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Mendeleev Commun., 2007, **17**, 279–280

Mendeleev Communications

Alkanes and cycloalkanes in the one-pot synthesis of amides

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DOI: 10.1016/j.mencom.2007.09.010

Alkanes (or cycloalkanes) and CO in the presence of the superelectrophilic systems $CX_4 \cdot 2AlBr_3$ (X = Cl, Br) have been used for the first time in the selective synthesis of amides from amines.

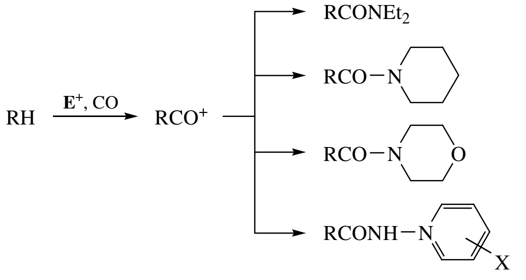
The transformations of saturated hydrocarbons into valuable chemicals are of considerable current interest.[1–4] This work presents the first one-pot synthesis of amides from amines in the presence of the superelectrophilic systems $CX_4 \cdot 2AlBr_3$ (X = Cl, Br). Amides are versatile building blocks or intermediates for the synthesis of fine chemicals, including biologically active compounds.[5–7]

Our approach was based on the use of new superelectrophilic systems, which can effectively generate carbocations from saturated hydrocarbons under very mild conditions.[8]

When the generation of carbocations occurs under a CO atmosphere, acylium cations are formed.[9] The one-pot acylation of alcohols[4,8] and aromatics, the acyldesilylation of tetraorganosilanes[10] and THF ring opening[11] by saturated hydrocarbons and CO were previously reported.

Acylium salts were generated[11] from alkanes and cycloalkanes under a CO atmosphere in the presence of the superelectrophilic complexes $CX_4 \cdot 2AlBr_3$ (**E**). Then, an amine was introduced to the *in situ* generated acylium salt. Both carbonylation of alkanes and following N-acylation reactions should be carried out under a CO atmosphere.[†]

When the procedure is strictly followed, only one isomer is formed in each reaction (Scheme 1). Amides containing isopropyl, *tert*-pentyl, cyclopentyl, 2-norbornyl and 1-adamantyl groups are formed from propane, *n*-pentane, cyclopentane, norbornane and adamantane, respectively.



RH = C_3H_8, *n*-C_5H_{12}, cyclopentane, norbornane, adamantane
XH = H, NO_2

Scheme 1

Various amines (aliphatic, cyclic and aromatic amines and, in some cases, even nitroanilines) are readily acylated with saturated hydrocarbons and CO in the presence of the above superelectrophiles to give amides in good or moderate yields. Amides **1–19** were prepared from alkanes (and cycloalkanes), CO and amines (the yields are given based on GC data) (Scheme 2).

The structures of amides were proved by ^{1}H and ^{13}C NMR spectroscopy, GC, GC-MS and in some cases by elemental analysis.[‡] To the best of our knowledge, amides **3–5**, **8**, **11**, **13**, **14** and **15** are new compounds.

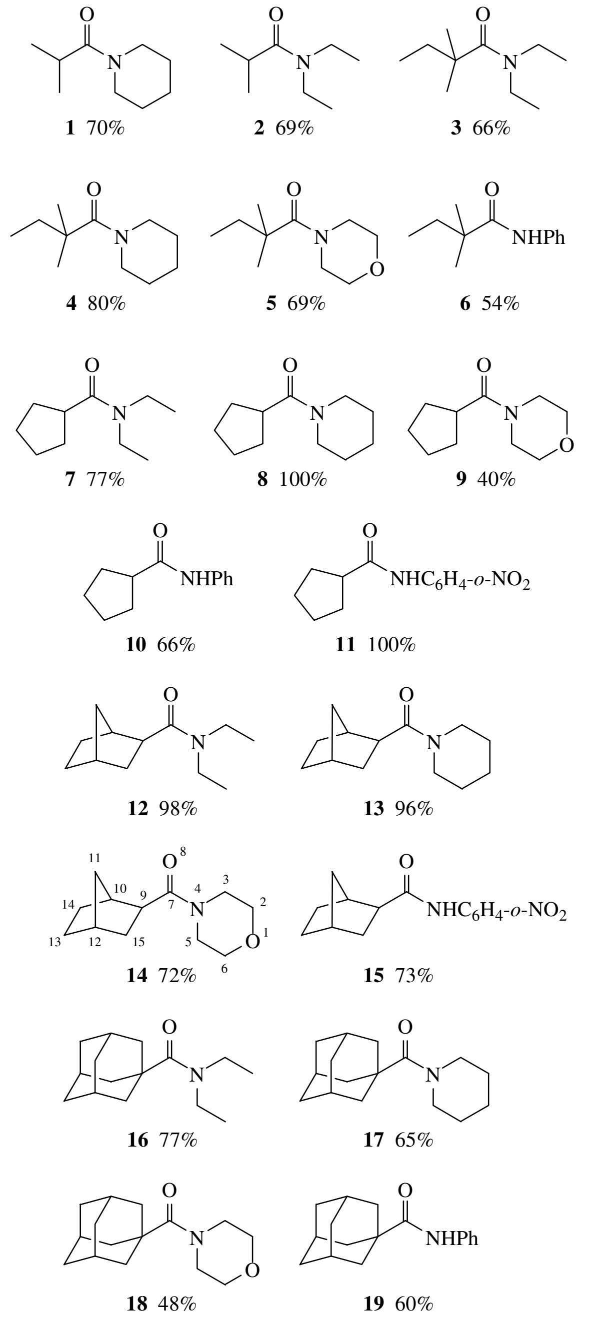
[†] *Conditions for the* in situ *generation of acylium salts (carbonylation stage) under atmospheric pressure of CO.*[11] **E** = $CX_4 \cdot 2AlBr_3$ in CH_2X_2 solution (X = Br, Cl; [$AlBr_3$] = 0.46 g cm^{-3}). [RH]:[**E**] molar ratio, temperature and reaction time: for *n*-pentane or cyclopentane, 10:1, –20 °C, 1 h; for norbornane, (1–1.2):1, –20 °C, 1 h; for adamantane, 1:1, 0 °C, 3 h (in this case [$AlBr_3$] = 0.04 g cm^{-3}). Isopropylcarboxonium salt was generated under propane/CO (3:2) gas atmosphere, *P* = 1 atm, –20 °C, 2 h.

Conditions for the acylation reactions. When the formation of an acylium salt was over, an amine ([**1–3**]:[**E**]) was added to a reaction mixture at the same temperature. Then, the temperature of the reaction mixture was increased to 20 °C. After 0.5 h, diethyl ether was added to the reaction mixture under cooling. The reactions of *in situ* generated RCO^+ with *o*-nitroaniline were carried out at 0 °C for 4 h (R = cyclopentyl) and at 35 °C for 1 h (R = C_7H_{11}, norbornyl). Then water was added dropwise. After diethyl ether extraction, washing organic layer with water, drying with $MgSO_4$, products were analyzed by GC and GC–MS. For NMR studies, diethyl ether and light products were removed from the extracts.

A typical procedure. At 0 °C under atmospheric pressure of CO, norbornane (0.247 g, 2.58 mmol) was added to a stirred solution of tetrachloromethane (0.2 ml, 2.15 mmol), anhydrous CH_2Br_2 (2 ml) and aluminum bromide (1.15 g, 4.3 mmol). The mixture was stirred for 2 h; then, morpholine (2.5 ml, 2.60 mmol) was added under similar conditions. After stirring for 30 min at 0 °C, diethyl ether was added to the reaction mixture with cooling. Then, water was added dropwise. After diethyl ether extraction, washing organic layer with water, drying with $MgSO_4$, products were analyzed by GC, GC–MS and NMR spectroscopy.

[‡] For **14**: yield, 72%; mp 84–85 °C (hexane); ^{1}H NMR (600 MHz, COSY ^{1}H-^{13}C, $CDCl_3$) δ: 1.18 ($^{13'}$CH), 1.24 ($^{11'}$CH), 1.25 ($^{13''}$CH) – (1.17, m, 3H), 1.20 ($^{14'}$CH) – (1.42, ddd, 1H, $^2J_{HH}$ 11.8 Hz, $^3J_{HH}$ 9.0 Hz, $^3J_{HH}$ 2.3 Hz), 1.48 ($^{14''}$CH) – (1.53, tm, 1H, $^2J_{HH}$ 11.8 Hz), 1.50 ($^{11''}$CH) – (1.53, tm, 1H, $^2J_{HH}$ 12.0 Hz), 1.67 ($^{15'}$CH) – (1.54, dm, 1H, $^2J_{HH}$ 12.0 Hz), 2.07 (^{12}CH) – (22.29, m, 1H), 2.93 ($^{15''}$CH) – (1.90, m, 1H, $^2J_{HH}$ 12.0 Hz), 2.18 (^{10}CH), 2.93 (^{9}CH) – (2.32, m, 2H), 3.20 ($^5CH_{ax}$), 3.28 ($^5CH_{eq}$) – (3.47, m, 2H), 3.46 ($^6CH_{ax}$), 3.54 ($^6CH_{ax}$) – (3.59, m, 2H), 3.53 ($^3CH_{eq}$), 3.55 ($^2CH_{ax}$), 3.61 ($^3CH_{eq}$), 3.63 ($^2CH_{eq}$) – (3.65, m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$, JMODECHO) δ: 28.46 (C^{14}), 28.96 (C^{13}), 34.30 (C^{15}), 35.50 (C^{12}), 36.26 (C^{11}), 40.04 (C^{10}), 41.65 (C^5), 43.52 (C^9), 45.43 (C^3), 66.19 (C^6), 66.50 (C^2), 173.47 (C^7). MS, *m/z*: 209 (M^+, 27), 181 (M – $C_2H_4^+$, 4), 180 (M – $C_2H_5^+$, 15), 168 (6), 155 (5), 152 (1), 145 (11), 144 (93), 142 (2), 129 (5), 123 ($C_7H_{11}CO^+$, 7), 122 (12), 114 (1), 113 (19), 111 (1), 96 (11), 95 ($C_7H_{11}^+$, 100), 94 (4), 93 (12), 91 (3), 88 (17), 87 (10), 86 ($C_4H_8NO^+$, 23), 85 (5), 81 (6), 80 (3), 79 (7), 78 (2), 77 (6), 72 ($C_4H_8O^+$, 2), 70 (22), 69 ($C_5H_9^+$, 3), 68 (4), 67 (30), 66 (9), 65 (7), 58 (2), 57 (17), 56 (18), 55 (30), 53 (9). Found (%): C, 68.91; H, 9.14; N, 6.46. Calc. for $C_{12}H_{19}O_2N$ (209.282) (%): C, 68.86; H, 9.15; N, 6.69.

Characteristics for other new amides obtained will be reported elsewhere.



1 70%
2 69%
3 66%
4 80%
5 69%
6 54%
7 77%
8 100%
9 40%
10 66%
11 100%
12 98%
13 96%
14 72%
15 73%
16 77%
17 65%
18 48%
19 60%

Scheme 2

In conclusion, the use of the polyhalomethane-based superelectrophilic systems allows us to use saturated hydrocarbons and CO as equivalents of acylium salts in the one-pot synthesis of amides from amines. These reactions occur to selectively give amides in high or moderate yields.

This work was supported by the Russian Foundation for Basic Research (project no. 06-03-32194).

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Received: 9th March 2007; Com. 072887