It is known that the general toxicity can be reduced via attachment of the isoniazid fragment to various scaffolds, e.g., by the synthesis of acylhydrazones from isoniazid (**1**) and various carbonyl compounds [1–3].

Herein we describe a procedure for the synthesis of isoniazid derivatives from alkenes by ozonolysis of the latter in methanol at 0°C and subsequent treatment of the resulting peroxides with excess isoniazid without isolation of intermediate carbonyl compounds. In this way, from natural monoterpenes, (+)-Δ^3-carene (**2**) and (–)-α-pinene (**3**) we obtained in good yields optically active acylhydrazones **4** and **5** containing cyclopropane and cyclobutane fragments. Analogous approach was applied by us previously to accomplish direct transformations of alkenes, including terpenes **2** and **3**, into tosylhydrazones [4] and semicarbazones [5].

Probable biological activity of compounds **4** and **5** was estimated using PASS (Prediction of Activity Spectra for Substances) computer program which is based on structure–activity relation analysis for a vast training set [6]. It was found that the probability of antitubercular, antimycobacterial, and antiviral activity of acylhydrazones **4** and **5** is lower than for isoniazid (**1**) and that the probability of antibacterial activity is comparable (Table 1).

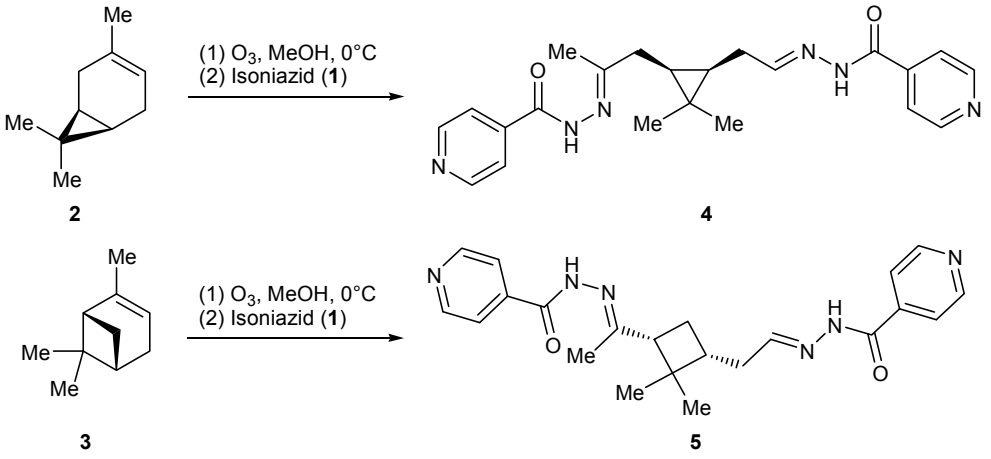

Table 1. Prediction of biological activity of compounds **4** and **5** and isoniazid (**1**) using PASS computer program[a]

Activity	1		4		5	
	*P*a	*P*i	*P*a	*P*i	*P*a	*P*i
Antitubercular	0.813	0.003	0.538	0.009	0.524	0.010
Antimycobacterial	0.801	0.004	0.505	0.018	0.514	0.017
Antiviral (Picornavirus)	0.613	0.017	0.408	0.103	0.485	0.057
Antibacterial	0.377	0.036	0.373	0.037	0.448	0.022

[a] *P*a stands for the probability of a given activity, and *P*i stands for the probability of inactivity.

Acylhydrazones 4 and 5 (*general procedure*). An ozone–oxygen mixture was bubbled through a solution of 3.3 mmol of terpene **2** or **3** in 20 mL of anhydrous methanol at 0°C until 4 mmol of ozone was absorbed. The mixture was purged with argon, 10.9 mmol of isoniazid (**1**) was added at 0°C, and the mixture was stirred at room temperature until peroxides were no longer detected by starch–iodine test. The solvent was distilled off, the residue was dissolved in chloroform, the solution was washed with brine, dried over Na_2SO_4, and evaporated, and the residue was purified by chromatography on silica gel using petroleum ether–*tert*-butyl methyl ether (10:1 to 1:1) and then methanol as eluents.

(*E*)-*N*′-{1-[(1*S*,3*R*)-2,2-Dimethyl-3-{(*E*)-2-[2-(pyridine-4-carbonyl)hydrazinylidene]ethyl}cyclopropyl]propan-2-ylidene}pyridine-4-carbohydrazide (4). Yield 63%, R_f 0.08 (petroleum ether–ethyl acetate, 1:1), $[\alpha]_D^{20}$ = –5° (*c* = 1.1, $CHCl_3$). IR spectrum (KBr): ν 1599 cm^{-1} (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.75–0.90 m (2H, 1-H, 3-H), 0.95 s (3H, CH_3), 1.05 s (3H, CH_3), 2.15 s (3H, C**H**$_3$CH), 2.20–2.35 m (4H, CH_2), 7.50–7.70 m (4H, H_{arom}), 7.45 m (1H, CH=N), 8.40–8.70 m (4H, H_{arom}), 9.25 br.s (2H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.55 q (CH_3), 19.10 s (C^2), 20.04 q (CH_3), 23.01 d (C^1), 23.23 d (C^3), 29.17 q (CH_3), 29.86 t (**C**H_2C=N), 32.86 t (CH_2), 121.24 d and 121.35 d (4C, CH_{arom}), 139.90 s (2C, C_{arom}), 149.22 d (CH=N), 150.14 d and 150.29 d (4C, CH_{arom}), 163.34 s (C=N), 164.34 s (2C, C=O). Mass spectrum: *m*/*z* 407 (I_{rel} 100%) $[M + H]^+$. Found, %: C 65.12; H 6.40; N 20.61. $C_{22}H_{26}N_6O_2$. Calculated, %: C 65.01; H 6.45; N 20.68. *M* 406.48.

(*E*)-*N*′-{1-[(1*R*,3*R*)-2,2-Dimethyl-3-{(*E*)-2-[2-(pyridine-4-carbonyl)hydrazinylidene]ethyl}cyclobutyl]ethylidene}pyridine-4-carbohydrazide (5). Yield 87%, R_f 0.08 (petroleum ether–ethyl acetate, 1:1), $[\alpha]_D^{20}$ = –14° (*c* = 0.192, $CHCl_3$). IR spectrum (KBr): ν 1601 cm^{-1} (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 s (3H, CH_3), 1.15 s (3H, CH_3), 1.60–1.70 m (2H, 4-H), 1.85 s (3H, CH_3C=N), 1.90–2.05 m (1H, 1-H), 2.10–2.35 m (2H, CH_2), 2.50–2.70 m (1H, 3-H), 7.40–7.60 m (4H, H_{arom}), 7.70–7.80 m (1H, CH=N), 8.40–8.70 m (4H, H_{arom}), 10.10 br.s (2H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.29 q (**C**H_3C=N), 22.48 q (CH_3), 24.22 t (C^4), 26.70 q (CH_3), 30.43 d (C^1), 34.59 t (CH_2), 43.44 s (C^2), 49.14 d (C^3), 121.32 d and 121.53 d (4C, CH_{arom}), 139.95 s (2C, C_{arom}), 153.27 d (CH=N), 150.16 d and 150.33 d (4C, CH_{arom}), 162.41 s (C=N), 162.91 s (2C, C=O). Mass spectrum: *m*/*z* 407 (I_{rel} 100%): $[M + H]^+$. Found, %: C 65.10; H 6.39; N 20.63. $C_{22}H_{26}N_6O_2$. Calculated, %: C 65.01; H 6.45; N 20.68. *M* 406.48.

The IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-500 spectrometer at 500.13 and 126.76 MHz, respectively, using tetramethylsilane as internal standard. The mass spectra were obtained on a Shimadzu LCMS-2010 EV instrument. Silica gel (70–230 mesh; Lancaster, UK) was used for column chromatography. The ozonizer efficiency was 40 mmol O_3/h.

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