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Synthesis of Chiral 3-Acylcamphors

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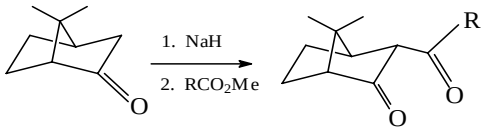
Abstract: 3-Acylcamphors were synthesized in moderate yields by the condensation of camphor with esters using sodium hydride as a base.

Keywords: Camphor, acylation, 3-acylcamphor, synthesis.

3-Acylcamphors were used as versatile reagents such as stationary phases in chromatography for enantiomer separation and as ligands of paramagnetic chiral lanthanide shifting reagents in NMR spectroscopy[1, 2]. Due to their rigid framework and ability to coordinate with metal ions, their potential importance has also been recognized in asymmetric reactions in recent years[3-6]. Design of ligand with high chiral recognizing ability in asymmetric reactions promoted us to prepare some 3-acylcamphors.

Acylation of camphor represents the most straightforward entry to 3- acylcamphors. However, after screening synthetic methods for this kind of compounds, we have found that the reported methods are associated with various problems such as low yield and side reaction (*O*-acylation). Benzoylcamphor, a typical one, was synthesized in yield of 5-7% and 15% respectively by using sodium and sodium amide as a base[7, 8]. Bases appeared critical to this reaction. For example, higher yield was obtained by using LDA as a base[3]. Regarding sodium hydride being superior to sodium and sodium amide in some cases, therefore, we synthesized 3-acylcamphors using sodium hydride as a base. We wish to report our results herein.



1 2a-2h

2a: R = phenyl
2b: R = 4-chlorophenyl
2c: R = 2-chlorophenyl
2d: R = 4-methoxyphenyl
2e: R = 3-fluorophenyl
2f: R = 3-pyridyl
2g: R = 4-pyridyl
2h: R = 1-Naphthyl

Reaction was performed in anhydrous solvents under nitrogen. A mixture of (+)-camphor and sodium hydride (2.35 equiv.) in 1,2-dimethoxyethane was refluxed for 1 h, and then a solution of methyl ester of carboxylic acid (1.1 equiv.) in the same solvent was added over a period of 1.5 h. The mixture was refluxed overnight, followed by cooling to room temperature. Ethanol was added to consume the excess sodium hydride, and water was added. The organic phase was separated, and aqueous phase was extracted with pentane. The combined organic phase was dried, concentrated, and cooled in refrigerator. Usually a precipitate was formed, and it was purified by recrystallization. When 2-pyridylcarboxylate was used as starting material, no precipitate was formed even after the resulting solution was cooled for several weeks, while ferric chloride gave a positive result. The product can be easily converted to its copper complex. However, we failed to get the corresponding acylcamphor by acid decomposition.

A much higher yield was obtained using sodium hydride as a base. **2a** and **2b** were obtained in 48% and 30% yields respectively, compared with their reported yield of 5-15%, and 4.0-20% in literatures using other bases[7, 8].

Using the same method, we synthesized compound **2c**-**2g** in moderate yields. Some physical data were listed in **Table 1.** All these compounds were identified by spectral analysis[9]. Details about their spectral data and structural analysis will be published elsewhere.

Table 1. Some Physical Data of 3-Acyl camphor

Compound	Yield (%)	m.p. (℃)	$[\alpha]_D$
2a	48	83-84	196.06 (c1.006, EtOH)
2b	26	123-124	187.74 (c1.010, EtOH)
2c	30	68.5-70	100.79 (c1.012, EtOH)
2d	52	80-82	134.34 (c0.990, EtOH)
2e	60	88.5-89.5	159.55 (c1.032, EtOH)
2f	55	101-102	201.79 (c1.006, EtOH)
2g	64	119-121	215.15 (c0.990, EtOH)
2h	46	92-94	160.78 (c1.020, EtOH)

References and Notes

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8. A. P. Terent'ev, G. V. Panova, N. B. Kuletskaya, *et al*., *Zh. Obshch, Khim*., **1972**, *42*(5), 1143. **2g**: IR 1687, 1630, 1600, 1557, 1506, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.20 (s, br, 0.932H), 8.75-7.81 (m, 2H), 7.72-7.55 (m, 2H), 4.24 (s, 0.069H), 3.80 (s, 0.028H), 2.88 (m, 1H), 2.20 (m, 1H), 1.64-1.54 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 213.15, 157.89, 150.06, 141.05, 120.91, 117.00, 57.46, 49.58, 47.95, 30.17, 26.57, 20.02, 18.31, 8.46.

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