PREPARATION OF 1-ADAMANTYL KETONES: STRUCTURE, MECHANISM OF FORMATION AND BIOLOGICAL ACTIVITY OF POTENTIAL BY-PRODUCTS

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Reactions between adamantane-1-carbonyl chloride and several Grignard reagents as well as interactions with solvents have been examined. Some new and unexpected adamantane derivatives were isolated, fully characterized and their biological activity determined. In particular, an unexpected isochromanone **16** was formed in an S_EAr process, in which a stable hydrocarbon was the leaving group.

Keywords: Adamantane; 1-Adamantyl alkyl/aryl ketones; Acyl chlorides; Side products; Biological activity; Grignard reagents.

Various amines containing the adamantane moiety have shown biological activity[1]. Since the first discovery of the antiviral effect of 1-adamantylamine[2] in 1964, a number of compounds containing the adamantane skeleton have been described as efficient antiviral[3,4], antitumor[5,6], hypoglycemic[7], antidepressant[8,9], antimicrobial[10], and anticonvulsant agents[11]. Several adamantane-containing drugs are currently being used in modern medicine in the prophylaxis and treatment of various viral diseases and Parkinsonism[9,12].

Among these, 1-(1-adamantyl)ethan-1-amine and similar amines play an important role with their unprecedented virostatic effect[13,14]. 1-(1-Adamantyl)-alkan-1-amines, which are usually prepared from appropriate ketones, belong to the most effective drugs. Established methods for the preparation of such ketones (Scheme 1) are generally based on the reaction of Grignard reagents with acyl chlorides[15,16]. We have recently developed a new efficient

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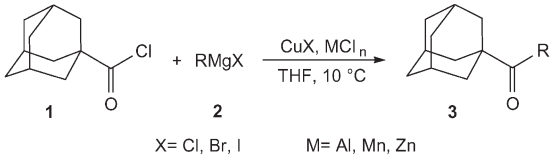
and fast method for the preparation of 1-adamantyl alkyl/aryl ketones using catalytic amounts of $AlCl_3$ and CuCl [17].



SCHEME 1

In this paper, we describe the side reactions and their products, the pathways of side products formation and their biological activity in the context of possible utilization of this method in drug synthesis.

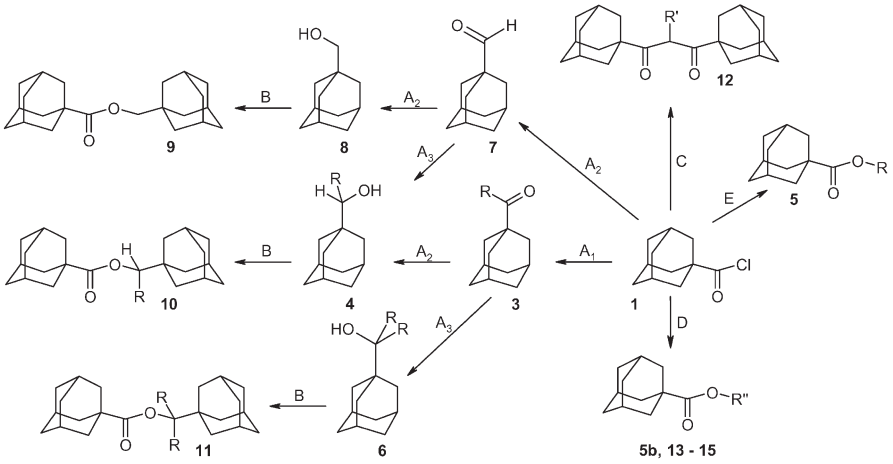
Thus, we performed reactions of adamantane-1-carbonyl chloride (**1**) with selected Grignard reagents – methylmagnesium iodide (**2a**), ethylmagnesium bromide (**2b**), propylmagnesium bromide (**2c**), isopropylmagnesium bromide (**2d**), benzylmagnesium bromide (**2e**) and phenylmagnesium bromide (**2f**) – with a focus on the identification of minor side products. Interactions of acyl chloride **1** with the solvents used in the presence of a Lewis acid (Scheme 2) were studied simultaneously.

RESULTS AND DISCUSSION

By the reaction of acyl chlorides with Grignard reagents, the corresponding ketones were formed. When a Grignard reagent is used without any additive, its strong nucleophilic character gives rise to the formation of a tertiary alcohol[18]. If the Grignard reagent has β-hydrogen atoms, the corresponding secondary alcohols can also arise from the reduction of the formed ketone with an excess of the reagent[19,20] and the corresponding alkene is formed as its oxidation product. The alcohols are the main undesirable side products in ketone synthesis, especially when catalytic amounts of metal halides are used for in situ transmetalation[17]. Such procedures are very sensitive to the rate of the Grignard reagent addition into the reaction mixture, and any deviation from its immediate optimum concentration leads to the formation of the side products mentioned above. This problem could arise in a large scale synthesis, where homogeneity of the reaction mixture during the addition of the Grignard reagent can be significantly disturbed. It was somewhat surprising that in all the cases when a Grignard reagent prone to causing reduction was used, 1,2-additions practically did not occur and we detected insignificant, if any, amounts of tertiary alcohols **6**. On the other hand, the reductions were frequent, and we found sec-

ondary alcohols **4** and also 1-adamantylmethanol (**8**), arising from the reduction of adamantane-1-carbonyl chloride[21]. The intermediate of this transformation, aldehyde **7**, was also detected in all the cases.

For the ketone-forming reactions in question, an equimolar ratio of acyl chloride **1** and Grignard reagent **2** was always used, but the reductions as well as the 1,2-additions to carbonyl required two molecules of **2** per one molecule of alcohol. Consequently, some starting material **1** must have remained and could react with alcohols upon being left in the reaction mixture for a sufficient period of time. Thus, esters **9** and **10b**–**10d** were also detected in the crude products. Even when ethylmagnesium bromide was used, ester **10b**, which easily crystallized during the work-up procedure, was the main product. Only in the cases where the structure of **2** did not allow reductions, 1,2-additions to carbonyl took place. Thus, in runs **a**, **e** and **f** (Table I), the corresponding tertiary alcohols **6** were detected and when methylmagnesium iodide was used, the corresponding ester **11a** was isolated.



Assumed reaction pathways leading to side products.

A – Reactions of Grignard reagent **2**: A_1 - substitution of chlorine, A_2 - reduction, A_3 - 1,2-addition.
B – Reaction with adamantane-1-carbonyl chloride (**1**).
C – Reaction with enolized ketone **3**.
D – Reaction with solvent catalyzed by Lewis acid.
E – Reaction with alkoxide derived from Grignard reagent.

R is alkyl/aryl of Grignard reagent, R' is by CH_2 shorter than R in case R≠ Ph, R'' is alkyl from the used solvent

SCHEME 2

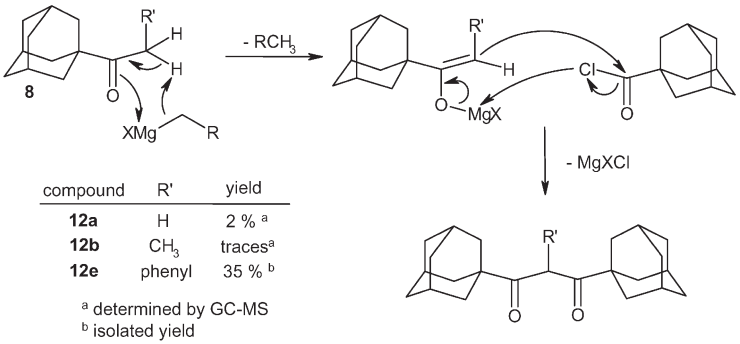
Every Grignard reagent can behave as a base abstracting an acidic hydrogen and furnishing the corresponding hydrocarbon. This behavior led to the formation of an interesting class of compounds, especially when an α-hydrogen was present in the synthesized ketone. The proposed mechanism of this reaction is shown in Scheme 3. The transiently formed magnesium enolate could react with a second molecule of acyl chloride **1** to yield 1,3-di(1-adamantyl)propane-1,3-diones **12**. The amount of the dione strongly depended on the structure of Grignard reagent **2**. Thus, when aliphatic Grignard reagent **2** was used in the reaction, the dione amount varied in the range 0–2%, whereas in the case of benzylmagnesium bromide (**2e**), when the enolate intermediate was stabilized by resonance, the

TABLE I
Composition (in %) of crude products determined by GC MS

Product	R in RMgX					
	CH_3 (**a**)	C_2H_5 (**b**)	C_3H_7 (**c**)	i-C_3H_7 (**d**)	benzyl (**e**)	phenyl (**f**)
3	48.0	8.3	7.0	2.5	32.1	88.6
4	–	9.7	30.8	13.7	–	–
5	0.0	6.6	5.7	0.0	0.5	<0.1
6	13.6	0.8	0.0	0.0	30.0	8.4
7	–	0.7	0.7	1.7	–	–
8	–	<0.1	1.6	5.1	–	–
9	–	2.2	34.0	42.8	–	–
10	–	71.7	18.0	33.5	–	–
11	27.1	0.0	0.0	0.0	0.0	0.0
12	2.0	<0.1	0.0	0.0	35.2	–
5b	2.2	–	2.2	0.3	0.3	3.1
16	–	–	–	–	0.5	–

Reaction conditions: Into the solution of 5.0 mmol of acyl chloride **1** in 40 ml of freshly distilled diethyl ether, one equivalent of a Grignard reagent solution in diethyl ether was added in one portion at 5 °C. The reaction mixture was allowed to warm up to room temperature, and stirred for 48 h. Compounds **3a**–**3c**, **3e**, **3f**, **4b**, **5a**–**5c**, **6a**, **6b**, **6e**, **6f**, **7**, **8**, **9**, **10b**, **11a**, **12e** and **16** were identified using a standard. Other compounds were identified by mass spectra.

amount of dione **12e** increased to 35%. The amount of the corresponding dione varied from 0.5 to 2.5% when the catalytic system $AlCl_3$/CuCl was used for the synthesis of ketones **3a**, **3b** and **3e**. Notably, these diones are the most undesirable side products in ketone synthesis because their separation is a difficult task (even in amounts lower than 1%) due to physicochemical properties similar to those of the ketones. Decreasing solvent polarity can suppress undesirable dione formation. Thus, using a toluene–THF



compound	R'	yield
12a	H	2 % [a]
12b	CH_3	traces[a]
12e	phenyl	35 % [b]

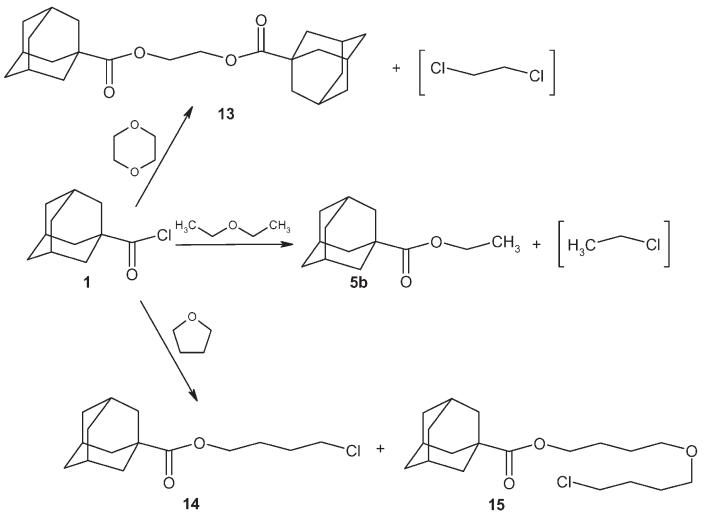
[a] determined by GC-MS
[b] isolated yield

SCHEME 3

mixture in the 70:30 volume ratio in place of THF for the preparation of ketone **3a** decreased the amount of dione **12a** from 2.5 to 0.4%.

In principle, Lewis acids such as $ZnCl_2$ or $AlCl_3$ used for transmetallation in ketone synthesis[17] as well as magnesium(II) halides formed in the reaction are capable of initiating the cleavage of ethers used as solvents[22–25].

Usual experimental procedures include the addition of a Grignard reagent solution in diethyl ether or in THF into the solution of acyl chloride and a catalyst in THF. Thus, ethyl adamantane-1-carboxylate (**5b**) was formed when the Grignard reagent was prepared in diethyl ether. The amount of **5b** obviously increased with increasing reaction time[17]. Surprisingly, the cleavage of diethyl ether was preferred when a mixture of diethyl ether and tetrahydrofuran was used. However, when only THF was present as solvent, the corresponding product **14** arose (Scheme 4). In addition, ester **14** reacted with THF to yield 4-(4-chlorobutoxy)butyl adamantane-1-carboxylate (**15**), which was isolated in an amount of ca. 5% (relative to **14**). On the contrary, when 1,4-dioxane was used, similar products were not detected, although the analogous 2-(2-chloroethoxy)ethyl adamantane-1-carboxylate seems to be an acceptable precursor of ethylene bis(adamantane-1-carboxylate) (**13**), which was the only isolated product.

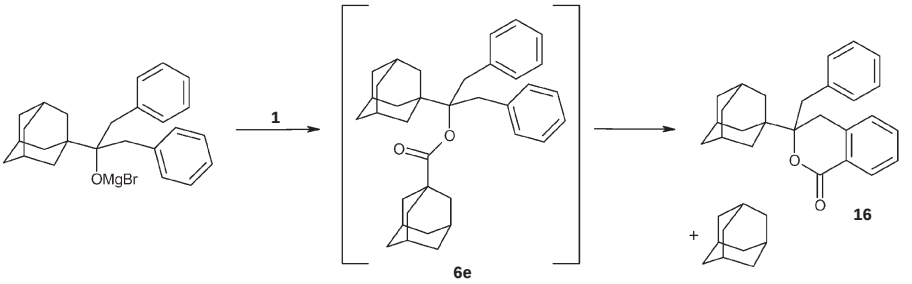


SCHEME 4

Small amounts of esters **5** came from the alcohols contained as impurities in the starting alkyl/aryl halides used for the preparation of the Grignard reagents. These alcohols formed the corresponding magnesium alkoxides and subsequently reacted with **1**. Air oxygen may also attack Grignard reagents[26,27] to yield alkoxides, but this was improbable in our case because all experiments were carried out under argon atmosphere.

When benzylmagnesium bromide was used in the reaction, an unexpected isochromanone derivative **16** was identified in the reaction mixture (Scheme 5). A probable intermediate of this reaction is the magnesium alkoxide of 2-(1-adamantyl)-1,3-diphenylpropan-2-ol (**6e**), which underwent an intramolecular cyclization under the formation of **16**. The only conceivable carbonyl source seemed to be an excess of **1**. Although the corresponding ester intermediate (Scheme 5) was not detected, we assume its formation and subsequent intramolecular electrophilic aromatic substitution with adamantane as a leaving group. The presence of adamantane in the reaction mixture was proved by gas chromatography with adamantane as a standard, and confirmed by mass spectrometry. Moreover, isochromanone **16** was detected as a product in a separate reaction of alcohol **6e** with acyl chloride **1** and 5 mole % of $AlCl_3$ in diethyl ether at room temperature. To the best of our knowledge, this reaction is the first described S_EAr substitution where a stable hydrocarbon is a leaving group. The structure of **16** was determined by 2D NMR experiments and confirmed by X-ray

diffraction analysis. Two distinct conformers were present in the asymmetric part of the unit cell, differing mainly in the mutual orientation of their benzyl and isochromanone groups. In the first conformer (Fig. 1, left), the least-squares planes through the aromatic rings were inclined by 24.0(1)°, while the rings were almost perpendicular (88.5(1)°) in the second conformer. The molecules formed a layered arrangement, extending in the crystallographic *ac* plane. In the *b*-direction, we therefore found alternating layers of both conformers, which were well separated from each other. Detailed study of the mechanism as well as the scope of this reaction will be the subject of further research.



SCHEME 5

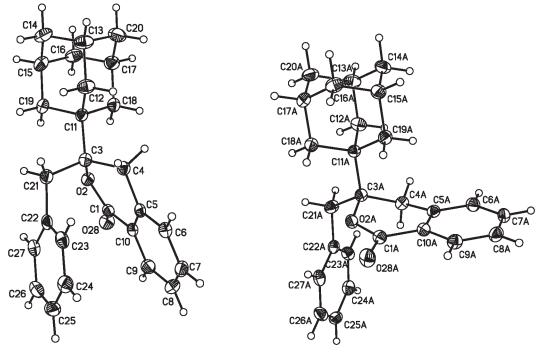


FIG. 1

ORTEP diagrams of two isochromanone **16** conformers. Each of them occupies own layer in crystal. Selected bond lengths (in Å), regular and torsion angles (in °) for both conformers are given: C1–O2 1.345(2), 1.352(2); C1–O28 1.210(2), 1.206(2); O2–C3 1.480(2), 1.471(2); C3–C11 1.568(2), 1.573(2); C3–C21 1.546(2), 1.546(2); C1–O2–C3 124.7(1), 124.6(1); O2–C3–C4 111.1(1), 110.6(1); O2–C3–C11 103.8(1), 107.2(1); O2–C3–C11 105.9(1), 103.4(1); C4–C3–C11 111.2(1), 114.3(1); C4–C3–C21 111.9(1), 109.7(1); C11–C3–C4–C5 –153.1(1), 82.0(2); C1–O2–C3–C11 145.9(2), –95.8(2); C11–C3–C21–C22 177.1(1), –176.1(1)

Finally, we tested some of the new isolated adamantane derivatives for their biological activity; the results are shown in Table II. None of the tested compounds displayed antimicrobial activity in the concentrations used, and only compound **6e** exhibited a slight cytotoxic effect.

TABLE II
Biological activity tests

Compd.	Antimicrobial activity, MIC, μg ml^{-1}							Cytotoxicity, GI_{50}, μM	
	Strain[a]							Cell line[b]	
	3953	4223	4224	4225	3988	3954	3955	K-562	MCF7
6e	>100	>100	>100	>100	>100	>100	>100	>167	144
9	NT[c]	NT[c]	NT[c]	NT[c]	NT[c]	NT[c]	NT[c]	>167	>167
11a	>50	>50	>50	>50	>50	>50	>50	>167	>167
10b	>50	>50	>50	>50	>50	>50	>50	>167	>167
12e	>50	>50	>50	>50	>50	>50	>50	NT	NT
13	NT[c]	NT[c]	NT[c]	NT[c]	NT[c]	NT[c]	NT[c]	>167	>167
14	>100	>100	>100	>100	>100	>100	>100	NT	NT
15	>100	>100	>100	>100	>100	>100	>100	NT	NT

[a] Microbial strains were obtained from Czech Collection of Microorganisms (CCM). 3953, 4223, Staphylococcus aureus; 4224, Entherococcus faecalis; 4225, 3988, 3954, Escherichia coli; 3955, Pseudomonas aeruginosa. [b] Cell lines: K-562, chronic myelosis; MCF7, carcinoma mammae. [c] Compounds were not soluble in DMSO. NT, not tested.

CONCLUSION

Reductions were the most frequently observed side reactions in the reactions of adamantane-1-carbonyl chloride (**1**) with Grignard reagents. However, when the structure of the Grignard reagent did not allow reductions, 1,2-additions to the carbonyl of the ketone primarily formed occurred. The alcohols formed in this way could react with acyl chloride **1** to produce the corresponding esters. The starting acyl chloride **1** also yielded the corresponding aldehyde **7**, alcohol **8** and subsequently 1-adamantylmethyl adamantane-1-carboxylate (**9**) in all cases where reductions could take place. In some cases, the basic nature of the Grignard reagents allowed the enolization of the ketones present, and subsequent substitution of chlorine

in **1** to produce substituted 1,3-diones **12**. The formation of these undesirable side products was suppressed by replacing up to 70% of THF by toluene. Acyl chloride **1** may attack oxygen-containing solvents to yield the corresponding esters. Nevertheless, this process requires long reaction times, and, consequently, the formation of the esters is not a serious complication in the ketone synthesis.

EXPERIMENTAL

General

All reactions were carried out under argon atmosphere. Solvents were dried by standard methods and were freshly distilled before use. Alkyl/aryl halides used for the Grignard reagent synthesis were obtained from commercial sources and were used without further purification. $ZnCl_2$ was purchased from Fluka and was dried under vacuum at 160 °C for 2 h before use. Standard samples of alkyl adamantane-1-carboxylates[28], 1-adamantylmethanol[29], 1-(1-adamantyl)ethan-1-ol[30], 1-(1-adamantyl)propan-1-ol[30], 2-(1-adamantyl)propan-2-ol[31], 3-(1-adamantyl)pentan-3-ol[31] and 1-adamantyl alkyl/aryl ketones[17] were prepared according to literature procedures. NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer operating at 300 MHz for ^1H and 75.5 MHz for ^{13}C, using TMS as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra (ν, cm^{-1}) were measured in KBr pellets on an FTIR ATI Mattson Genesis Series device. GC MS (EI at 70 eV, ion source at 200 °C) analyses were run on a GC 8000 Series with detector Trio 1000 (Fison Instruments) on a Zebron-5 column, 30 m long, with helium carrier gas; *m/z* values are given along with their relative intensities (in %). In spectra presentations, adamantyl is abbreviated to Ad. The following temperature program was used: 120 °C (7 min), temperature increase 25 °C/min up to 250 °C. Melting points are uncorrected. Diffraction data for compound **16** were collected on a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined using a SHELXTL program package (SHELXTL, Version 5.10, 1997, Bruker AXS Inc., Madison (WI), USA). The hydrogen atoms were placed in calculated idealized positions and refined as riding. CCDC 256207 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Tests for biological activity were performed in the Laboratory of Growth Regulators, Institute of Experimental Botany, Academy of Sciences of the Czech Republic, Olomouc.

Adamantane-1-carbonyl Chloride (**1**)

Into a suspension of adamantane-1-carboxylic acid (25.0 g, 0.126 mol) in toluene (32 ml), $SOCl_2$ (19.6 g, 0.164 mol) was dropwise added at 70 °C. The reaction mixture was then stirred at this temperature for 8 h. Excess $SOCl_2$ was then removed as an azeotrope with toluene. Finally, the mixture was cooled and left crystallizing at –15 °C. The pale yellow needles obtained were filtered off and dried in the stream of an inert gas (yield 22.3 g, 89%, m.p. 47–48 °C; lit.[32] 49–51 °C). NMR data were identical with those reported[32].

Grignard Reagents **2a**–**2f**

Grignard reagents were prepared in the usual way[33] using the corresponding alkyl bromides or alkyl chlorides and 1.3 mol excess of magnesium turnings in diethyl ether, and were immediately used in subsequent reactions. The concentrations of their clear solutions were determined by acid/base titration[34].

Reaction of Acyl Chloride **1** with Grignard Reagents **2**. General Procedure

Into a well-stirred solution of 5.0 mmol (1.00 g) of acyl chloride **1** in 40 ml of freshly distilled diethyl ether, one equivalent of a Grignard reagent solution in diethyl ether was added in one portion at 5 °C. The reaction mixture was allowed to warm up to room temperature, and stirred for 48 h. After a usual work-up involving quenching with 1 M hydrochloric acid, and subsequent washing the organic layer with a saturated K_2CO_3 solution and brine, the mixture was analyzed by GC MS. The crude product was obtained by solvent removal. In some cases, compounds could not be isolated by both column chromatography or crystallization.

Reaction of Acyl Chloride **1** with Methylmagnesium Iodide

A colorless solid (269 mg, 30%) precipitated after the treatment of the crude product with diethyl ether. The product was filtered off, crystallized from acetone and identified as 2-(1-adamantyl)propan-2-yl adamantane-1-carboxylate (**11a**) (m.p. 182–185 °C). For $C_{24}H_{36}O_2$ (356.5) calculated: 80.85% C, 10.18% H; found: 80.50% C, 10.08% H. ^{1}H NMR: 1.63 s, 6 H ($C(CH_3)_2$); 1.67–1.71 overlapped m, 18 H (adamantane CH_2); 2.03 m, 6 H (adamantane CH). ^{13}C NMR: 19.7 ($C(\mathbf{C}H_3)_2$), 28.4 (AdCOO C3, C5, C7), 28.8 (Ad C3, C5, C7), 36.2 (Ad C4, C6, C9), 36.9 (AdCOO C4, C6, C9), 37.4 (Ad C2, C8, C10), 39.4 (AdCOO C2, C8, C10), 40.3, 42.3 (AdCOO C1), 86.2 ($\mathbf{C}(CH_3)_2$), 177.3 (COO). IR: 2987–2850 s, 1720 s, 1454 w, 1385 w, 1360 w, 1323 w, 1275 w, 1250 m, 1227 w, 1192 w, 1140 m, 1103 w, 1074 m, 1018 w, 976 w, 868 w, 806 w, 741 w. EI MS: 176 (M^+ – Ad – CO_2 – 1, 16), 161 (3), 135 (Ad, 100), 119 (12), 107 (10), 105 (12), 93 (42), 91 (49), 79 (81), 77 (48), 67 (30), 65 (20), 55 (29), 53 (32).

Reaction of Acyl Chloride **1** with Ethylmagnesium Bromide

The colorless solid obtained after solvent removal was crystallized from acetone to yield 610 mg (68%) of 1-(1-adamantyl)propyl adamantane-1-carboxylate (**10b**) (m.p. 122–124 °C). For $C_{24}H_{36}O_2$ (356.5) calculated: 80.85% C, 10.18% H; found: 80.47% C, 9.89% H. ^{1}H NMR: 0.82 overlapped m, 3 H ($CHCH_2C\mathbf{H}_3$); 1.54–1.74 overlapped m, 20 H; 1.95–2.03 overlapped m, 12 H; 4.53 overlapped m, 1 H ($C\mathbf{H}CH_2CH_3$). ^{13}C NMR: 11.0 ($CHCH_2\mathbf{C}H_3$), 21.1 ($CH\mathbf{C}H_2CH_3$), 28.3 (AdCOO C3, C5, C7), 28.5 (Ad C3, C5, C7), 36.8 (Ad C1), 36.9 (AdCOO C4, C6, C9), 37.4 (Ad C4, C6, C9), 38.5 (AdCOO C2, C8, C10), 39.5 (Ad C2, C8, C10), 41.4 (AdCOO C1), 81.7 ($\mathbf{C}HCH_2CH_3$), 177.7 (COO). IR: 2966–2848 s, 1724 s, 1452 w, 1385 m, 1342 w, 1321 w, 1269 w, 1236 s, 1184 w, 1103 w, 1072 m, 978 w, 941 w, 897 w, 812 w, 739 w, 675 w, 640 w. EI MS: 221 (M^+ – Ad, 1), 181 (7), 176 (M^+ – Ad – CO_2 – 1, 65), 163 (Ad + CO, 7), 135 (Ad, 100), 93 (11), 91 (9), 79 (20), 77 (5), 67 (7).

Reaction of Acyl Chloride **1** with Propylmagnesium Bromide

The colorless solid (250 mg, 29%) precipitated after the treatment of the crude product with ether was filtered off, crystallized from acetone and identified as 1-adamantylmethyl adamantane-1-carboxylate (**9**) (m.p. 251–252 °C; lit.[35] 247–250 °C). NMR data were identical with those reported[35].

Reaction of Acyl Chloride **1** with Isopropylmagnesium Bromide

From the crude mixture, compound **9** (302 mg, 35%) was isolated after treatment with acetone. A second crop (73 mg, 7%) was obtained after repeated column chromatography (hexane–ethyl acetate, 8:1; silica gel). The colorless needles (m.p. 35–37 °C) were identified as 1-(1-adamantyl)-2-methylpropan-1-ol (**4d**). Spectral data corresponded to those reported[36].

Reaction of Acyl Chloride **1** with Phenylmagnesium Bromide

Two compounds were isolated from the crude reaction mixture by repeated column chromatography (chloroform; silica gel). The first, flat colorless crystals (1.028 g, 85.1%, m.p. 49–51 °C; lit.[37] 48–50 °C), was identified as 1-adamantyl phenyl ketone (**3f**). NMR data were identical with those reported[38]. The other compound (1-adamantyl)diphenylmethanol (**6f**) was isolated as colorless needles (120 mg, 7.5% relative to **1**, m.p. 126–128 °C; lit.[39] 127–128 °C). Spectral data corresponded to those reported[40].

Reaction of Acyl Chloride **1** with Benzylmagnesium Bromide

Three compounds were isolated from the crude mixture by column chromatography (silica gel; hexane–ethyl acetate, 8:1).

2-(1-Adamantyl)-1,3-diphenylpropan-2-ol (**6e**). Compound **6e** was crystallized from hexane giving 504 mg (28.9% relative to **1**) of colorless waxy flat crystals (m.p. 119–122 °C). For $C_{25}H_{30}O$ (346.5) calculated: 86.66% C, 8.73% H; found: 86.50% C, 8.67% H. ^{1}H NMR: 1.74–1.86 overlapped m, 12 H (Ad CH_2); 2.09 m, 3 H (Ad CH); 2.75 d, 2 H, $J(CH_AH_B)$ = 13.9 (CH_AH_BPh); 3.10 d, 2 H, $J(CH_AH_B)$ = 13.5 ($CH_A\mathbf{H}_BPh$); 7.00 m, 4 H (CH_2**Ph**); 7.20 m, 6 H (CH_2**Ph**). ^{13}C NMR: 29.0 (Ad C3, C5, C7), 36.7 (Ad C4, C6, C9), 37.4 (Ad C2, C8, C10), 40.5 (CH_2Ph), 41.4 (Ad C1), 76.8 ($C(CH_2Ph)_2$), 126.3 (Ph C4), 128.2 (Ph C3, C5), 131.4 (Ph C2, C6), 138.7 (Ph C1). IR: 3584 m, 3080 w, 3061 w, 3023 w, 2909 s, 2849 m, 1600 w, 1493 m, 1452 m, 1345 m, 1085 m, 1031 w, 993 w, 967 w, 817 w, 748 m, 699 s, 604 w, 535 m. EI MS: 345 (M^+ – 1, 3), 330 (3), 329 (M^+ – OH, 3), 328 (5), 255 (M^+ – benzyl, 96), 237 (M^+ – benzyl – H_2O, 5), 211 (M^+ – Ad, 8), 210 (M^+ – Ad-1, 14), 193 (11), 163 (M^+ – benzyl – phenyl, 5), 136 (adamantane, 42), 135 (Ad, 100), 119 (13), 118 (9), 115 (9), 107 (32), 105 (17), 93 (60), 92 (25), 91 (benzyl, 94), 81 (21), 79 (60), 77 (phenyl, 18), 67 (20), 65 (14), 55 (10).

1,3-Di(1-adamantyl)-2-phenylpropane-1,3-dione (**12e**). Compound **12e** was crystallized from diethyl ether giving 357 mg (34.1% relative to **1**) of colorless needles (m.p. 185–188 °C). For $C_{29}H_{36}O_2$ (416.6) calculated: 83.61% C, 8.71% H; found: 83.41% C, 8.66% H. ^{1}H NMR: 1.54–1.84 m, 24 H (Ad CH_2); 2.18 m, 6 H (Ad CH); 5.73 s, 1 H (C**H**Ph); 7.18 m, 2 H (CH**Ph**); 7.20–7.34 m, 3 H (CH**Ph**). ^{13}C NMR: 28.3 (Ad C3, C5, C7), 36.7 (Ad C4, C6, C9), 39.2 (Ad C2, C8, C10), 47.7 (Ad C1), 59.6 (**C**HPh), 127.6 (Ph C4), 128.7 (Ph C3, C5), 130.1 (Ph C2, C6), 133.7 (Ph C1), 207.4 (CO). IR: 2903 s, 2849 s, 1715 m, 1677 m, 1495 w, 1453 m, 1343 w, 1279 m, 1237 w, 1144 w, 1104 w, 1010 m, 930 w, 720 m, 698 w, 599 w, 555 w. EI MS:

416 (M^+, 1), 163 (Ad + CO, 17), 135 (Ad, 100), 118 (3), 107 (11), 93 (23), 91 (benzyl, 14), 79 (20), 77 (phenyl, 6), 67 (6).

3-(1-Adamantyl)-3-benzylisochromane-1-one (**16**). Compound **16** was crystallized from hexane to give 15 mg (1.6% relative to **1**) of colorless crystals (m.p. 176–179 °C). ^{1}H NMR: 1.71–1.84 m, 12 H (Ad CH_2); 2.07 m, 3 H (Ad CH); 2.86 d, 1 H, $J(CH_AH_B)$ = 13.9 (CH_AH_BPh); 2.96 d, 1 H, $J(CH_AH_B)$ = 16.9 (CH_CH_D); 3.32 d, 1 H, $J(CH_CH_D)$ = 13.8 (CH_AH_BPh); 3.38 d, 1 H, $J(CH_CH_D)$ = 16.9 (CH_CH_D); 6.95–7.12 m, 7 H; 7.27–7.32 m, 1 H; 7.76–7.79 m, 1 H. ^{13}C NMR: 28.7 (Ad C3, C5, C7), 29.5 (C4), 36.5 (Ad C4, C6, C9), 37.1 (Ad C2, C8, C10), 40.9 (CH_2Ph), 41.4 (Ad C1), 88.6 (C3), 125.2 (C8a), 126.5 (C6), 126.6 (Ph C4), 127.4 (C5), 128.2 (Ph C3, C5), 129.5 (C8), 131.2 (Ph C2, C6), 133.4 (C7), 136.9 (C4a), 138.7 (Ph C1), 158.8 (C1). IR: 3060 w, 3030 w, 2902 s, 2846 m, 1695 s, 1604 w, 1493 w, 1458 m, 1344 w, 1302 m, 1225 w, 1124 m, 1030 w, 993 w, 748 m, 702 m, 609 w. EI MS: 373 (M^+ + 1, 4), 281 (M^+ – benzyl, 78), 236 (M^+ – Ad – 1, 10), 135 (Ad, 100), 118 (11), 107 (9), 93 (28), 91 (benzyl, 72), 79 (33), 67 (10).

Reaction of Acyl Chloride **1** with Tetrahydrofuran

In a 100-ml flask, $ZnCl_2$ (110 mg, 0.8 mmol) was dried by heating to the melting point under vacuum. After cooling to laboratory temperature, the flask was filled with argon and 50 ml of freshly distilled THF was added. Adamantane-1-carbonyl chloride 5 g (25.16 mmol) was then added in one portion. The reaction mixture was stirred under reflux for 8 h. The reaction was quenched with 20 ml of 1 M HCl and the water layer was extracted three times with diethyl ether. The combined organic layers were washed twice with a saturated K_2CO_3 solution, once with brine and dried over anhydrous Na_2SO_4. The solvent was removed to obtain 6.47 g (95% yield) of a pale yellow oil. The crude product was purified by column chromatography (silica gel; hexane–ethyl acetate, 8:1) and two compounds were isolated as viscous colorless oils.

The major product was 4-chlorobutyl adamantane-1-carboxylate (**14**). For $C_{15}H_{23}ClO_2$ (270.8) calculated: 66.53% C, 8.56% H; found: 66.38% C, 8.63% H. ^{1}H NMR: 1.67–1.89 overlapped m, 16 H; 2.02 m, 3 H (Ad CH); 3.58 t, 2 H, J = 5.9 ($O(CH_2)_3CH_2Cl$); 4.09 t, 2 H, J = 5.9 ($OCH_2(CH_2)_3Cl$). ^{13}C NMR: 26.3 ($OCH_2CH_2(CH_2)_2Cl$), 28.1(Ad C3, C5, C7), 29.4 ($O(CH_2)_2CH_2CH_2Cl$), 36.7 (Ad C4, C6, C9), 39.1 (Ad C2, C8, C10), 40.9 (Ad C1), 44.8 ($O(CH_2)_3CH_2Cl$), 63.4 ($OCH_2(CH_2)_3O$), 177.9 (COO). IR: 2907–2852 s, 1725 s, 1563 w, 1453 s, 1345 m, 1324 s, 1268 s, 1234 s, 1184 s, 1104 s, 1077 s, 1004 w, 978 w, 886 w, 740 m, 676 m, 653 m. EI MS: 271 (M^+ + 1, 2), 235 (M^+ – Cl, 3), 181 (15), 179 (Ad + CO_2, 6), 135 (Ad, 100), 107 (6), 93 (15), 91 (12), 79 (13), 77 (4), 67 (7), 55 (11).

The minor product was 4-(4-chlorobutoxy)butyl adamantane-1-carboxylate (**15**). For $C_{19}H_{31}ClO_3$ (342.9) calculated: 66.55% C, 9.11% H; found: 66.62% C, 8.97% H. ^{1}H NMR: 1.60–1.69 overlapped m, 12 H; 1.77–1.81 overlapped m, 8 H; 1.93 m, 3 H (Ad CH); 3.37 m, 4 H ($(CH_2)_3CH_2OCH_2(CH_2)_3$); 3.50 t, 2 H, J = 6.6 ($O(CH_2)_3CH_2Cl$); 3.99 t, 2 H, J = 6.2 ($OCH_2(CH_2)_3O$). ^{13}C NMR: 25.7 ($O(CH_2)_2CH_2CH_2O$), 26.4 ($OCH_2CH_2(CH_2)_2O$), 27.2 ($OCH_2CH_2(CH_2)_2Cl$), 28.1 (Ad C3, C5, C7), 29.7 ($O(CH_2)_2CH_2CH_2Cl$), 36.7 (Ad C4, C6, C9), 39.0 (Ad C2, C8, C10), 40.9 (Ad C1), 45.1 ($OCH_2)_3CH_2Cl$), 64.0 ($OCH_2(CH_2)_3O$), 70.1 ($OCH_2(CH_2)_3Cl$), 70.5 ($O(CH_2)_3CH_2O$), 177.9 (COO). IR: 2908–2798 s, 1725 s, 1560 w, 1453 s, 1364 m, 1345 s, 1324 w, 1268 m, 1235 s, 1184 m, 1105 s, 1077 s, 979 w, 963 w, 813 w, 741 w, 676 w, 651 w. EI MS: 343 (M^+ + 1, 12), 235 (M^+ – OC_4H_8Cl, 14), 163 (Ad + CO, 100), 135 (adamantane, 70), 93 (10), 91 (16), 71 (5), 55 (5).

Reaction of Acyl Chloride **1** with Dioxane

Acyl chloride **1** (5 g, 25 mmol) was dissolved in 50 ml (0.59 mol) of dry dioxane. A solution of $ZnCl_2$ (0.1 g, 0.7 mol) was than added, and the mixture was stirred for 48 h. After this period, 20 ml of 1 M HCl were added, and the mixture was stirred for another 15 min. The water layer was separated, and extracted three times with diethyl ether. The combined organic phases were washed several times with a 1.6 M K_2CO_3 solution, and dried over anhydrous Na_2SO_4. A pale yellow solid was obtained after solvent removal. The remainder of the starting material was recovered from the alkaline extracts after acidification as adamantane-1-carboxylic acid.

The crude product was crystallized from acetone to yield 1.42 g (29.2%, m.p. 122–123 °C) of 2-(1-adamantanoyloxy)ethyl adamantane-1-carboxylate (**13**). For $C_{24}H_{34}O_4$ (386.5) calculated: 74.58% C, 8.87% H; found: 74.73% C, 8.91% H. ^{1}H NMR: 1.71 m, 12 H (Ad CH_2); 1.89 m, 12 H (Ad CH_2); 2.16 m, 6 H (Ad CH); 4.24 s, 4 H ($O(C\mathbf{H}_2)_2O$). ^{13}C NMR: 28.1 (Ad C3, C5, C7), 36.7 (Ad C4, C6, C9), 39.0 (Ad C2, C8, C10), 40.9 (Ad C1), 62.0 ($O(CH_2)_2O$), 177.5 (COO). IR: 2066–2847 s, 1723 s, 1476 w, 1451 m, 1363 w, 1333 m, 1317 w, 1270 w, 1238 s, 1184 m, 1104 s, 1085 s, 999 w, 972 w, 936 w, 894 w, 811 w, 766 w, 741 w, 679 w. EI MS: 385 (M^+ – 1, 18), 251 (M^+ – Ad, 19), 250 (M^+ – Ad – CO, 32), 207 (M^+ – Ad – CO_2, 100), 163 (Ad + CO, 12), 136 (adamantane, 17), 135 (Ad, 91), 107 (6), 93 (16), 91 (6), 78 (5).

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