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Synthesis of various camphor-based chiral pyridine derivatives

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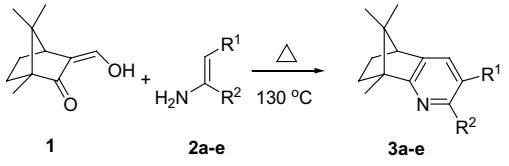
Abstract—(+)-β-Hydroxymethylenecamphor **1** and enamines **2a–e** were transformed into chiral camphor-based pyridine derivatives **3a–e** via a tandem condensation reaction in good yields.

1. Introduction

Since the design of chiral ligands plays a key role in the development of enantioselective reactions, many recent studies have addressed the development of novel chiral ligands for metal-catalyzed reactions.[1] Various camphor-based chiral pyridines have been synthesized[2–9] and some of them tested for their uses in asymmetric catalysis.[9,10] In such compounds the bicyclic bridged system adds a further constraint to the aliphatic portion of the molecule and this is expected to result in a higher stereodifferentiating ability of the chiral ligands derived from these pyridines.[4] It is well known that nicotinic acid and its derivatives exhibit qualitatively the biological activity of nicotinamide, which acts as an electron acceptor in many biological redox reactions. In connection with our previous work,[5] we attempted to develop a short and convenient method to prepare various camphor-derived chiral pyridine or nicotinic acid derivatives. Here we report our results obtained from the annulation of (+)-β-hydroxymethylenecamphor **1** with various enamines derived from active methylene compounds (Scheme 1).

2. Results and discussion

(+)-β-Hydroxymethylenecamphor **1** was chosen as a feasible chiral pool representative since it can be readily assembled from (+)-camphor, which is easily available and inexpensive. In our synthetic approach, the hydroxymethylene unit was anchored to the host camphor system by a known procedure.[11] Enamines **2a–c** were prepared from the corresponding active methylene compounds using a slightly modified literature procedure.[12] Enamines **2d–e** were synthesized from acetonitrile and the corresponding arylnitriles.[13]



a: R^1=CO_2Et, R^2=Me
b: R^1=COMe, R^2=Me
c: R^1=CN, R^2=Me
d: R^1=CN, R^2=*p*-BrC_6H_5
e: R^1=CN, R^2=C_6H_5

Scheme 1.

Enamines **2a–e** reacted with the (+)-β-hydroxymethylenecamphor **1** efficiently, allowing the preparation of the desired chiral pyridines **3a–e** in good yields (Scheme 1). As a starting point, we studied the annulation reaction of (+)-β-hydroxymethylenecamphor **1** with ethyl 3-aminocrotonate **2a**, which was chosen as a model compound. In the annulation reactions, the general procedure given below was applied: a mixture of (+)-β-hydroxymethylenecamphor **1** (360 mg, 2.00 mmol) and enamine **2a** (439 mg, 3.40 mmol) containing a catalytic amount of ammonium acetate (10 mg, 0.13 mmol) was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated for 12 h at 130 °C. The resulting crude product was purified by flash column chromatography to afford 73% of (5*S*,8*R*)-(+)-**3a** (EtOAc/

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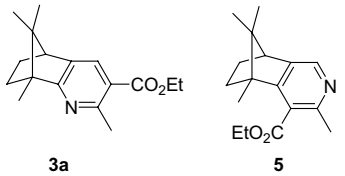


Figure 1.

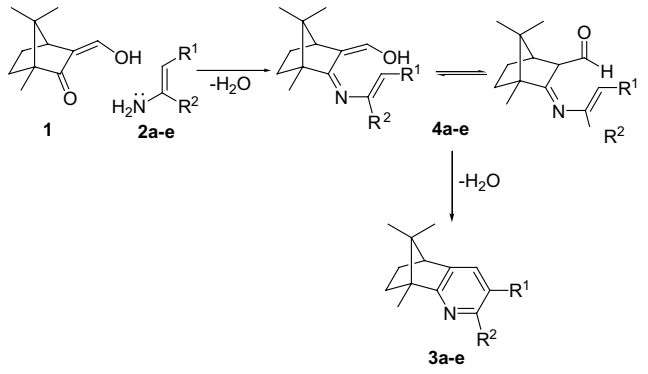
hexane, 1:6). When the same reaction was carried out in toluene as the solvent, the isolated yield of product **3a** was drastically decreased to 27%. The annulation reaction could yield the two possible products **3a** and **5** (Fig. 1). The structure of the product isolated was elucidated using HMQC and HMBC techniques. The HMQC spectrum showed that the aromatic proton at 7.77 ppm was attached to aromatic carbon at 130.2 ppm. In the HMBC spectrum, we observed the interaction of the aromatic carbon at 130.2 ppm with the bridge proton of the camphor moiety. Furthermore, the relation between the carbonyl carbon at 173.5 ppm and the aromatic proton at 7.77 ppm strongly supports the structure of the product as **3a**.[14]

As a natural extension of this study, we pursued a complementary investigation aimed at subjecting the various enamines **2b–e** to this reaction. Selected examples are listed in Table 1. In the synthesis of **3b** and **3e** (entries 2 and 5), we isolated the uncyclized intermediates **4b** and **4e** in 12% and 8% chemical yields, respectively.[15] In entry 2, the unexpected deacetylation product **3b** was obtained, the structure of which was in accordance with literature data.[4] The following mechanistic scheme is consistent with these results (Scheme 2).

Table 1. Annulation of (+)-β-hydroxymethylenecamphor **1** with enamines **2a–e**

Entry	Enamine	Product	Yield (%)[b]
1	**2a**	**3a**	73
2	**2b**	**3b**[a] ($R^1 = H$)	71
3	**2c**	**3c**	35
4	**2d**	**3d**	56
5	**2e**	**3e**[a]	58

[a] Uncyclized intermediates were isolated.
[b] All annulation reactions were carried out for 12 h.



Scheme 2.

The reaction presumably proceeds via the formation of imines **4a–e** via a tandem addition–cyclization reaction.

In conclusion, the reaction of (+)-β-hydroxymethylenecamphor **1** with enamines **2a–e** proceeded efficiently to give the corresponding camphor-based chiral pyridine derivatives **3a–e** in good yields. This one-step reaction offers complete regioselectivity and opens up a new method for the synthesis of chiral pyridines. Further studies on the synthesis of new derivatives are in progress.

Acknowledgements

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13. Yamaguchi, Y.; Katsuyama, I.; Funabiki, K.; Matsui, M.; Shibata, K. *J. Heterocycl. Chem.* **1998**, *35*, 805.
14. Spectroscopic data for **3a**: Pale yellow solid Mp 71–73 °C; $[\alpha]_D^{20}$ +48.2 (*c*, 0.93, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (in ppm): 7.77 (s, 1H), 4.28 (q, $J = 7.0$ Hz, 2H), 2.79 (d, $J = 4.0$ Hz, 1H), 2.73 (s, 3H), 2.08–2.01 (m, 1H), 1.83–1.77 (m, 1H), 1.32 (t, $J = 7.0$ Hz, 3H), 1.25 (s, 3H), 1.16–1.02 (m, 2H), 0.92 (s, 3H), 0.48 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (in ppm): 173.5, 168.0, 157.4, 138.6, 130.2, 122.8, 61.2, 57.2, 54.9, 51.4, 31.9, 26.4, 25.2, 20.3, 19.5, 14.7, 10.6; HRMS calcd for $C_{17}H_{24}NO_2$ (M+H): 274.1807. Found $(M+H)^+$ 274.1802.
15. Spectroscopic data for **4b**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (in ppm): 12.28 (d, $J = 11.9$ Hz, 1H), 7.20 (d, $J = 12.8$ Hz, 1H), 5.24 (s, 1H), 2.77 (d, $J = 3.8$ Hz, 1H), 2.06 (s, 3H), 2.01 (s, 3H), 1.68–1.61 (m,

2H), 1.39–1.29 (m, 2H), 0.90 (s, 3H), 0.90 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (in ppm): 208.0, 198.9, 156.4, 124.9, 124.5, 101.6, 58.6, 47.7, 47.2, 31.5, 30.2, 26.7, 20.8, 18.9, 18.8, 9.6; HRMS calcd for $C_{16}H_{24}NO_2$ (M+H): 262.1808. Found $(M+H)^+$ 262.1806. Spectroscopic data for **4e**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (in ppm): 10.35 (d, $J = 10.8$ Hz, 1H), 7.52 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H), 6.95 (d, $J = 11.0$ Hz, 1H), 4.34 (s, 1H), 2.39 (d, $J = 3.5$ Hz, 1H), 2.00–1.93 (m, 1H), 1.66–1.58 (m, 1H), 1.40–1.29 (m, 2H), 0.91 (s, 3H), 0.86 (s, 3H), 0.78 (s, 3H), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (in ppm): 210.5, 155.6, 133.7, 132.8 (2C), 129.9, 129.5 (2C), 125.8, 120.9, 118.3, 70.4, 59.3, 49.2 (2C), 30.4, 28.1, 21.0, 19.0, 9.3; HRMS calcd for $C_{20}H_{22}N_2OBr$ (M+H): 385.0916. Found $(M+H)^+$ 385.0918.