Niobium Pentachloride Promoted Conversion of Carboxylic Acids to Carboxamides: Synthesis of the 4-Aryl-1,2,3,4-tetrahydroisoquinoline Alkaloid Structures

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Abstract: A practical method for the conversion of carboxylic acids to the corresponding carboxamides mediated by niobium pentachloride under mild conditions is described. The synthesis of the 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid structures was accomplished via benzylic lithiation of *N*-methyl-3,4-dimethoxy-2-(4′-methoxybenzyl)benzamide.

Key words: carboxamides, niobium pentachloride, carboxylic acids, alkaloid, tetrahydroisoquinoline

Unusual biologically active peptides are isolated from marine sponges, fungi, bacteria, and other lower animal forms. Through the use of modern synthetic strategies, these compounds are synthesized[1] by processes involving as key step the formation of carboxamides under mild conditions employing reagents such as: 2-oxopiperazine[2] derivatives, DCC, HOBt, BOP, isobutylchloroformate,[1] etc.

There also exists a direct approach involving the pyrolytic dehydration of the appropriate substituted ammonium carboxylate salts.[3] Amines in the vapor phase[4] at 270–290 °C or after a long period of reflux[5] with the use of Lewis acid catalysts,[6] aliphatic and aromatic carboxylic acids can be converted to the desired carboxamides. The classical two step synthesis involves the conversion of aliphatic or aromatic acids to the corresponding acyl chlorides with suitable reagents ($SOCl_2$, PCl_5, ClCOCOCl),[7] followed by treatment with the appropriate amine.

Niobium compounds are useful catalysts for various reactions.[8] The compound niobium pentachloride ($NbCl_5$) is a yellow solid, quickly hydrolyzed by water to the hydrated pentoxides and hydrochloric acid. Initially, due to its potential as a donor of chloride species, low cost and abundance in Brazil, $NbCl_5$[9] was chosen as promoter for the reactions between carboxylic acids (**1a**–**l**) and diethylamine, butylamine or ammonia to obtain the corresponding *N*,*N*-diethylcarboxamides **(2a**–**l)**, *N*-butylcarboxamides (**3a**–**l**) or carboxamides (**4a**–**l**).

Aromatic *N*,*N*-diethylcarboxamides (**2a** and **g**) and *N*,*N*-diethylcarbamates have been used as DoM starting materials in lithiation reactions aimed at the synthesis of natural products, such as pancreatistatin[10] and substituted 4-hydroxy-coumarins.[11] With this as the main objective, we have developed a practical experimental procedure to obtain *N*,*N*-diethylcarboxamides (**2a**–**l**). In addition, it was possible to extend the method to the formation of *N*-butylcarboxamides (**3a**–**l**) and carboxamides (**4a**–**l**) under mild conditions by the following procedure: a solution of 3.0 equivalents of the appropriate carboxylic acids (**1a**–**l**) and 1.0 equivalent of niobium pentachloride was obtained in dichloromethane or dioxane as solvent and after a certain period of time with the addition of an excess of diethylamine, butylamine or ammonia (Table 1).

The low yields of oxygenated aromatic acids may be attributed to the formation of stable coordinated species[12] with niobium pentachloride and electron donating groups attached at the aromatic ring instead the formation of corresponding acylium species during the course of these reactions. Moreover, in the case of piperonylic acid, the low yield was also related to the cleavage of the methylenedioxy ring by coordination of niobium pentachloride with one oxygen atom, followed by nucleophilic attack of chloride species on the methylene portion generating catechol intermediates which form stable coordinating compounds. This type of ring opening is also observed in methylenedioxy aromatic systems in the presence of $AlCl_3$[13] and BCl_3.[14]

This procedure described herein contrasts with most literature procedures[3–7] occurring under mild conditions without the generation of free hydrogen chloride gas or other irritant side products such as sulfur dioxide or phosphorus oxychloride.

The use of niobium pentachloride to promote the formation of the *N*,*N*-diethylcarboxamide of pivalic acid was achieved in good yield. The same chemical transformation failed when titanium tetrachloride[15] was used as promoter.

Brown and co-workers,[16] have published a different approach for the preparation of acyl chloride, oxoniobium and oxotitanium carboxylates in moderate yields. The formation of these intermediates occurs at the same time when a carboxylic acid is submitted to treatment with $TiCl_4$ or $NbCl_5$. However, the oxotitanium carboxylates structures formation requires more equivalents of carboxylic acid than oxoniobium carboxylates.[16,17] A possible

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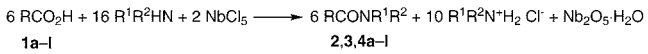
Table 1 Conversion of Carboxylic Acids to *N*,*N*-Diethylcarboxamides, *N*-Butylcarboxamides and Carboxamides with Niobium Pentachloride



Carboxylic Acids	Carboxamides	Time (h)	Solvent	Yield (%)
benzoic acid **1a**	**2a**, **3a**, **4a**	2, 0.5, 0.5	CH_2Cl_2	89, 96, 97
m-toluic acid **1b**	**2b**, **3b**, **4b**	2.5, 0.5, 0.5	CH_2Cl_2	85, 93, 95
octanoic acid **1c**	**2c**, **3c**, **4c**	2.5, 0.5, 0.5	CH_2Cl_2	79, 89, 89
crotonic acid **1d**	**2d**, **3d**, **4d**	3, 0.5, 1	CH_2Cl_2	70, 81, 90
propanoic acid **1e**	**2e**, **3e**, **4e**	2.5, 0.5, 1	CH_2Cl_2	84, 88, 96
butyric acid **1f**	**2f**, **3f**, **4f**	3, 0.5, 1	CH_2Cl_2	88, 89, 98
piperonylic acid **1g**	**2g**, **3g**, **4g**	5, 0.5, 2	dioxane	8, 47, 48
pivalic acid **1h**	**2h**, **3h**, **4h**	10, 0.5, 1	CH_2Cl_2	78, 83, 88
nicotinic acid **1i**	**2i**, **3i**, **4i**	12, 0.5, 2	dioxane	73, 84, 83
phenylacetic acid **1j**	**2j**, **3j**, **4j**	5, 0.5, 0.5	CH_2Cl_2	63, 93, 93
p-hydroxybenzoic acid **1k**	**2k**, **3k**, **4k**	10, 0.5, 1	dioxane	12, 54, 51
3,4-dimethoxybenzoic acid **1l**	**2l**, **3l**, **4l**	8, 0.5, 3	CH_2Cl_2	45, 77, 74

explanation could be as follows: When the pivalic acid is used in this procedure, the steric effects contribute to a decrease in the stability of corresponding oxotitanium carboxylate and consequently generate less amount of pivaloyl chloride.

The experimental procedure described in this work is a practical way to produce carboxamides (**2**, **3**, **4a–l**) from carboxylic acids (**1a–l**) under mild conditions and the HCl generated is trapped under the form of an ammonium salt, which together with Nb_2O_5 can be recycled at the end of reaction.

A useful synthetic application of this methodology is described in Schemes 1 and 2 involving the preparation of the 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid structures related with racemic *O*-dimethyl latifine (**5a**), a derivative of the natural product (+)-latifine (**5b**) isolated from *Crinum latifolium L.*, which would be expected to demonstrate potential pharmacological activities of biological relevance (Figure 1).[18]

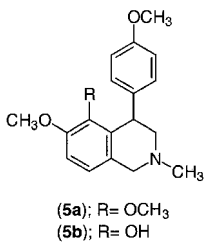
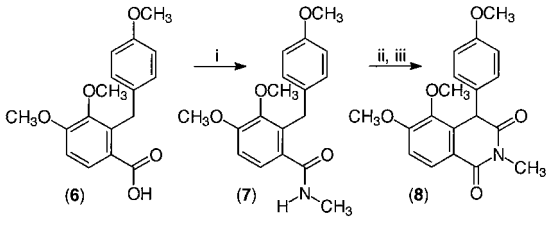


Figure 1

The acid (**6**) was obtained by the same sequence of reactions described in our previous work.[19] By treatment of acid (30.0 mmol) (**6**) under the same conditions as described in experimental section below, the *N*-methylbenzamide (**7**) was obtained in 86% yield. The interesting point of this chemical transformation was the addition of an aqueous solution containing an excess of methylamine hydrochloride (45%) to quench the oxoniobium carboxylate intermediate and furnish the desired product. Traditionally, standard acylation procedures with aliphatic or aromatic acyl chlorides require anhydrous free amines to condense and form the appropriated carboxamides.

Benzylic lithiation of **7** was carried out in the presence of 3.0 equivalents of BuLi, 1.3 M hexane solution in THF followed by dropwise addition of a solution of triphosgene in THF to afford the *N*-methylimide **8** in 93% yield. In our hands, the use of DMF as electrophile[20] afforded poor yields of corresponding 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid derivative (Scheme 1). Reduction of **8** with a suspension of $LiAlH_4$ in THF gave a complex mixture of products.

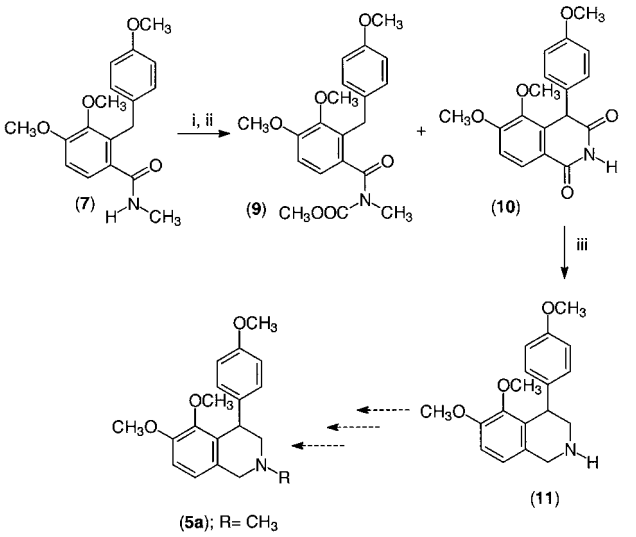


Scheme 1 *Reagents and conditions*: i) $NbCl_5/CH_2Cl_2$, $CH_3NH_2{\cdot}HCl/H_2O$ (45% w/v), 0 °C, 86% ii) BuLi/THF (3.0 equiv), 0 °C iii) Triphosgene/THF, 93%.

An unexpected result was observed on the benzylic lithiation reaction of amide (**7**) using methyl chloroformate instead of triphosgene as electrophile. After the same work up and purification by flash chromatography, the amide derivative (**9**) was obtained in 31% yield together with an imide (**10**) in 30% yield.

An explanation for these results might be visualized by the difference of reactivity between triphosgene and methylchloroformate used as eletrophile. Each equivalent of triphosgene affords 2.0 equivalents of CCl_3O^- species which are unstable producing phosgene and LiCl. The ring closure product **8** with triphosgene produces phosgene which is even more reactive than triphosgene. To complete a ring closure only a third of an equivalent is necessary since each mole of triphosgene releases 2 additional phosgenes. However, we obtained best yields in the formation of *N*-methylimide **8** using an excess of triphosgene. Probably, the *N*-methylimide **8** is also an intermediate of the reaction when methyl chloroformate used as electrophile and the CH_3O^- species formed can react by two different ways to generate the amide derivative (**9**) and the imide (**10**). The first compound was obtained by the nucleophilic attack on the carbonyl group at the 3 position and the second by nucleophilic attack at the *N*-methyl group of compound **8**.

The reduction of **10** with a suspension of $LiAlH_4$ in THF gave the corresponding 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid (**11**) in 71% yield (Scheme 2).



Scheme 2: *Reagents and conditions*: i) BuLi/THF (3.0 equiv), 0 °C ii) $ClCO_2CH_3$/ THF, **9** (31%), **10** (30%) iii) $LiAlH_4$/THF, 71%.

In conclusion, to finish this project, different alkyl groups will be attached at the nitrogen atom of 5,6-dimethoxy-4(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**11**) by well known synthetic methodology established by Brossi and coworkers.[21] This involves acylation and further reduction to make *O*-dimethyl latifine (**5a**) and new *N*-aliphatic derivatives whose biological properties will be evaluated.

Melting points were determined on a Melt-Temp apparatus. ^1H and ^{13}C NMR spectra were recorded on Gemini-200 MHz, Bruker AM-250 MHz and Bruker-300 MHz spectrometers with Me_4Si (δ = 0.00) as internal standard in DMSO-d_6 or $CDCl_3$ solvents. The following abbreviations are used to describe the multiplicity of signals (s, singlet; d, doublet; dd, doublet of a doublet; t, triplet; dt, doublet of a triplet; m, multiplet). Chemical shifts were expressed as δ values (part per million) from tetramethylsilane. Mass spectra were determined on a Auto Specq EI at 70 eV and HRMS was determined on a Varian MAT-CH7 instrument at 70 eV by the Department of Chemistry, Queen's University, Kingston, Canada. All commercial chemicals were purchased from Aldrich Co, Sigma and Vetec (Brazilian Chemical Co).

Synthesis of Carboxamides (2,3,4a–l); General Procedure

In a 100.0 mL round-bottomed flask equipped with a magnetic stirrer, argon-inlet, and a reflux condenser $NbCl_5$ (4.71 mmol) was added followed by addition of a soln in CH_2Cl_2 or dioxane (30.0 mL), (see Table 1) of the carboxylic acid (14.13 mmol) (**1a–l**). After a few min of vigorous stirring, a suspension formed and diethylamine, butylamine or ammonia (37.68 mmol) was introduced into the reaction mixture. In 0.5 h, the temperature was slowly raised to 45–50 °C and the reaction time was maintained as described in Table 1, for each carboxylic acid. The reaction mixture was cooled and the solids formed were removed by filtration. The filtrate was extracted with EtOAc or Et_2O (200 mL), washed with a soln of $NaHCO_3$ (5%, 60 mL), brine (2 × 60 mL), H_2O (3 × 60 mL), evaporated and distilled to give the desired carboxamides (**2**,**3**,**4a–l**). The boiling, melting points and other analytical data were compatible with the chemical structures of carboxamides as described in references.[3–7] The yields reported in Table 1, were obtained after distillation or recrystallization of the crude materials.

***N*-Methyl-3,4-dimethoxy-2-(4′-methoxybenzyl)benzamide (7)**

In a 100 mL round-bottomed flask equipped with a magnetic stirrer, argon-inlet, and a reflux condenser $NbCl_5$ (1.0 mmol, 0.270 g) were added followed by addition of a soln in CH_2Cl_2 (12.0 mL) of the 3,4-dimetoxy-2-(4′-methoxybenzyl) benzoic acid (3.0 mmol, 0.905 g) (**1a–l**). After a few min of vigorous stirring, the suspension formed was kept at 0 °C and chloride salt of methylamine (7.0 mmol) 45% (w/v) were added. In 0.5 h, the temperature was slowly raised to r.t. and the reaction maintained for 1 h. The reaction mixture was cooled and the solids formed were removed by filtration. The filtrate was introduced into a soln of $NaHCO_3$ (5%, 25.0 mL) and extracted with CH_2Cl_2 (80 mL). The organic layer was washed with a soln of brine (2 × 30 mL), H_2O (3 × 30 mL), dried (Na_2SO_4), the solvent was evaporated in vacuo, and the brown crude product purified by fast filtration on silica gel with hexane–EtOAc (2:1) as eluent to give (**7**) (819 mg, 86%) as an amorphous white solid.

Mp 146–148 °C (lit.[20] mp 145–147 °C).

IR (film): 3291, 3074, 3014, 2942, 2841, 1626, 1542, 1512, 1488, 1290, 1251, 1084, 1060, 1032, 1004 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.80 (d, 3 H, *J* = 4.6 Hz), 3.72 (s, 3 H), 3.75 (s, 3 H), 3.88 (s, 3 H), 4.15 (s, 2 H), 5.51 (s, 1 H), 6.76 (d, 2 H, *J* = 8.5 Hz), 6.78 (d, 1 H, *J* = 8.0 Hz), 7.11 (d, 2 H, *J* = 8.4 Hz), 7.13 (d, 1 H, *J* = 7.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 31.5, 55.3, 55.8, 60.7, 110.0, 113.8, 123.5, 129.7, 130.6, 133.4, 133.7, 147.6, 154.2, 157.9, 170.5.

MS: *m*/*z* (%) = 315 (100), 283 (10), 207 (13).

5,6-Dimethoxy-4-(4′-methoxyphenyl)-2-methyl-4-tetrahydroisoquinoline-1,3-dione (8)

The *N*-methylbenzamide (**7**) (0.315 g, 1.0 mmol) was dissolved in THF (20.0 mL) and cooled to 0 °C. A soln of BuLi in hexane (1.3 M, 2.3 mL, 2.3 mmol) was added to generate a deep red soln of the

corresponding dilithiated amide. After 60 min, triphosgene (0.476 g, 1.6 mmol) in THF (6 mL) was added in one portion and the reaction mixture became pale white. The soln was stirred for a further 30 min and $NaHCO_3$ (5 mL, 10%) was added. The reaction mixture was extracted with EtOAc (120 mL), the organic layer was washed with H_2O (2 × 30 mL) and dried with Na_2SO_4. The solvent was removed by reduced pressure to give a viscous brown oil which was purified by flash chromatography using hexane–EtOAc (2:1) as eluent affording **8** (0.317 g, 93%) as a white solid.

Mp 137–139 °C.

IR (film): 3488, 3000, 2939, 2840, 1759, 1716, 1670, 1602, 1509, 1502, 1453, 1419, 1357, 1285, 1249, 1178, 1155, 1084, 1032, 995, cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.31 (s, 3 H), 3.71 (s, 6 H), 3.85 (s, 3 H), 6.28 (s, 1 H), 6.77 (d, 1 H, *J* = 8.6 Hz), 6.97 (d, 2 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.1 Hz), 7.62 (d, 1 H, *J* = 7.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 36.7, 55.4, 56.1, 60.6, 77.4, 112.2, 112.6, 116.6, 120.7, 125.3, 131.0, 131.8, 143.6, 156.0, 158.5, 160.0, 161.8.

MS: *m*/*z* (%) = 341 (19), 313 (100), 285 (15), 249 (22), 179 (23), 176 (24).

HRMS: *m*/*z* calcd for $C_{19}H_{19}NO_5$, 341.3647; found, 341.3643.

N,*N*-Carboxymethyl-methyl-3,4-dimethoxy-2-(4′-methoxybenzyl)benzamide (9) and 5,6-Dimethoxy-4-(4′-methoxyphenyl)-2,4-tetrahydroisoquinoline-1,3-dione (10)

The same experimental procedure described above for obtaining compound **8** was used except the electrophile was changed to methyl chloroformate (0.46 mL, 6.0 mmol) instead of triphosgene.

9

Yellow pale oil; yield: 0.115 g (31%).

IR (film): 3503, 3211, 3068, 3005, 2934, 2840, 2840, 2555, 1762, 1670, 1611, 1570, 1497, 1457, 1342, 1275, 1256, 1178, 1090, 1073, 1029, 970 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.11 (s, 3 H), 3.52 (s, 3 H), 3.70 (s, 3 H), 3.78 (s, 1 H), 3.84 (s, 3 H), 3.91 (s, 3 H), 6.77 (d, 2 H, *J* = 8.6 Hz), 7.13 (d, 2 H, *J* = 9.0 Hz), 7.21 (d, 1 H, *J* = 8.6 Hz), 8.30 (d, 2 H, *J* = 9.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 55.4, 56.1, 56.3, 60.6, 106.6, 112.0, 113.0, 119.3, 125.5, 127.6, 130.9, 131.2, 141.9, 144.1, 152.3, 156.6, 158.7, 161.7.

MS *m*/*z* (%) = 373 (11), 315 (100), 287 (55), 272 (21).

HRMS: *m*/*z* calcd for $C_{20}H_{23}NO_6$, 373.4068; found: 373.4070.

10

White crystaline solid; yield: 0.098 g (30%); mp 172–173 °C.

IR (film): 3503, 3211, 3068, 3005, 2934, 2840, 2840, 2555, 1762, 1670, 1611, 1570, 1497, 1457, 1342, 1275, 1256, 1178, 1090, 1073, 1029, 970, cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.32 (s, 3 H), 3.72 (s, 3 H), 3.86 (s, 3 H), 6.28 (s, 1 H), 6.79 (d, 2 H, *J* = 8.7 Hz), 7.02 (d, 1 H, *J* = 8.3 Hz), 7.12 (d, 2 H, *J* = 8.7 Hz), 7.59 (d, 1 H, *J* = 8.3 Hz).

^{13}C NMR ($CDCl_3$): δ = 55.4, 56.4, 60.2, 80.9, 114.1, 114.3, 119.1, 121.9, 128.5, 128.9, 129.9, 142.6, 143.3, 157.6, 160.3, 170.2.

HRMS: *m*/*z* calcd for $C_{18}H_{17}NO_5$, 327.3378; found, 327.3381.

5,6-Dimethoxy-4(4′-methoxyphenyl) 1,2,3,4-Tetrahydroisoquinoline (11)

To a suspension of $LiAlH_4$ (0.155 g, 4.0 mmol) in THF (8 mL) a soln of **10** (0.161 g, 0.5 mmol) was added under strong stirring. The reaction mixture was refluxed for 4 h and after this time it was cooled to –15 °C. H_2O (2.0 mL) was slowly added, and additional stirring was continued for a further 30 min. EtOAc (50.0 mL) was added, the organic layer washed with H_2O (2 × 30 mL) and dried (Na_2SO_4). The solvent was removed by reduced pressure evaporation giving a crude residue which after fast filtration on flash silica gel using hexane–EtOAc (1:1) provided the compound **11** (0.107g, 71%) as a clear white oil.

IR (film): 3439, 3000, 2935, 2935, 2837, 2049, 1609, 1581, 1509, 1458, 1419, 1273, 1246, 1173, 1082, 1032 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.21 (s, 1 H), 3.64 (s, 3 H), 3.73 (m, 1 H), 3.77 (s, 3 H), 3.86 (s, 3 H), 4.35 (dd, 2 H), 4.67 (d, 1 H), 6.32 (s, 1 H), 6.81 (d, 2 H, *J* = 8.7 Hz), 6.83 (d, 1 H), 7.01 (d, 1 H, *J* = 8.4 Hz), 7,22 (d, 2 H, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 55.3, 55.8, 61.1, 63.7, 68.1, 69.0, 111.4, 113.6, 126.6, 126.8, 131.7, 136.3, 136.7, 147.3, 152.7, 158.5.

HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_3$, 299.3706; found, 299.3711.

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