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Stereoselective N-Acylation of a New Chiral Auxiliary Compound; 3-Phenyl-*l*-menthopyrazole

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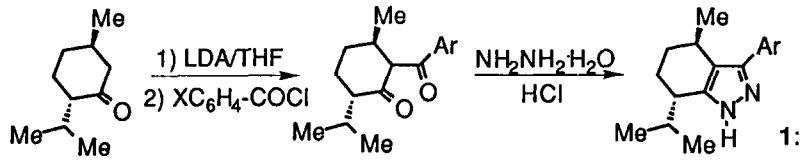
Abstract: As a new chiral auxiliary compound having a pyrazole ring system, the synthetic utility of (4R,7S)-3-phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole (3-phenyl-*l*-menthopyrazole), which was prepared from *l*-menthone, was discussed.

Although N-acylpyrazoles were paid attentions as the potent substances of various biological activities such as antidiabetic[1], hypoglycemic[1,2], antiinflammatory[3], and antihystaminic activities[3], a small number of papers in the literature have appeared in the preparation and the chemical reactions of N-acylpyrazoles due to their low reactivity. However, this low reactivity of N-acylpyrazoles are expected to be sometimes preferable for their controlled reactions as well as the advantages of convenient preparation and the storage. Actually, we have recently found[4] that N-acylpyrazoles were easily alcoholyzed into the corresponding carboxylic esters in the presence of boron trifluoride etherate, while it was almost inert toward alcohol in the absence of catalyst. Moreover, N-acylation of pyrazoles was controlled chemo- and regioselectively by the steric repulsion between the substituent group on pyrazole ring and the acyl chloride. Here, we will communicate the preparation and the stereoselective N-acylation of optically active pyrazole as a new chiral auxiliary compound.

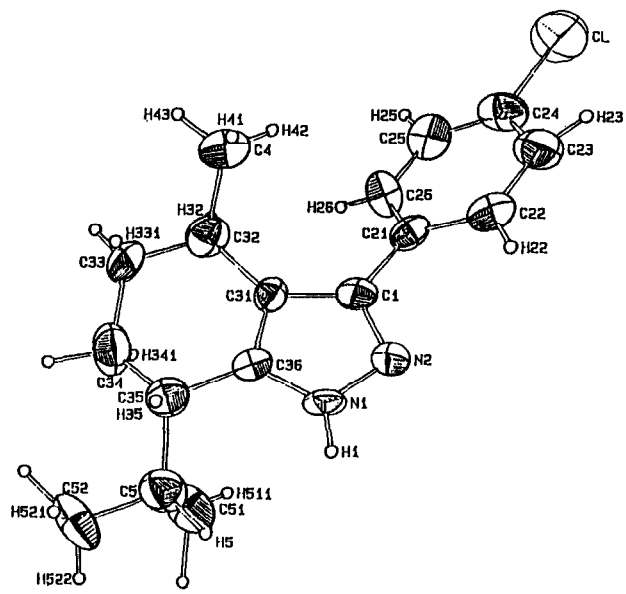
From the viewpoints of the synthetic conveniences and the chemical stability, 3-substituted (4R,7S)-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole (*l*-menthopyrazole) was regarded as the most attractive chiral pyrazole compound. By the molecular dynamic calculation[5] of the most stable conformations, 3-unsubstituted and 3-methyl-*l*-menthopyrazole were predicted to be less effective to the stereoselective reactions either on the N-1 or the N-2 nitrogen atoms. In a meanwhile, the steric hindrance of 3-aryl-*l*-menthopyrazoles was anticipated to be relaxed by twisting the aryl ring, which expanded the chirality of (4R)-methyl group onto N-2 nitrogen atom by the induction of the torsional asymmetry.

3-Phenyl-*l*-menthopyrazole (**1**, Ar=Ph)[6] was prepared by 2 step reactions from *l*-menthone in about 65 % overall yield with high optical purity, illustrated in Scheme 1. The optical purity of **1** (Ar=Ph) was proved by the NMR spectroscopic method using the Morsher's MTPA derivative.[7] Also, 3-(4-chlorophenyl)-*l*-menthopyrazole (**1**, Ar=4-ClC_6H_4) was prepared from 4-chlorobenzoyl chloride. The X-ray structural analysis of **1** (Ar=4-ClC_6H_4) showed that the aryl ring was twisted about 40° from the pyrazole ring and overlaid on one side of the N-2 nitrogen atom. This structural feature of 3-aryl-*l*-menthopyrazoles should be promising for the stereo-controlled reactions.



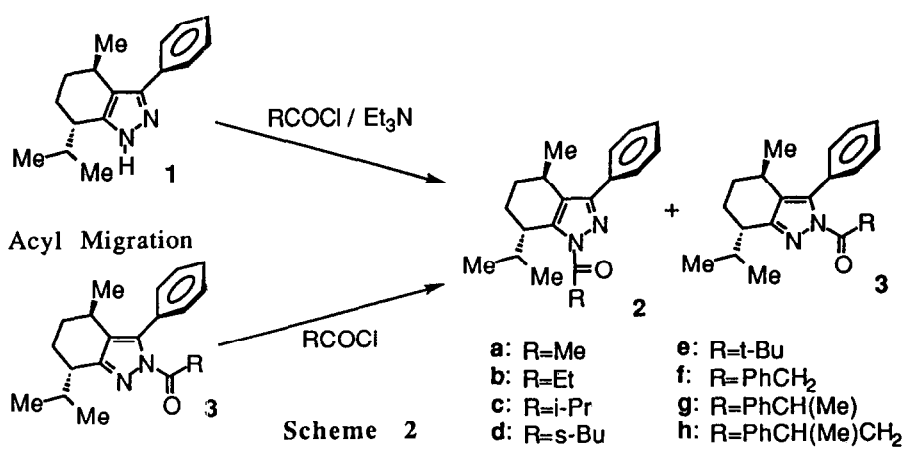
Scheme 1

Ar= Ph Yield 69 % Ar= Ph Yield 96 %
Ar= 4-ClC$_6$H$_4$ Yield 46 % Ar= 4-ClC$_6$H$_4$ Yield 58 %



Molecular Structure of 3-(4-Chlorophenyl)-*l*-menthopyrazole (**1**, Ar=4-ClC$_6$H$_4$)

N-Acylation



Scheme 2

Table

The Product Ratio (**2** : **3**) in the N-Acylation of **1** (Ar=Ph) and Acyl Migration Reaction of **3**

R	N-Acylation of **1** (Ar=Ph)		Acyl Migration of **3**	
	Yield	**2** : **3** (% de, Conf.)	Yield	**2** : **3** (% de, Conf.)
Me (**a**)	96	31 : 69	88	92 : 8
Et (**b**)	100	17 : 83	83	91 : 9
i-Pr (**c**)	100	5 : 95	85	90 : 10
s-Bu (**d**)	100	3 (–, –) : 97 (1, R)	95	89 (8, S) : 11 (2, S)
t-Bu (**e**)	100	3 : 97	94	86 : 14
$PhCH_2$ (**f**)	97	37 : 63	78	90 : 10
PhCH(Me) (**g**)	79	40 (16, R) : 60 (7, R)	74	80 (7, R) : 20 (19, R)
$PhCH(Me)CH_2$ (**h**)	87	28 (16, S*) : 72 (3, R)	86	90 (2, S*) : 10 (6, R)

* The % de and configuration were presumed from NMR spectra based on the data of **2d**.

When **1** (Ar=Ph) was treated with various acyl chlorides in the presence of triethyl amine, the acyl group was introduced on the N-2 position to afford 2-acyl-3-phenyl-*l*-menthopyrazole (**3**) with a small portion of 1-acyl-3-phenyl-*l*-menthopyrazole (**2**), summarized in the Table. The products **2** and **3** were able to be isolated easily by chromatography, and to be distinguished with each other in their NMR spectra,[8] where the aromatic protons of **2** appeared separately in two regions like as those of benzoyl group. On the contrary, **2** was predominantly formed by the treatment of **3** with the same acyl chloride in the absence of triethyl amine, where the acyl migration reaction proceeded. The Table showed that the product ratios (**2** : **3**) differed delicately by the bulkiness of acyl group in the N-acylation of **1** (Ar=Ph). In the acyl migration reaction of **3**, the proportion of **2** was gradually decreased with the bulkiness of acyl group. When the racemic acyl chloride having the asymmetric carbon was used, an asymmetric induction was observed either in N-acylation of **1** (Ar=Ph) or in the acyl migration reaction of **3**. The % de and the configuration of acyl group were determined by the comparison of NMR spectra of the authentic samples, which were derived from (S)-2-methylbutyric and (R)-2-phenylpropionic acids. In the case of 2-(2-phenylpropionyl)-3-phenyl-*l*-menthopyrazole (**3g**), the % de was evaluated by HPLC. Furthermore, the separation of the optical isomers of **3g** were accomplished by means of simple silica gel column chromatography, where **1** (Ar=Ph) acted as the chiral auxiliary.

This structural feature of **1** was expected to be emphasized by the introduction of o-substituent on aryl group. Although the preparations of 2-methylphenyl, 2-chlorophenyl, 2,6-disubstituted phenyl and 9-anthranyl derivatives were unsuccessful owing to their severe steric hindrance, 3-(2-methoxyphenyl)- (**1**, Ar=2-$MeOC_6H_4$) and 3-(1-naphthyl)-*l*-menthopyrazole (**1**, Ar=1-Naph) were prepared in moderate yields. When these o-substituted 3-aryl-*l*-menthopyrazoles (**1**) were treated with acetyl chloride, the complicated mixture of N-acetylated products were afforded including the atrop isomers due to the restricted rotation of aryl group. Therefore, the introduction of o-substituent on aryl group gave no practical advantage.

After all, (4R,7S)-3-phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole (3-phenyl-*l*-menthopyrazole, **1**, Ar=Ph) was easily prepared from *l*-menthone in good yield with a high optical purity. As expected by molecular dynamic calculations, the aryl ring in **1** was twisted by the steric repulsion from (4R)-

methyl group, and overlaid on one side of the N-2 nitrogen atom. This steric feature affected regio- and stereoselectively to the N-acylation on pyrazole ring. Moreover, the separation of the optical isomers of 2-acyl derivatives of **1** (Ar=Ph) was accomplished by the simple silica gel column chromatography. From these facts, 3-phenyl-*l*-menthopyrazole (**1**, Ar=Ph)) has a bright prospect of use as a chiral auxiliary compound for the stereo-controlled synthetic reactions.

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6 3-phenyl-*l*-menthopyrazole (**1**, Ar=Ph) Mp 122.5-124°C (from Hexane); $[\alpha]_D$: -158.5° (c 1.9, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$); 0.81 (3H, d, J=7 Hz), 0.97 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.18-1.37 (1H, m), 1.50-1.63 (1H, m), 1.77-1.88 (1H, m), 1.99-2.22 (1H, m), 2.55-2.65 (1H, m), 2.98-3.14 (1H, m), 7.27-7.39 (3H, m), 7.57-7.65 (2H, m), 11.25 (1H, broad d); ^{13}C NMR (270 MHz, $CDCl_3$); (DEPT) 18.3 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.9 (CH_2), 27.1 (CH), 30.3 (CH), 31.6 (CH_2), 39.7 (CH), 118.7 (C), 127.6 (CH), 127.7 (C), 128.4 (CH), 133.2 (CH), 145.4 (C), 146.7 (C); IR ($CHCl_3$ Solution); 3395, 3175, 2930, 1450, 700. Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01; Obsd: C, 80.18; H, 8.56; N, 10.95.

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8 For example: 1-Acetyl-3-phenyl-*l*-menthopyrazole (**2a**). Bp 150°C/ 5 mmHg; ^1H NMR (270 MHz, $CDCl_3$); 0.88 (3H, d, J=7 Hz), 0.96 (3H, d, J=7 Hz), 0.99 (3H, d, J=7 Hz), 1.43-1.51 (1H, m), 1.76-1.83 (2H, m), 2.00-2.19 (2H, m), 2.73 (3H, s), 3.17-3.22 (1H, m), 3.37-3.42 (1H, m), 7.35-7.47 (3H, m), 7.75-7.80 (2H, m). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Obsd: C, 77.17; H, 8.23; N, 9.46. 2-Acetyl-3-phenyl-*l*-menthopyrazole (**3a**). ^1H NMR (270 MHz, $CDCl_3$); 0.69 (3H, d, J= 7 Hz), 0.94 (3H, d, J= 7 Hz), 1.09 (3H, d, J= 7 Hz), 1.18-1.31 (1H, m), 1.46-1.55 (1H, m), 1.83-2.00 (2H, m), 2.36-2.44 (1H, m), 2.59-2.79 (2H, m), 2.63 (3H, s), 7.27-7.41 (5H, m). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Obsd: C, 76.75; H, 8.07; N, 9.42.

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