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Conversion of carboxylic acids to amides under the action of tantalum(V) chloride

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Abstract: It was found that the reaction of aliphatic carboxylic acids with secondary amines under the action of tantalum (V) chloride leads to the selective formation of carboxamides. *N*,*N*-Diethyladamantane-1-carboxamide were synthesized with a yield of 73% as well.

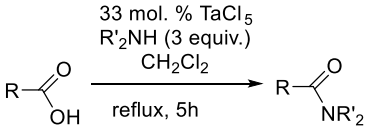
Introduction

It is known that tantalum compounds can be useful for the synthesis of various classes of organic compounds. The $TaCl_5$-Mg reagent system is an effective tool for the reduction of non-functionalized alkynes and 1-alkynyl sulfones to the corresponding olefins [1]. Recently, we have developed a regio- and stereoselective method for the synthesis of substituted 3-alkenyl amines and 4-alkynylols based on the reduction of alkynyl amines and alcohols using a similar reagent system $NbCl_5$-Mg [2]. The possibility of creating a new carbon-carbon bond was demonstrated by the example of the $TaCl_5$-catalyzed carbomagnesiation reaction of 1-alkenes with *n*-alkyl Grignard reagents [3-5]. Thus, low-valence tantalum complexes are effective reagents for the transformation of the triple bond of various acetylenic compounds. The closest electronic analogue of the tantalum atom is niobium. According to [6], $NbCl_5$ promotes the conversion of carboxylic acids into carboxamides. In this work, in order to study the possibility of conversion of carboxylic acids under the conditions of organotantalum synthesis, we studied the reaction of carboxylic acids with secondary amines in the presence of catalytic amounts of $TaCl_5$.

Results and discussion

We found that the reaction of carboxylic acids **1** with 3 equivalents of a secondary amine in the presence of 33 mol. % of $TaCl_5$ in a solution of methylene chloride after refluxing for 5 hours gave amides **2** in 51-87 % yield (Table 1). In the case of amination of heptanoic acid with dibenzylamine, the yield of carboxamide was 51% (Entry 4). Apparently, the decrease in the yield of the formed amide in the case of dibenzylamine is associated with steric hindrances arising from the interaction of heptanoyl chloride formed *in situ* with dibenzylamine. At present, we have failed to obtain betulinic acid amide in methylene chloride solution. It is possible that the inertness of betulinic acid is caused by the presence of hydroxyl group in the A ring that binds $TaCl_5$ reagent. The quantitative formation of oxoniobium and oxotitanium carboxylates as a result of the treatment of carboxylic acids with $NbCl_5$ and $TiCl_4$ is described in the literature [7,8]. However, the generation of oxotitanium carboxylates requires the use of more amount of carboxylic acid than the formation of oxoniobium carboxylates. At the same time, the effect of steric factors on the yield of the formed amide (31%) was demonstrated by the example of the $TiCl_4$-promoted amination reaction of pivalic acid using pyrrolidine in a tetrahydrofuran solution [9]. The reaction of pivalic acid with diethylamine in a solution of methylene chloride in the presence of $NbCl_5$ gave the corresponding amide in 78% yield [6].

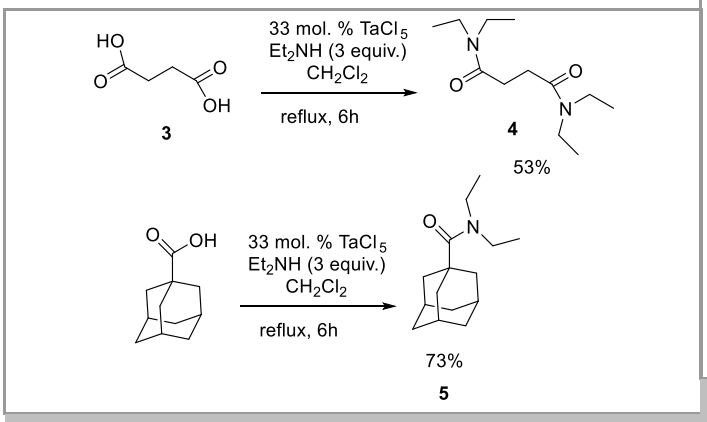
Table 1



1 2

Entry	R–C(=O)–OH, **1**	R′$_2$NH	Isolated yeld **2**, %
1	R = *n*Pent	R = *n*Bu	**2a** (77)
2	R = *n*Hept	R = *n*Bu	**2b** (81)
3	R = *n*Hex	R = *n*Bu	**2c** (83)
4	R = *n*Hex	R = Bn	**2d** (51)
5	R = $C_{15}H_{31}$	R = *n*Bu	**2e** (86)
6	R = $C_{17}H_{35}$	R = *n*Bu	**2f** (87)

$TaCl_5$-promoted reaction of succinic acid **3** with diethylamine in methylene chloride solution gave dicarboxamide **4** in 53% yield (Scheme 1). In the present work, we also found that the reaction under study allows the selective conversion of 1-adamantanecarboxylic acid under the action of diethylamine to the corresponding amide **5**.



Scheme 1 Conversion of carboxylic acids to amides under the action of tantalum(V) chloride.

Conclusions

Thus, we have demonstrated for the first time that the reaction of aliphatic mono- and dicarboxylic acids with secondary amines under the action of catalytic amounts of tantalum (V) chloride leads to the selective formation of carboxamides.

Experimental section

General information

The carboxylic acids and secondary amines were obtained from Sigma-Aldrich or Acros. Dichloromethane were distilled over P_2O_5. Nuclear magnetic resonance spectroscopy was performed on a Brucker Avance 500. The ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C-{1H} NMR spectra at 100 MHz in $CDCl_3$. The chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. The numbering of atoms in the ^{13}C-{1H} and ^{1}H NMR spectra of the compounds **2a**-**f**, **4**, **5** is shown in Figures 1. Elemental analysis was performed using a Carlo-Erba CHN 1106 elemental analyser. Mass spectra were obtained on a Finnigan 4021 instrument. The yields were calculated from the isolated amount of carboxamides obtained from starting 2-alkynylamines.

Preparation of carboxamides **2a**-**f**, **4**,**5** via conversion of carboxylic acids to amides under the action of tantalum(V) chloride.

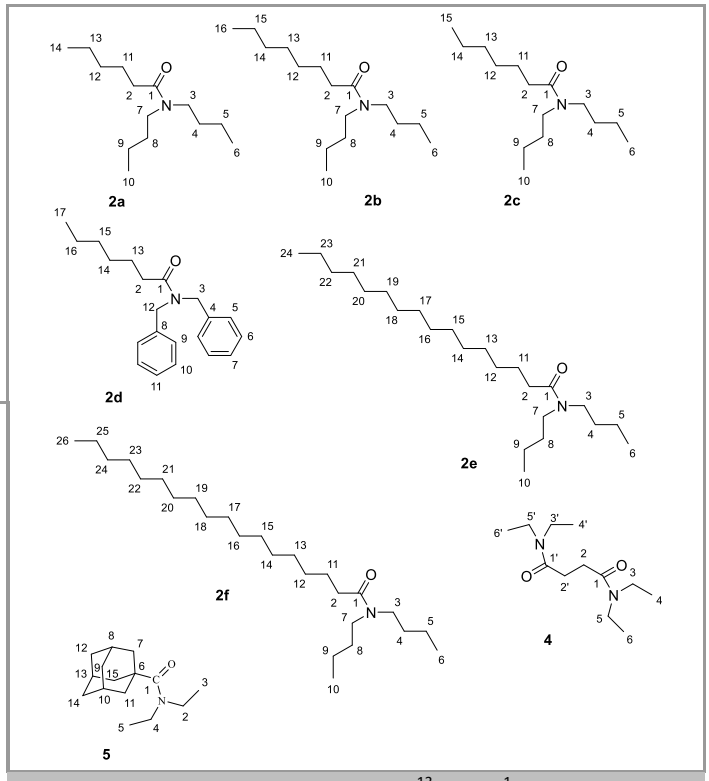


Figure 1 The numbering of atoms in the ^{13}C- and ^{1}H-NMR spectra of the compounds **2a-f**, **4**, **5.**

N,*N*-dibutylhexanamide; Typical Procedure.

In a 50.0 mL round-bottomed flask equipped with a magnetic stirrer, argon-inlet, and a reflux condenser $TaCl_5$ (238 mg, 0.666 mmol) was added followed by addition of a soln in CH_2Cl_2 (4.0 mL), of the hexanoic acid (232 mg, 2.0 mmol). After a few min of vigorous stirring, a suspension formed and dibutylamine, (258 mg, 5.26 mmol) was introduced into the reaction mixture. In 0.5 h, the temperature was slowly raised to 45 °C and the reaction time was maintained 5 h or 6h at 45 °C. The reaction mixture was diluted with Et_2O (5 mL), and 25 wt% KOH solution (3 mL) was added dropwise while the reaction flask was cooled in an ice bath. The aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$. The residue was distilled through a micro column at 20 mmHg to give **2a** (248 mg, 77%) as a colourless oil. b.p. 77 – 79 °C (20 mmHg). Evaporation of solvent and purification of the residue by column chromatography (hexane/ethyl acetate, 5:1) gave a yellow oil; yield: 350 mg, (77%); R_f = 0.69 (hexane/ethyl acetate, 5:1).

^{1}H NMR (500MHz, $CDCl_3$): δ = 0.89 - 0.98 (m, 9H), 1.28 - 1.36 (m, 6H), 1.47 – 1.57 (m, 4H), 1.62 – 1.68 (m, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 3.31 (t, *J* = 7.7 Hz, 2H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 13.83, 13.89, 13.98, 20.11, 20.27, 22.54, 25.23, 29.95, 31.29, 31.72, 33.13, 45.61, 47.73, 172.68.

MS (EI): m/z, % = 227 (3) [M^+], 184 (6), 128 (17), 100 (10), 86 (100), 43 (17).

Anal. calcd for $C_{14}H_{29}NO$, (%): C, 73.95; H, 12.86; N, 6.16. Found, %: C, 74.11; H, 13.01; N, 5.99.

***N,N*-dibutyloctanamide (2b)**

Using the procedure described above 288 mg of octanoic acid (2 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **2b** (413 mg, 81%) as colorless oil. R_f 0.67.

MS (EI): m/z, % = 255 (5) [M^+], 226 (2), 184 (11), 128 (37), 100 (15), 86 (100), 41 (18).

Anal. calcd for $C_{16}H_{33}NO$, (%): C, 75.23; H, 13.02; N, 5.48; Found, %: C, 75.31; H, 13.11; N, 5.33.

***N,N*-dibutylheptanamide (2c)**

Using the procedure described above 260 mg of heptanoic acid (2 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **2c** (400 mg, 83%) as colorless oil. R_f 0.70.

^{1}H NMR (500MHz, $CDCl_3$): δ = 0.88 - 0.98 (m, 9H), 1.27 - 1.36 (m, 8H), 1.47 – 1.56 (m, 4H), 1.61 – 1.68 (m, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 3.22 (t, *J* = 7.7 Hz, 2H), 3.31 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 13.83, 13.89, 14.05, 20.11, 20.27, 22.54, 25.52, 29.20, 29.94, 31.29, 31.70, 33.18, 45.61, 47.74, 172.72.

MS (EI): m/z, % = 241 (4) [M^+], 198 (4), 184 (11), 128 (34), 100 (12), 86 (100), 43 (26).

Anal. calcd for $C_{15}H_{31}NO$, (%): C, 74.63; H, 12.94; N, 5.80; Found, %: C, 74.71; H, 12.87; N, 6.01.

N,N-dibenzylheptanamide (2d)

Using the procedure described above 260 mg of heptanoic acid (2 mmol) and dibenzylamine (394 mg, 2 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **2d** (315 mg, 51%) as colorless oil. R_f 0.57.

^{1}H NMR (500MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3H), 1.27 – 1.31 (m, 4H), 1.33 – 1.38 (m, 2H), 1.71 – 1.77 (m, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 4.47 (s, 2H), 4.63 (s, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 7.28 – 7.30 (m, 2H), 7.32 – 7.35 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 14.05, 22.54, 25.44, 29.12, 31.63, 33.29, 48.05, 49.92, 126.39 (2C), 128.29 (2C), 127.34, 127.58, 128.58 (2C), 128.94 (2C).

MS (EI): m/z, % = 309 (4) [M^+], 218 (38), 148 (3), 106 (100), 43 (18).

Anal. calcd for $C_{21}H_{27}NO$, (%): C, 81.51; H, 8.79; N, 4.53; Found, %: C, 81.61; H, 8.57; N, 4.51.

***N,N*-dibutylpalmitamide (2e)**

Using the procedure described above 512 mg of palmitic acid (2 mmol) and dibutylamine, (258 mg, 5.26 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **2e** (633 mg, 86%) as colorless oil. R_f 0.66.

^{1}H NMR (500MHz, $CDCl_3$): δ = 0.87-0.97 (m, 9H), 1.26 (s, 18H), 1.29 - 1.35 (m, 10H), 1.47 – 1.57 (m, 4H), 1.61 – 1.65 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.21 (t, *J* = 7.6 Hz, 2H), 3.31 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 13.83, 13.89, 14.10, 20.11, 20.27, 22.68, 25.54, 29.36, 29.49, 29.53 (2C), 29.65 (3C), 29.68 (3C), 29.95, 31.29, 31.92, 33.17, 45.59, 47.73, 172.67.

MS (EI): m/z, % = 368 (2) [M^+], 240 (2), 184 (17), 156 (62), 128 (94), 86 (100), 43 (31).

Anal. calcd for $C_{24}H_{49}NO$, (%): C, 78.40; H, 13.43; N, 3.81; Found, %: C, 78.52; H, 13.45; N, 3.63.

***N,N*-dibutylstearamide (2f)**

Using the procedure described above 568 mg of stearic acid (2 mmol) and dibutylamine, (258 mg, 5.26 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **2f** (689 mg, 87%) as colorless oil. R_f 0.69.

^{1}H NMR (500MHz, $CDCl_3$): δ = 0.86 - 0.96 (m, 9H), 1.25 (s, 22H), 1.28 -1.33 (m, 10H), 1.47 – 1.54 (m, 4H), 1.59 – 1.64 (m, 2H), 2.26 (t, *J* = 7.3Hz, 2H), 3.19 (t, *J* = 7.3 Hz, 2H), 3.29 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 13.81, 13.86, 14.09, 20.09, 20.25, 22.67, 25.51, 29.35, 29.49, 29.52 (2C), 29.64 (3C), 29.68 (5C), 29.93, 31.28, 31.91, 33.14, 45.57, 47.70, 172.62.

Anal. calcd for $C_{26}H_{53}NO$, (%): C, 78.92; H, 13.50; N, 3.54; Found, %: C, 79.07; H, 13.39; N, 3.61.

***N*^{1},*N*^{1},*N*^{4},*N*^{4}-tetraethylsuccinamide (4)**

Using the procedure described above 236 mg of succinic acid (2 mmol) and diethylamine, (146 mg, 5.26 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **4** (242 mg, 53%) as colorless oil. R_f 0.69.

^{1}H NMR (500MHz, $CDCl_3$): δ = 1.53 (t, *J* = 7.1 Hz, 6H), 1.22 (t, *J* = 7.1 Hz, 6H), 2.69 (s, 4H), 3.37 – 3.41 (q, *J* = 7.1 Hz, J = 7.2 Hz, 6H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 13.12 (2C), 14.23 (2C), 28.26 (2C), 40.30 (2C), 41.90 (2C), 171.26 (2C).

Anal. calcd for $C_{12}H_{24}N_2O_2$, (%): C, 63.12; H, 10.59; N, 12.27; Found, %: C, 63.21; H, 11.13; N, 12.18.

(*3r,5r,7r*)-*N,N*-diethyladamantane-1-carboxamide (5)

Using the procedure described above 360 mg of (3*r*,5*r*,7*r*)-adamantane-1-carboxylic acid (2 mmol) and diethylamine, (146 mg, 5.26 mmol) gave crude product that was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to afford **5** (343 mg, 73%) as colorless oil. R_f 0.64.

^{1}H NMR (500MHz, $CDCl_3$): δ = 1.53 (t, *J* = 6.8 Hz, 6H), 1.74 (br. s, 6H), 2.01 (br.s, 6H), 2.05 (br.s, 6H), 2.05 (br.s, 3H), 3.44 (br.s, 4H).

^{13}C NMR (500MHz, $CDCl_3$): δ = 13.72(2C), 28.62 (3C), 36.72 (3C), 38.68, 39.18 (3C), 41.81 (2C), 176.09.

MS (EI): m/z, % = 235 (22) [M^+], 206 (5), 135 (100), 93 (12), 79 (14), 41 (6).

Anal. calcd for $C_{15}H_{25}NO$, (%): C, 76.55; H, 10.71; N, 5.95; Found, %: C, 76.61; H, 10.68; N, 4.89.

Conflicts of interest

The authors declare no competing financial interest.

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