A FACILE SYNTHESIS OF CARBOXAMIDES BY DEHYDRATION CONDENSATION BETWEEN FREE CARBOXYLIC ACIDS AND AMINES USING *O,O′*-DI(2-PYRIDYL) THIOCARBONATE AS A COUPLING REAGENT

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Received February 14, 2000
Accepted April 7, 2000

This paper is dedicated to Professor Otakar Červinka on the occasion of his 75th birthday in recognition of his outstanding contributions to the area of organic chemistry.

Carboxamides are prepared in high yields by dehydration condensation between nearly equimolar amounts of free carboxylic acids and amines both of which involve secondary or tertiary alkyl substituted ones with *O,O′*-di(2-pyridyl) thiocarbonate, a coupling reagent, in the presence of a catalytic amount of 4-(dimethylamino)pyridine.

Key words: *O,O′*-Di(2-pyridyl) thiocarbonate; 4-(Dimethylamino)pyridine; 2-Pyridyl esters; Dehydration condensation; Carboxamides; Amides.

In the previous paper[1], it was presented that carboxylic esters were obtained in high yields by dehydration condensation where nearly equimolar amounts of carboxylic acids and alcohols were treated with a coupling reagent, *O,O′*-di(2-pyridyl) thiocarbonate (DPTC). Esterification of 7-TES baccatin III with a side-chain, protected phenylisoserine, was carried out by the above method by which the total synthesis of Taxol[2] was completed in 1997. In this paper, we would like to report an effective method for the synthesis of carboxamides from nearly equimolar amounts of carboxylic acids and amines by using DPTC in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP).

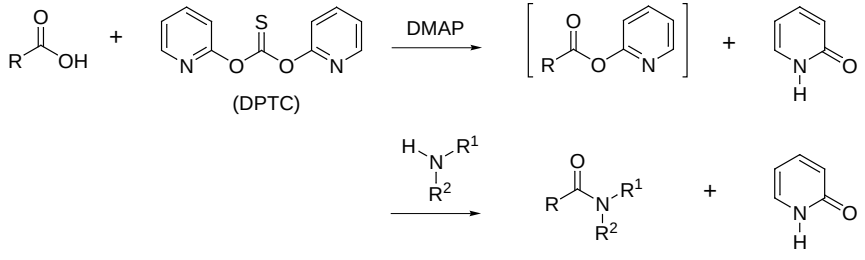
In general, carboxamides are prepared in good yields by acylation of amines with activated carboxylic acid derivatives such as esters, anhydrides or acyl halides[3]. However, in the case of preparing carboxamides from free

carboxylic acids and amines, the reaction is carried out by simple refluxing where one of the starting materials has to be used in excess and thus synchronously produced water has to be removed continuously from the reaction mixture by heating, usually at or above 100 °C. In addition, there have been reported many useful and well-known methods[3] for the direct synthesis of carboxamides under mild conditions from free carboxylic acids and free amines by dehydration condensation *via in situ* formed activated carboxylic acid derivatives by using such coupling reagents as 1,1′-carbonyldiimidazole[4], 1,3-dicyclohexylcarbodiimide (DCC)[5], diethylphosphoryl cyanide[6], diphenylphosphoryl azide[7] and triphenylphosphine–dipyridyl disulfide[8].

RESULTS AND DISCUSSION

In 1985, Kim *et al.* reported that isothiocyanates or thiocarbamates were formed in high yields from primary or secondary amines, respectively, along with 2-hydroxypyridine (2(1*H*)-pyridone) using DPTC (ref.[9]) (or 1,1′-(thiocarbonyl)di(2(1*H*)-pyridone)[10], a regioisomer of DPTC).

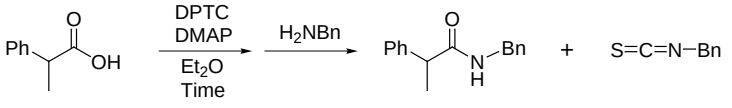
In the previous communication, an efficient method for the synthesis of carboxylic esters using the DPTC–DMAP system was reported[1,2]. It was indicated there that 2-pyridyl esters, reactive acylating reagents[11], were formed from carboxylic acids on treatment with DPTC in the presence of a catalytic amount of DMAP. It was considered then that the desired carboxamides might exclusively be obtained when amines were added to the above reaction mixture after 2-pyridyl esters were completely formed (Scheme 1).



SCHEME 1

At first, the reaction rate for the 2-pyridyl ester formation was evaluated by measuring the amounts of *N*-benzyl-2-phenylpropanamide (**1**) produced when the *in situ* formed 2-pyridyl 2-phenylpropanoate was treated with benzylamine (Scheme 2).

When benzylamine was added to the reaction mixture of 2-phenylpropanoic acid and DPTC in the presence of a catalytic amount of DMAP after being stirred for 3 min, **1** and benzyl isothiocyanate were obtained in



1

SCHEME 2

34 and 59% yields, respectively. This result shows that the reaction time for the formation of 2-pyridyl 2-phenylpropanoate from 2-phenylpropanoic acid and DPTC was not long enough. As shown in Fig. 1, the yield of **1** increased when 2-phenylpropanoic acid and DPTC were allowed to react at least 20 min before adding benzylamine. Furthermore, it was observed that 2-phenylpropanoic acid did not react with DPTC in the absence of DMAP while the separately prepared 2-pyridyl 2-phenylpropanoate quite smoothly reacted with benzylamine to afford **1** even in the absence of DMAP. These results indicate that the first step of the present reaction determines the total reaction rate. It was also proven that a variety of free carboxylic acids reacted with DPTC first to give the corresponding 2-pyridyl esters, which in turn reacted with amines to produce carboxamides and 2-hydroxypyridine as shown in Scheme 1.

Several examples of the synthesis of carboxamides according to the present method are shown in Table I. When using bulky or less nucleophilic

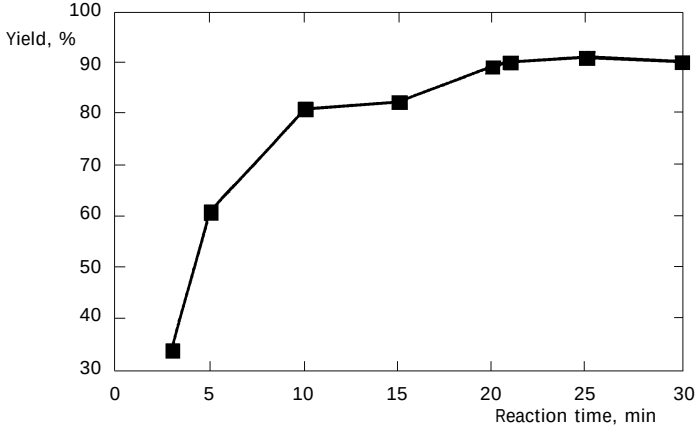


FIG. 1

Yields of **1** by treating 2-phenylpropanoic acid, benzylamine and DPTC in the presence of DMAP

amines such as diphenylmethylamine and 1-phenylethylamine, the reaction required relatively high temperature to obtain the desired amides in high yields (entries 11 and 12). It is noteworthy that even highly hindered amines such as 1-adamantanamine reacted with *in situ* formed 2-pyridyl 2-phenylpropanoate to afford the corresponding carboxamide (entry 13).

Thus, the effective synthesis of carboxamides from nearly equimolar amounts of carboxylic acids and amines is performed *via* 2-pyridyl esters without forming any by-products such as isothiocyanates and thiocarbamates when amines are added after 2-pyridyl esters are completely formed by treating equimolar amounts of carboxylic acids (listed in Table I) with DPTC for over 25 min in the presence of a catalytic amount of DMAP.

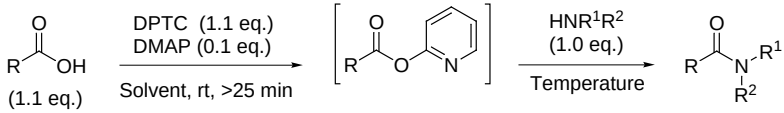
In order to compare the efficiency of the present coupling reagents with commonly employed DCC, the reaction using DCC was carried out under nearly the same conditions (the molar ratio of carboxylic acid to amine and to reagents was 1.1 : 1 : 1.1, room temperature, 3 h). The DPTC–DMAP combined system gave (2-phenylpropanoyl)piperidine (**11**) in nearly quantitative yield as shown in entry 15 while **11** was obtained in 78% yield when DCC was employed. Polar solvents such as DMF work similarly as shown in entries 2 and 3. Therefore, carboxamides are also synthesized in THF or DMF when the substrates are not completely soluble in ether.

It should be noted that the present reaction provides a convenient and high-yield method for the preparation of carboxamides from nearly equimolar amounts of free carboxylic acids and amines when both of which are substituted with bulky alkyl groups. The reaction also afforded chiral carboxamides (–)-**1** and (–)-**5** in high yields without any loss of optical purities (98% ee, respectively) when either chiral carboxylic acid (98% ee) or amine (98% ee) was employed as one of the starting materials probably because intermediate active 2-pyridyl esters were *in situ* formed by using only a catalytic amount of DMAP (see entries 4 and 8). It is also noted that the present experimental procedure is quite simple and almost pure carboxamides are obtained just by removing 2-hydroxypyridine, a co-product, by filtration or extraction with water.

EXPERIMENTAL

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Infrared spectra (wavenumbers in cm^{-1}) were recorded on a Horiba FT-300 infrared spectrometer. Proton and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were recorded on a JEOL JNM-EX270L, a JEOL JNM-EX400 or a JEOL LAMBDA-500 spectrometer with tetramethylsilane (TMS) or chloroform (in $CDCl_3$) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-AX505HA instrument using 4-nitrobenzyl alcohol as a matrix. Column chroma-

TABLE I
Examples of the synthesis of carboxamides according to the present method



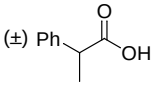
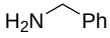
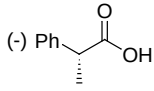
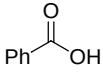
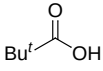
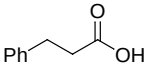
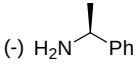
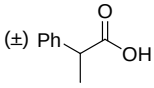
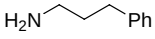
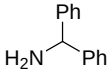
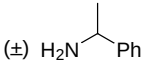
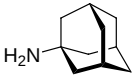
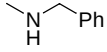
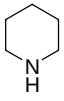
Entry	Carboxylic acid	Amine	Solvent	Temp., °C	Yield, %	Product
1			Ether	rt	91	(±)-**1**
2	-"-	-"-	THF	rt	81	(±)-**1**
3	-"-	-"-	DMF	rt	86	(±)-**1**
4		-"-	Ether	rt	89	(–)-**1**
5		-"-	Ether	rt	83	**2**
6		-"-	Benzene	50	73	**3**
7		-"-	Ether	rt	98	**4**
8	-"-		Ether	rt	94	(–)-**5**

TABLE I
(*Continued*)

Entry	Carboxylic acid	Amine	Solvent	Temp., °C	Yield, %	Product
9			Benzene	rt	94	(±)-**6**
10	-"-		Ether	rt	75	(±)-**7**
11	-"-	-"-	Benzene	50	89	(±)-**7**
12	-"-		Benzene	50	81	(±)-**8a**, **8b**[a]
13	-"-		Benzene	reflux	91	(±)-**9**
14	-"-		Benzene	rt	quant.	(±)-**10**
15	-"-		Benzene	rt	95	(±)-**11**

[a] **8a**/**8b** = 54/46.

tography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin-layer chromatography was performed on Wakogel B5F. Values of $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}.

All reactions were carried out under argon atmosphere in dried glassware. Benzene was distilled from diphosphorus pentoxide and dried over MS 4Å. Diethyl ether and THF were distilled from sodium/benzophenone immediately prior to use. DMF was distilled from calcium hydride and dried over MS 4Å.

DPTC was prepared by a literature method[9]. The structure of DPTC was determined by X-ray crystallography as shown in ORTEP diagram below (Fig. 2). The conformation showed that the molecule has C_2 symmetric structure and two identical reaction sites exist on α-

and β-faces of the thiocarbonyl group. Crystallographic data are as follows: FW 232.26, space group $P2_1$, cell constants a = 12.195(5), b = 6.8016(9), c = 13.373(4) Å and β = 94.75(4)°, V = 1 105.4(6) Å^3, Z = 4, $R1$ (I > 2s) = 0.0488, and number of unique reflections 2 536 (I > 2s). Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-140551. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.

Preparation of Amides. General Procedure

A typical experimental procedure is described for the reaction of 2-phenylpropanoic acid with benzylamine: To DMAP (2.3 mg, 0.019 mmol) was added a solution of 2-phenylpropanoic acid (31.1 mg, 0.20 mmol) in ether (0.6 ml) and DPTC (46.1 mg, 0.20 mmol). After having been stirred for 25 min under an argon atmosphere, a solution of benzylamine (20.4 mg, 0.19 mmol) in ether (0.6 ml) was added to the reaction mixture. The reaction mixture was stirred for 2 h at room temperature and then the mixture was filtered. The filtrate was evaporated and the resulting mixture was further purified for identification by preparative TLC to afford the corresponding *N*-benzyl-2-phenylpropanamide (**1**) (41.5 mg, 91%) as white solid (entry 1). Various carboxamides which were prepared according to this procedure are listed in Table I.

N-Benzyl-2-phenylpropanamide ((±)-**1**). M.p. 78 °C. IR (KBr): 3 278, 1 643, 1 550. ^{1}H NMR ($CDCl_3$): 7.32–7.09 m, 10 H (ArH); 6.02 br s, 1 H (NH); 4.34 dd, 1 H, J = 14.9, J' = 5.9 (Bn); 4.30 dd, 1 H, J = 14.9, J' = 5.9 (Bn); 3.57 q, 1 H, J = 7.1 (CHCO); 1.51 d, 3 H, J = 7.1 (Me). ^{13}C NMR ($CDCl_3$): 174.1 (CO); 141.3 (Ph); 138.4 (Ph); 128.8 (Ph); 128.5 (Ph); 127.6 (Ph); 127.4 (Ph); 127.2 (Ph); 127.2 (Ph); 47.0 (CHCO); 43.4 (Bn); 18.5 (Me). HR MS: calculated for $C_{16}H_{17}NONa$ $[M + Na]^+$ 262.1208, found 262.1210.

(R)-N-Benzyl-2-phenylpropanamide ((–)-**1**, 98% ee). M.p. 60 °C. $[\alpha]_D^{20}$ –27.4 (c 1.01, EtOH). HPLC (CHIRALCEL OD, iPrOH–hexane 1 : 9, flow rate 0.8 ml/min): t_R = 13.5 min ((+)-**1**), t_R = 15.0 min ((–)-**1**).

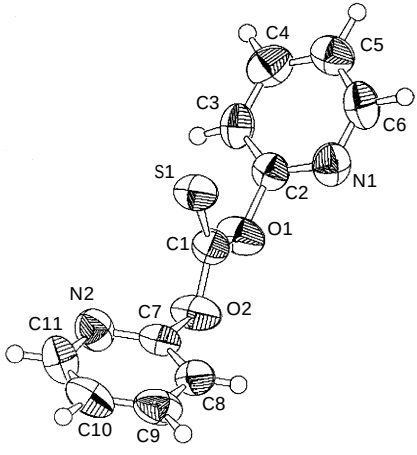


FIG. 2
X-Ray crystallographic structure of DPTC

N-Benzylbenzamide (**2**). M.p. 104 °C. IR (KBr): 3 270, 1 643, 1 550. ^{1}H NMR ($CDCl_3$): 7.70 d, 2 H, *J* = 6.9 (ArH); 7.40–7.20 m, 8 H (ArH); 6.37 br s, 1 H (NH); 4.55 d, 2 H, *J* = 5.6 (Bn). ^{13}C NMR ($CDCl_3$): 167.3 (CO); 138.2 (Ph); 134.4 (Ph); 131.5 (Ph); 128.8 (Ph); 128.6 (Ph); 127.9 (Ph); 127.6 (Ph); 126.9 (Ph); 44.1 (Bn).

N-Benzyl-2,2-dimethylpropanamide (**3**). M.p. 79 °C. IR (KBr): 3 278, 2 954, 1 651, 1 527. ^{1}H NMR ($CDCl_3$): 7.39–7.23 m, 5 H (ArH); 5.95 br s, 1 H (NH); 4.41 d, 2 H, *J* = 5.6 (Bn); 1.14 s, 9 H (*t*-Bu). ^{13}C NMR ($CDCl_3$): 178.3 (CO); 138.5 (Ph); 128.7 (Ph); 127.6 (Ph); 127.4 (Ph); 43.6 (Bn); 38.7 (C in *t*-Bu); 27.6 (Me in *t*-Bu).

N-Benzyl-3-phenylpropanamide (**4**). M.p. 80 °C. IR (KBr): 3 286, 1 651, 1 535. ^{1}H NMR ($CDCl_3$): 7.30–7.09 m, 10 H (ArH); 5.68 br s, 1 H (NH); 4.36 d, 2 H, *J* = 5.6 (Bn); 2.96 t, 2 H, *J* = 7.6 (CH_2Ph); 2.48 t, 2 H, *J* = 7.6 (CH_2CO). ^{13}C NMR ($CDCl_3$): 171.8 (CO); 140.7 (Ph); 138.1 (Ph); 128.6 (Ph); 128.5 (Ph); 128.4 (Ph); 127.7 (Ph); 127.4 (Ph); 126.2 (Ph); 43.5 (Bn); 38.4 (CH_2CO); 31.7 (CH_2Ph).

(S)-3-Phenyl-N-1-phenylethylpropanamide ((–)-**5**, 98% ee). M.p. 92 °C. $[\alpha]_D^{21}$ –63.6 (*c* 1.03, EtOH). IR (KBr): 3 278, 1 635, 1 558. ^{1}H NMR ($CDCl_3$): 7.21–7.00 m, 12 H (ArH); 5.90 br s, 1 H (NH); 4.97 quin, 1 H, *J* = 7.6 (CHN); 2.83 t, 2 H, *J* = 7.3 (CH_2Ph); 2.35 t, 2 H, *J* = 7.3 (CH_2CO); 1.28 d, 3 H, *J* = 7.6 (Me). ^{13}C NMR ($CDCl_3$): 171.1 (CO); 143.1 (Ph); 140.7 (Ph); 128.4 (Ph); 128.4 (Ph); 128.3 (Ph); 127.1 (Ph); 126.1 (Ph); 126.0 (Ph); 48.4 (CHN); 38.4 (CH_2CO); 31.7 (CH_2Ph); 21.5 (Me). HPLC (CHIRALCEL OD, iPrOH–hexane 1 : 14, flow rate 1.0 ml/min): t_R = 18.8 min ((+)-**5**), t_R = 24.1 min ((–)-**5**).

2-Phenyl-N-(3-phenylpropyl)propanamide ((±)-**6**). M.p. 93 °C. IR (KBr): 3 248, 1 643, 1 558, 756, 702. ^{1}H NMR ($CDCl_3$): 7.34–7.05 m, 10 H (ArH); 5.44 br s, 1 H (NH); 3.50 q, 1 H, *J* = 7.3 (CHCO); 3.24–3.15 m, 2 H (CH_2N); 2.51 br t, 2 H (CH_2Ph); 1.76–1.69 m, 2 H (CH_2); 1.50 d, 3 H, *J* = 7.3 (Me). ^{13}C NMR ($CDCl_3$): 174.1 (CO); 141.4 (Ph); 141.3 (Ph); 128.8 (Ph); 128.3 (Ph); 128.2 (Ph); 127.5 (Ph); 127.2 (Ph); 125.9 (Ph); 47.0 (CHCO); 39.1 (CH_2N); 33.0 (CH_2Ph); 31.0 (CH_2); 18.4 (Me). HR MS: calculated for $C_{18}H_{21}NONa$ [M + Na]$^+$ 290.1521, found 290.1495.

N-(Diphenylmethyl)-2-phenylpropanamide ((±)-**7**). M.p. 134 °C. IR (KBr): 3 278, 1 643. ^{1}H NMR ($CDCl_3$): 7.37–6.95 m, 15 H (ArH); 6.19–6.00 m, 2 H (CHNH); 3.59 q, 1 H, *J* = 7.1 (CHCO); 1.48 d, 3 H, *J* = 7.1 (Me). ^{13}C NMR ($CDCl_3$): 173.1 (CO); 141.5 (Ph); 141.3 (Ph); 141.2 (Ph); 128.8 (Ph); 128.5 (Ph); 128.3 (Ph); 127.5 (Ph); 127.4 (Ph); 127.3 (Ph); 127.2 (Ph); 127.1 (Ph); 127.0 (Ph); 56.7 (CHN); 46.8 (CHCO); 18.3 (Me). HR MS: calculated for $C_{22}H_{21}NONa$ [M + Na]$^+$ 338.1521, found 338.1528.

(2R)-2-Phenyl-N-((1S*)-1-phenylethyl)propanamide* ((±)-**8a**). M.p. 127 °C. IR (KBr): 3 348, 1 643, 1 535. ^{1}H NMR ($CDCl_3$): 7.37–7.19 m, 10 H (ArH); 5.56 br d, 1 H (NH); 5.09 quin, 1 H, *J* = 6.9 (CHN); 3.53 q, 1 H, *J* = 7.1 (CHCO); 1.51 d, 3 H, *J* = 7.1 (Me in acyl group); 1.34 d, 3 H, *J* = 6.9 (Me in amino group). ^{13}C NMR ($CDCl_3$): 173.2 (CO); 143.2 (Ph); 141.4 (Ph); 128.9 (Ph); 128.6 (Ph); 127.6 (Ph); 127.2 (Ph); 127.2 (Ph); 126.0 (Ph); 48.7 (CHN); 47.1 (CHCO); 21.5 (Me in amino group); 18.6 (Me in acyl group). HR MS: calculated for $C_{17}H_{19}NONa$ [M + Na]$^+$ 276.1365, found 276.1374.

(2R)-2-Phenyl-N-((1R*)-1-phenylethyl)propanamide* ((±)-**8b**). M.p. 127 °C. IR (KBr): 3 237, 1 643, 1 542. ^{1}H NMR ($CDCl_3$): 7.34–7.17 m, 8 H (ArH); 7.08 dd, 2 H, *J* = 7.7, *J*′ = 1.2 (ArH); 5.59 d, 1 H, *J* = 7.1 (NH); 5.08 quin, 1 H, *J* = 7.1 (CHN); 3.57 q, 1 H, 7.3 (CHCO); 1.51 d, 3 H, *J* = 7.3 (Me in acyl group); 1.39 d, 3 H, *J* = 7.1 (Me in amino group). ^{13}C NMR ($CDCl_3$): 173.1 (CO); 143.2 (Ph); 141.3 (Ph); 128.8 (Ph); 128.5 (Ph); 127.6 (Ph); 127.2 (Ph); 127.1 (Ph); 125.7 (Ph); 48.6 (CHN); 47.1 (CHCO); 21.9 (Me in the amino group); 18.4 (Me in the acyl group). HR MS: calculated for $C_{17}H_{19}NONa$ [M + Na]$^+$ 276.1365, found 276.1320.

N-Adamantan-1-yl-2-phenylpropanamide ((±)-**9**). M.p. 136 °C. IR (KBr): 3 301, 2 908, 1 643, 1 550. ^{1}H NMR ($CDCl_3$): 7.34–7.22 m, 5 H (ArH); 5.11 br s, 1 H (NH); 3.45 q, 1 H, *J* = 7.1 (CHCO); 2.02 br s, 3 H (CH in adamantyl group); 1.90 br d, 6 H (CH_2 in adamantyl group); 1.63 br t, 6 H (CH_2 in adamantyl group); 1.46 d, 3 H, *J* = 7.1 (Me). ^{13}C NMR ($CDCl_3$): 173.2 (CO); 142.1 (Ph); 128.7 (Ph); 127.5 (Ph); 127.0 (Ph); 51.7 (CN); 47.8 (CHCO); 41.4 (CH_2); 36.3 (CH_2); 29.4 (CH); 18.7 (Me). HR MS: calculated for $C_{19}H_{25}NONa$ $[M + Na]^+$ 306.1834, found 306.1841.

N-Benzyl-N-methyl-2-phenylpropanamide ((±)-**10**) (a mixture of two conformational isomers A and B). IR (neat): 2 970, 1 635, 1 450, 733, 710. ^{1}H NMR ($CDCl_3$): 7.31–7.15 m, 8 H (ArH); 7.01 d, 2 H, *J* = 7.3 (ArH); 4.66 d, 1a H, *J* = 14.6 (Bn of A); 4.65 d, 1b H, *J* = 16.7 (Bn of B); 4.54 d, 1a H, *J* = 14.6 (Bn of A); 4.24 d, 1b H, *J* = 16.7 (Bn of B); 3.92 q, 1a H, *J* = 6.8 (CHCO of A); 3.87 q, 1b H, *J* = 6.8 (CHCO of B); 2.93 s, 3 H (MeN of B); 2.79 s, 3 H (MeN of A); 1.49 d, 3a H, *J* = 6.8 (Me of A); 1.46 d, 3b H, *J* = 6.8 (Me of B). ^{13}C NMR ($CDCl_3$): 174.1 (CO of B); 173.7 (CO of A); 141.9 (Ph of B); 141.7 (Ph of A); 137.4 (Ph of A); 136.6 (Ph of B); 128.8 (Ph); 128.8 (Ph); 128.8 (Ph); 128.4 (Ph); 127.8 (Ph); 127.4 (Ph); 127.3 (Ph); 127.2 (Ph); 127.1 (Ph); 126.8 (Ph); 126.7 (Ph); 126.2 (Ph); 52.9 (Bn of B); 51.1 (Bn of A); 43.4 (CHCO of A); 43.1 (CHCO of B); 34.7 (MeN of A); 34.2 (MeN of B); 20.9 (Me of B); 20.8 (Me of A). HR MS: calculated for $C_{17}H_{19}NONa$ $[M + Na]^+$ 276.1365, found 276.1349.

(2-Phenylpropanoyl)piperidine ((±)-**11**). IR (neat): 1 643, 1 442. ^{1}H NMR ($CDCl_3$): 7.33–7.19 m, 5 H (ArH); 3.88 q, 1 H, *J* = 6.8 (CHCO); 3.70–3.35 br m, 4 H (CH_2N); 1.52–1.37 m, 6 H (CH_2); 1.44 d, 3 H, *J* = 6.8 (Me). ^{13}C NMR ($CDCl_3$): 171.7 (CO); 142.4 (Ph); 128.8 (Ph); 127.2 (Ph); 126.6 (Ph); 43.2 (CHCO); 43.2 (CH_2N); 25.7 (CH_2); 24.5 (CH_2); 20.8 (Me). HR MS: calculated for $C_{14}H_{19}NONa$ $[M + Na]^+$ 240.1365, found 240.1377.

This work was supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture.

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