NOVEL ONE STEP TRANSFORMATION OF CARBAMATES INTO AMIDES#

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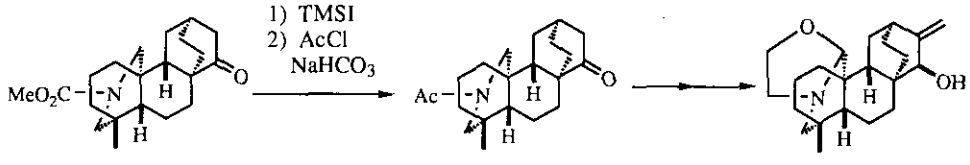
Abstract--A novel method for the one step conversion of carbamates into amides was developed by the action of acyl chlorides and sodium iodide.

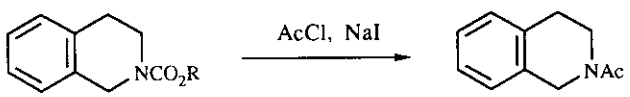
In the course of total synthesis of atisine (**3**),[1] the key synthetic intermediate (**2**) was synthesized from the carbamate (**1**) in two steps; treatment with trimethylsilyl iodide,[2] followed by acetylation. As far as we know, there is no methodology for the direct conversion of carbamates into amides. In order to develop the one step formation of amides from carbamates, a number of reaction conditions have been examined for various carbamates. The desired transformation was consequently achieved by the action with acyl chlorides and sodium iodide.[3] Now, we wish to report the direct preparation of amides from carbamates, which must be useful for syntheses of natural products and biologically active compounds.



1 **2** **3**

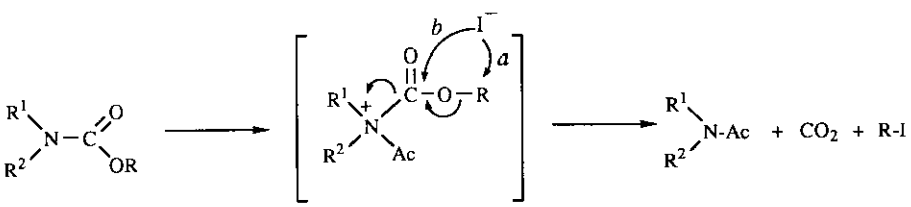
This paper is dedicated to Emeritus Professor M. Hamana on the occasion of his 75th birthday.

The methoxycarbonyl group of the tetrahydroisoquinoline derivative (**4**) was directly replaced with the acetyl group by the heating **4** with 10 equivalent moles of acetyl chloride and sodium iodide in acetonitrile at 60 °C. After the reaction for 40 h, the acetamide (**7**) was obtained in 92% yield. The acetamide (**7**) was provided in 61% and 84% yields, respectively, from the *tert.*-butyl carbamate (**5**) and the benzyl carbamate (**6**) under the same reaction conditions for 42 h and for 7 h. It is known that acetyl iodide, formed by the reaction of acetyl chloride with sodium iodide, cleaves selectively the less substituted α-carbon-oxygen bond of ethers.[3] Therefore the production of the acetamide (**7**) from the *tert.*-butyl carbamate (**5**) is noteworthy. The reaction would proceed through the attack of the iodide to the alkyl group (*a*) or the carbonyl group (*b*) of the quaternary nitrogen intermediate (**8**).



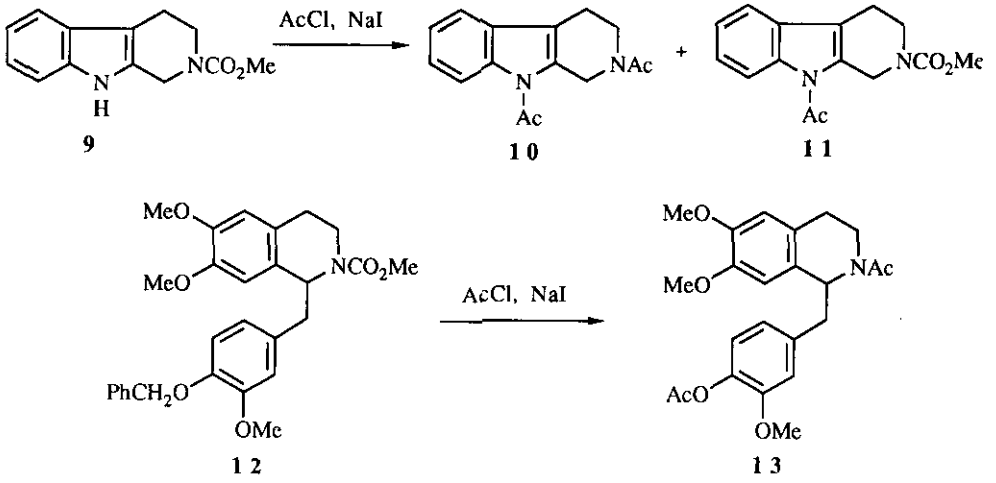
4: R = Me
5: R = Bu^t
6: R = CH_2Ph

7

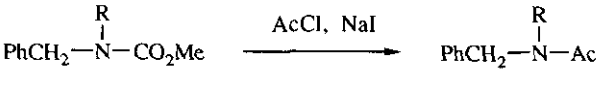


8

Treatment of the carbamate (**9**) of tetrahydro-β-carboline for 42 h under the same conditions produced the *N,N'*-diacetyl compound (**10**) in 41% yield together with *N'*-acetyl carbamate (**11**) in 7% yield. The same treatment of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivative (**12**) for 45 h gave the *N,O*-diacetyl product (**13**) in 59% yield. The result indicates that the amide formation is faster than the fission of the aryl methyl ether.

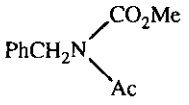


Methyl carbamate (**14**) of *N*-methylbenzylamine was transformed into the acetamide (**16**) in 52% yield, while the corresponding secondary amide (**17**) was produced in 65% yield by the same treatment of the carbamate (**15**). When the latter reaction was carried out using 1.4 equivalent moles of reagents, the *N*-methoxycarbonylacetamide (**18**) was isolated as a labile product. The formation of **18** would support the above mechanism.



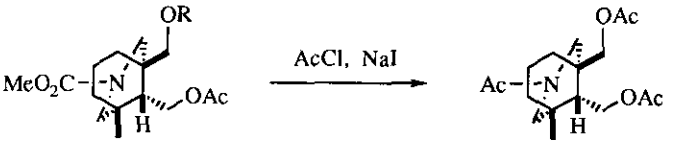
14 R = Me
15 R = H

16 R = Me
17 R = H



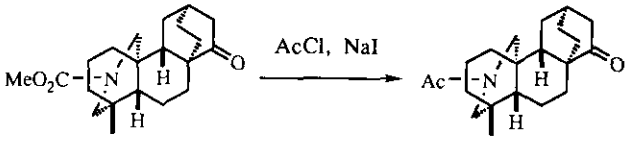
18

The reaction of the methoxymethyl ether (**19**), derived from the synthetic intermediate of atisine,[1] carrying out under the same conditions as above provided in 43% yield the acetamide (**21**), which was obtained in 43% yield from the diacetate (**20**) by the same treatment. The direct transformation of the carbamate (**1**) into the synthetic precursor (**2**) to atisine was accomplished in 52% yield by the application of the above reaction.



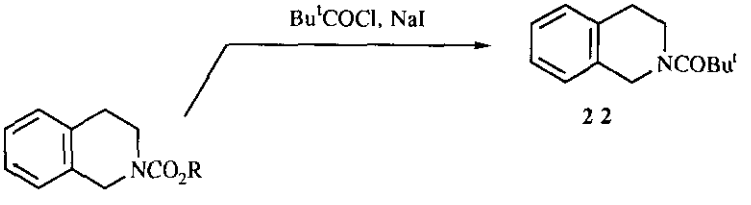
19 R = CH_2OMe
20 R = Ac

21



1 **2**

On the other hands, the treatments of the carbamates (**4**, **5**, and **6**) with pivaloyl chloride in the presence of sodium iodide in acetonitrile at 60 °C produced the pivaloyl amide (**22**) in 43, 45, and 41% yields, respectively. Furthermore, the benzoyl amide (**23**) was obtained, in 87, 99, and 99% yields, respectively, by the reactions of **4**, **5**, and **6** with benzoyl chloride in the presence of sodium iodide. Thus a general method for the conversion of carbamates into amides was developed.



4 R = Me
5 R = Bu^t
6 R = CH_2Ph

22

23

EXPERIMENTNAL

General Methods.--Ir spectra were recorded on a JASCO-IR-Report-100 spectrophotometer, while ^1H nmr spectra were measured on Hitachi R-1200 and JEOL-GX-500 spectrometers. Chemical shifts are reported relative to internal $SiMe_4$. Mass spectra were taken on a JEOL-DX-300 or JEOL-DX-303 spectrometer. Optical rotations were determined on a JASCO-DIP-340 polarimeter.

2-Acetyl-1,2,3,4-tetrahydroisoquinoline (7).

Method A--To a mixture of the methyl carbamate (**4**) (50 mg, 0.27 mmol) and sodium iodide (406 mg, 2.7 mmol) in dry acetonitrile (5 ml) was slowly added at 0 °C acetyl chloride (0.19 ml, 2.7 mmol). The resulting mixture was heated at 60 °C for 40 h under stirring and nitrogen atmosphere. After addition of saturated aqueous sodium hydrogen sulfite and saturated aqueous sodium hydrogen carbonate under ice cooling, the mixture was thoroughly extracted with chloroform. The extract was washed with brine, dried over potassium carbonate, and evaporated under reduced pressure. Purification of the product using silica gel column chromatography gave the acetamide (**7**) (43 mg, 92% yield) as an oil, which was identical with the authentic compound, prepared by the acetylation of 1,2,3,4-tetrahydroisoquinoline under usual conditions.

Method B--The *tert.*-butyl carbamate (**5**) was converted into **7** in 61% yield by the same treatment as above for 42 h.

Method C--The benzyl carbamate (**6**) was transformed into **7** in 84% yield by the same reaction as above for 7 h.

2,9-Diacetyl-1,2,3,4-tetrahydro-β-carboline (**10**). The reaction of the carbamate (**9**) of 1,2,3,4-tetrahydro-β-carboline carrying out under the same conditions as above for 42 h gave the title compound (**10**) in 41% yield as an oil; Anal. Calcd for $C_{15}H_{16}N_2O_2 \cdot 0.25H_2O$: C, 69.06; H, 6.38; N, 10.74. Found: C, 68.92; H, 6.33; N, 10.74; ir (neat): 1700 and 1640 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 2.20 (3 H, s, 2-Ac), 2.80 (3 H, s, 9-Ac), 4.86-5.10 (2 H, m, 1-H_2), and 7.14-7.96 (4 H, m, 4 x ArH); ms m/z: 256 (M^+); exact mass calcd for $C_{15}H_{16}N_2O_2$ 256.1211 (M^+), found 256.1212, and the 9-acetyl carbamate (**11**) in 7% yield as an oil; Anal. Calcd for $C_{15}H_{16}N_2O_3 \cdot 0.6H_2O$: C, 63.62; H, 6.13; N, 9.90. Found: C, 63.58; H, 5.66; N, 9.59; ir (neat): 1710 and 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 2.75 (3 H, s, 9-Ac), 3.75 (3 H, s, OMe), 4.94 (2 H, br s, 1-H_2), and 7.14-7.92 (4 H, m, 4 x ArH); ms m/z: 272 (M^+); exact mass calcd for $C_{15}H_{16}N_2O_3$ 272.1160 (M^+), found 272.1161.

1-(4-Acetoxy-3-methoxybenzyl)-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**13**). On the same treatment as above for 45 h, the carbamate (**12**) of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline was transformed into the title compound (**13**) in 59% yield as an oil; ir (neat): 1758 and 1625 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 1.72 and 2.14 [3 H (1:2), each s, NAc], 2.27 (3 H, s, OAc), 3.60 and 3.72 [3 H (2:1), each s, OMe], 3.77 (3 H, s, OMe), 3.83 (3 H, s, OMe), and 6.13-

7.05 (5 H, m, 5 x ArH); ms m/z: 413 (M^+); exact mass calcd for $C_{23}H_{27}NO_6$ 413.1837 (M^+), found 413.1838, the physical properties of which were identical with those of the authentic sample, prepared by the acetylation of 1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxybenzyl)-6,7-dimethoxyisoquinoline.

N-Benzyl-*N*-methylacetamide (**16**).

The carbamate (**14**) of *N*-methylbenzylamine was converted, by the same reaction as above for 20 h, in 52% yield into the acetamide (**16**), which was identical with the authentic specimen.

N-Benzylacetamide (**17**).

The same treatment as above for 15 h of the carbamate (**15**) of benzylamine provided in 65% yield the acetamide (**17**), which was identical with the authentic specimen.

(-)-(1R,5R,9R)-3-Acetyl-1,9-diacetoxymethyl-5-methyl-3-azabicyclo[3.3.1]nonane (**21**).

Method A--The reaction of the carbamate (**19**), {$[\alpha]_D^{22}$ -7.20° (c 0.94 in $CHCl_3$); Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.44; H, 8.52; N, 4.08. Found: C, 59.01; H, 8.50; N, 4.03; ir (neat): 1740 and 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 0.94 (3 H, s, 5-Me), 2.02 (3 H, s, OAc), 3.30 (2 H, s, 1-CH_2), 3.34 (3 H, s, $CH_2O\mathit{Me}$), 3.70 (3 H s, CO_2Me), and 4.58 (2 H, s, OCH_2O); ms m/z: 343 (M^+)}, derived from the intermediate[1] of atisine as usual method, carrying out the same conditions as above for 5 h provided the title compound (**21**) in 43% yield as an oil, $[\alpha]_D^{24}$ -2.48° (c 0.48 in $CHCl_3$); Anal. Calcd for $C_{17}H_{27}NO_5 \cdot 0.3H_2O$: C, 61.60; H, 8.42; N, 4.23. Found: C, 61.59; H, 8.09; N, 4.10; ir (neat): 1735 and 1642 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 1.01 (3 H, s, 5-Me), and 2.03, 2.07, and 2.09 (each 3H, each s, 3 x Ac); ms m/z: 325 (M^+); exact mass calcd for $C_{17}H_{27}NO_5$ 325.1888 (M^+), found 325.1889.

Method B--The reaction of the carbamate (**20**), {$[\alpha]_D^{22}$ -2.58° (c 1.50 in $CHCl_3$); Anal. Calcd for $C_{17}H_{27}NO_6 \cdot 0.1H_2O$: C, 59.47; H, 7.99; N, 4.08. Found: C, 59.23; H, 7.87; N, 4.04; ir (neat): 1738 and 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 0.97 (3 H, s, 5-Me), 2.03 and 2.08 (each 3H, each s, 2 x Ac), and 3.72 (3 H, s, CO_2Me); ms m/z: 341 (M^+); exact mass calcd for $C_{17}H_{27}NO_6$ 341.1837 (M^+), found 341.1838}, carrying out under the same conditions as above for 5 h gave in 43% yield the acetamide (**21**), which was identical with the above compound, prepared by the method A.

(-)-*N*-Acetyl-8α,12α-ethano-16,17-imino-14-oxo-5β,9β,10α-podocarpane (**2**). The same treatment of the carbamate (**1**)[1] for 16 h provided the acetamide (**2**) in 52% yield, which was identical with the authentic compound in all respects including 500 MHz ^{1}H-nmr spectroscopy.

N-Benzyl-*N*-methoxycarbonylacetamide (**18**).

To a mixture of the carbamate (**15**) (49.8 mg, 0.30 mmol) and sodium iodide (63.3 mg, 0.42 mmol) in dry acetonitrile (5 ml) was added at 0 °C acetyl chloride (0.03 ml, 0.42 mmol). The mixture was heated for 23 h at 60 °C under stirring and nitrogen atmosphere. The resulting mixture was filtered through Celite. The combined filtrates and washings with chloroform were evaporated under reduced pressure to give a residue, which was washed with 2M aqueous sodium thiosulfate, saturated aqueous potassium carbonate, and brine, dried over potassium carbonate, and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel. Elution with hexane-AcOEt (7:3 v/v) afforded the title compound (**18**) (40.8 mg, 65%) as an oil; ir (neat): 1740 and 1690 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 2.56 (3 H, s, Ac), 3.78 (3 H, s, CO_2Me), 4.92 (2 H, s, NCH_2Ph), and 7.26 (5 H, s, 5 x ArH); ms m/z: 207 (M^+); exact mass calcd for $C_{11}H_{13}NO_3$ 207.0895 (M^+), found 207.0895.

1,2,3,4-Tetrahydro-2-pivaloylisoquinoline (**22**).

Method A--The methyl carbamate (**4**) was transformed, by the same reaction as above for 14 h, in 43% yield into the amide (**22**) as an oil, ir (neat): 1620 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$; 60 MHz) δ: 1.32 (9 H, s, Bu^t), 2.86 (2 H, t, *J* 6.0 Hz, 4-H_2) 3.85 (2 H, t, *J* 6.0 Hz, 3-H_2), 4.74 (2 H, s, 1-H_2), and 7.13 (4 H, br s, 4 x ArH); ms m/z: 217 (M^+); exact mass calcd for $C_{14}H_{19}NO$ 217.1466 (M^+), found 217.1467.

Method B--The *tert.*-butyl carbamate (**5**) was converted into **22** in 45% yield by the same treatment as above for 14 h.

Method C--The benzyl carbamate (**6**) was converted into **22** in 41% yield by the same treatment as above for 12 h.

2-Benzoyl-1,2,3,4-tetrahydroisoquinoline (**23**).

Method A--The methyl carbamate (**4**) was transformed, by the same reaction as above for 20 h, in 87% yield into the amide (**23**), which was identical with the authentic compound[4] in all respects.

Method B--The *tert.*-butyl carbamate (**5**) was converted into **23** in 99% yield by the same treatment as above for 11 h.

Method C--The benzyl carbamate (**6**) was converted into **23** in 99% yield by the same treatment as above for 12 h.

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REFERENCES

1. M. Ihara, M. Suzuki, K. Fukumoto, T. Kametani, and C. Kabuto, *J. Am. Chem. Soc.*, 1988, **110**, 1963; M. Ihara, M. Suzuki, K. Fukumoto, and C. Kabuto, *J. Am. Chem. Soc.*, 1990, **112**, 1164.
2. M. E. Jung and M. A. Lyster, *J. Chem. Soc., Chem. Commun.*, 1978, 315.
3. A. Oku, T. Harada, and K. Kita, *Tetrahedron Lett.*, 1982, **23**, 681.
4. E. Bamberger and W. Dieckmann, *Ber.*, 1893, **26**, 1205.

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