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NEW SYNTHETIC ROUTE TO KETONES FROM CAMPHENE AND β-PINENE

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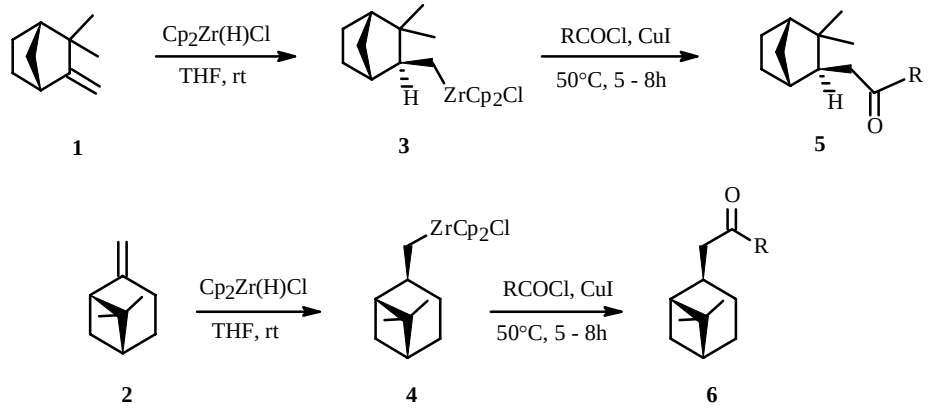
Camphene or β-pinene was treated with $Cp_2Zr(H)Cl$ ($Cp = h^5–C_5H_5$) in THF to give organozirconium (IV) complexes, which were trapped with acetyl chloride or benzoyl chloride in the presence of CuI to afford ketones in yields of 63% to 74%.

Key words: ketones, regioselectivity, camphene, β-pinene, hydrozirconation, synthesis.

Ketones made from terpene, such as camphene or β-pinene, usually have a pleasant odor [1]. It was reported [2] that Vismeir-Haack reaction of camphene gave ω-formylcamphene, which treated with Grignard reagents followed by hydrolysis and oxidation to give ω-acylcamphene compounds [3]. But the yields were not high and the reaction process was complex.

Recently an organometallic reagent was used for the preparation of ketones from terpene. For example, the reaction of a diorganozinc compound, prepared from β-pinene, with acid chlorides in the presence of $CoBr_2$ [4] or CuCl×2LiCl [5] afforded (–)-(1S, 2S)-6,6-dimethyl-2-(2-oxo-2-phenylethyl)-bicyclo[3.1.1]heptane. The same ketone was also prepared by reaction of the appropriate 8-(acyloxy)quinoline with an organoaluminum reagent [6]. But the organozinc reagent and the organoaluminum reagent are not easily available.

Hydrozirconation has recently been developed as a procedure for functionalizing alkenes and alkynes via organozirconium (IV) intermediates. These intermediates react with a variety of electrophilic reagents to give organic products in high yield [7–9].



Now we report a new synthetic route to the ketones from camphene or β-pinene. Camphene (**1**) or β-pinene (**2**) was treated with $Cp_2Zr(H)Cl$ ($Cp = h^5$-C_5H_5) in THF to give organozirconium (IV) complexes **3** or **4**, which were trapped respectively with acetyl chloride or benzoyl chloride in the presence of CuI to afford ketones **5** or **6** (Table 1).

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TABLE 1. Synthesis of Ketones **5** and **6**

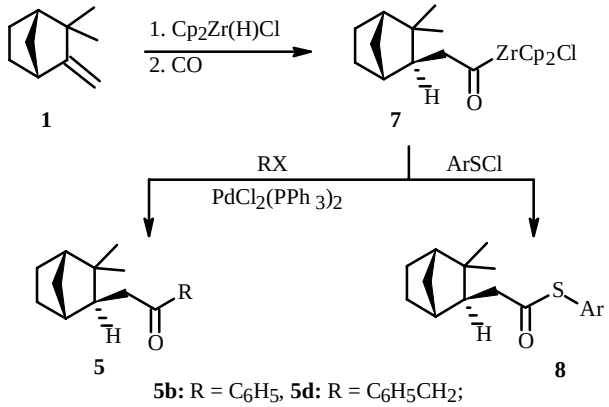
Product	R	Yield*, %
5a	CH_3	63
5b	Ph	72
5c	4-ClC_6H_4	70
6a	CH_3	68
6b	Ph	74

*Isolated yield based on camphene or β-pinene.

TABLE 2. Synthesis of Ketones **5** and Thioesters **8**

Product*	R (Ar)	Temperature, °C	Time, h	Yield,* %
5b	Ph	40	8	38
5d	$PhCH_2$	40	8	29
8a	Ph	0	1	54
8b	4-MeC_6H_4	0	1	61

*Isolated yield based on camphene.



5b: R = C_6H_5, **5d:** R = $C_6H_5CH_2$;
8a: R = C_6H_5S, **8b:** R = 4-MeC_6H_4S

All the compounds **5** and **6** were purified by preparative TLC on silica gel and fully characterized by NMR spectroscopy. The ^{1}H NMR spectra of **5a** [10], **6a** [6], and **6b** [5] were identical to those reported in the references cited. The endo configuration was confirmed by ^{1}H NMR.

The method has some attractive advantages such as mild reaction conditions, simple procedure, shorter reaction time, and high regio- and stereoselectivity.

The ketones **5** and thioesters **8** could also be obtained given as follows. Camphene **1** reacted with $Cp_2Zr(H)Cl$ and CO to give acylzirconocene chloride derivative **7**, which was trapped with aryl halides and arylsulfenyl chlorides to afford ketones **5** and thioesters **8** [11] (Table 2).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Brucker AC-300MHz in $CDCl_3$ with TMS as internal standard. Mass spectra were determined using a Finrigan 8230 mass spectrometer. IR spectra were obtained in neat capillary cells on a Shimadzu IR-408 instrument. Microanalyses were performed using a Yamaco MT-3 CHN micro-elemental analyzer. The reaction were carried out in pre-dried glassware (150°C, 4 h) and cooled under a stream of dry nitrogen. All solvents were dried, deoxygenated, and redistilled before use. Analytical data of all compounds corresponded to those calculated.

General Procedure for the Synthesis of 5a–c and 6a–b. A mixture of $Cp_2Zr(H)Cl$ [8] (2 mmol) and camphene (**1**) or β-pinene (**2**) (2 mmol) in THF (8 mL) was stirred at room temperature for 40 min. The resulting solution was injected into a reaction vessel which contained acyl halide (2.5 mmol), CuI (1.0 mmol) and 6 ml THF. The reaction mixture was stirred at 50°C for 8 h. Then it was treated with a saturated aqueous solution of ammonium chloride and extracted with Et_2O (3 ×10 mL). The residue was purified by preparative TLC on silica gel using hexane as eluent to afford **5** and **6**.

General Procedure for the Synthesis of 5b and 5d. A mixture of $Cp_2Zr(H)Cl$ [8] (1.5 mmol) and camphene (**1**) (3 mmol) in THF (10 mL) was stirred at room temperature for 30 min to yield a clear solution. After the mixture had been stirred under an atmosphere of CO for 3 h, C_6H_5I or $C_6H_5CH_2Br$ (1 mmol), $PdCl_2(PPh_3)_3$ (0.1 mmol) was added at 40°C, and the mixture was stirred for 8 h. After removal of solvent, the residue was purified by preparative TLC on silica gel eluting with hexane to afford **5b** and **5d**.

General Procedure for the Synthesis of 8a–b. A mixture of $Cp_2Zr(H)Cl$ [8] (1.5 mmol) and camphene (**1**) (3 mmol) in THF (10 mL) was stirred at room temperature for 30 min to yield a clear solution. After the mixture had been stirred under an atmosphere of CO for 3 h, C_6H_5SCl or 4-MeC_6H_4SCl (1 mmol) was added at 0°C, and the mixture was stirred for 1 h. After removal of solvent, the residue was purified by preparative TLC on silica gel eluting with hexane to afford **8a** and **8b**.

5a: [10] $C_{12}H_{20}O$, oil. IR (film, ν, cm^{-1}) 2980, 2920, 2850, 1740, 1440, 1370, 1235, 1040; ^{1}H NMR: 4.05–3.90 (m, 1 H, CHR_3), 3.55 (s, 3H, $COCH_3$), 3.50–3.40 (m, 2H, CH_2CO). 2.00–1.55 (m, 8 H, CH_2 and CH), 1.16 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); MS: *m/z* 165 (M-15, 5.33), 91 (88.60), 43 (100%).

5b: $C_{17}H_{22}O$, oil. IR (film, ν, cm^{-1}) 3020, 2920, 2850, 1740, 1440, 1370, 1235, 1040; ^{1}H NMR: 8.25–7.90 (m, 2H, Ph), 7.55–7.40 (m, 3H, Ph), 4.35–4.20 (m, 1H, CHR_3), 3.60–3.45 (m, 2H, CH_2CO), 2.00–1.55 (m, 8H, CH_2 and CH), 1.18 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); MS: *m/z* 226 (M-16, 0.40), 122 (53.27), 105 (100), 77 (38.96%).

5c: $C_{17}H_{21}ClO$, oil. IR (film, ν, cm^{-1}) 3015, 29150, 2855, 1730, 1440, 1375, 1240, 1040; ^{1}H NMR: 8.10, 7.50 (4H, AB-system, J = 7.4 Hz, Ph), 4.30–4.15 (m, 1H, CHR_3), 3.65–3.50 (m, 2H, CH_2CO), 2.00–1.50 (m, 8H, CH_2 and CH), 1.20 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); MS: *m/z* 260 (M-16, 2.60), 139 (100), 111 (45.32%).

5d: $C_{18}H_{24}O$, oil. IR (film, ν, cm^{-1}) 3020, 1720, 1508; ^{1}H NMR: 7.30–7.00 (m.5H), 3.95 (s, 2H, CH_2Ph), 3.15 (m, 1H), 2.15 (m, 2H, CH_2CO), 2.00–0.80 (m, 8H), 0.92 (s, 3H), 0.85 (s, 3H); MS: *m/z* 256 (M^+, 4.0), 226 (M-30, 100), 165 (M-91, 20), 135 (18), 91 (16%).

6a [6]: $C_{12}H_{20}O$, oil. IR (film, ν, cm^{-1}) 2940, 2850, 1735, 1440, 1375, 1230, 1100, 1020; ^{1}H NMR: 4.05–3.95 (m, 2 H, CH_2CO), 3.30 (s, 3H, $COCH_3$), 2.05–1.35 (m, 9H, CH_2 and CH), 1.20 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); MS: *m/z* 165 (M-15, 6.14), 91 (100), 43 (96.47%).

6b [5]: $C_{17}H_{22}O$, oil. IR (film, ν, cm^{-1}) 3030, 2920, 2860, 1785, 1720, 1595, 1455, 1280, 1210, 1100, 1020; ^{1}H NMR: 8.10–7.95 (m, 2H, Ph), 7.50–7.35 (m, 3H, Ph), 4.50–4.35 (m, 2H, CH_2CO), 2.50–1.35 (m, 9H CH_2 and CH), 1.15 (s, 3H, CH_3), 0.65 (s, 3H, CH_3); MS: *m/z* 226 (M-16, 0.77), 122 (37.91), 105 (100), 77 (54.45%).

8a: $C_{17}H_{22}OS$, oil. IR (film, ν, cm^{-1}) 3020, 1720, 1510; ^{1}H NMR: 7.20–6.80 (m, 5H, Ph), 3.15 (m, 1H,), 2.30 (m, 2H, CH_2CO), 2.00–0.85 (m, 8H), 0.93 (s, 3H), 0.86 (s, 3H); MS: *m/z* 274 (M^+, 1.5), 244 (M-30, 100), 165 (M-SPh, 4), 135 (25), 77 (6.5%).

8b: $C_{18}H_{24}OS$, oil. IR (film, ν, cm^{-1}) 3025, 1725, 1500; ^{1}H NMR: 7.15–6.75 (dd, J = 7Hz, 4H, Ph), 3.10 (m; 1H), 2.30 (m, 2H, CH_2CO), 2.21 (3H, s, CH_3Ph), 0.80–2.00 (m, 8H), 0.92 (s, 3H), 0.86 (s, 3H); MS: *m/z* 287 (M-1, 1.0), 258 (M-30, 100), 165 (M-SC_6H_4Me, 2), 135 (31), 91(4.3 %).

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