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The first one-pot 'alkane-like' reactions of carbonyl-containing adamantanes

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ABSTRACT

A novel 'alkane-like' methodology for the direct and very simple one-pot functionalization of amides and an ester of 1-adamantanecarboxylic acid provides access to new and synthetically challenging 1,3-dicarbonyl-containing adamantanoid compounds with the same or different functional groups.

1. Introduction

Selective, one-pot C–H functionalization of monofunctional organic molecules is a promising method for the synthesis of bifunctional compounds with desired properties. However, finding reagents and conditions for such transformations represents a considerable challenge, as most functional groups have low tolerance to the highly reactive species and catalysts that are able to cleave non-activated sp^3 C–H bonds.

Examples of the one-pot C–H selective functionalization of monofunctional organic compounds are very rare.[1,2] The reactions of aliphatic alcohols, ketones, and aldehydes with ozone and magic acid in SO_2ClF or FSO_3H solvent have been reported.[1] Tertiary or secondary C–H bonds of primary alcohols located at the γ-position, or further removed from the functional group were shown to undergo insertion reactions with protonated ozone to give oxidation products in good yields. In contrast, secondary C–H bonds at the γ-position of aldehydes and ketones remained unreactive toward ozone under similar conditions. Such reactions with protonated ozone occurred only with higher ketone and aldehyde homologues.[1] Attempts to perform selective carbonylation of methyl *n*-alkyl ketones with CO in the presence of excess HF-SbF_5 were unsuccessful.[2] Under these conditions, only methyl *n*-alkyl ketones $MeCOC_nH_{2n-1}$ (n = 7–9) having tertiary C–H bonds were selectively carbonylated with the conversions of the ketones being only 16–66%.[2] Initial attempts to react carbonyl-containing adamantanes with CO or HCOOH in protic superacids were unsuccessful.[3]

Herein we report a novel method for the introduction of a carbonyl-containing functional group, via C–H activation, into the saturated hydrocarbon moiety of monofunctionalized adamantanoid compounds. Remarkably, the initial functional group remains intact during the reaction which occurs in a highly selective manner under very mild conditions.

Our strategy for the one-pot functionalization of alkanes was based on the use of the superelectrophiles $CX_4{\cdot}2AlBr_3$ (X = Cl, Br),[4,5] which, as we have found, can easily generate R^+ carbocations from RH even below room temperature. In the presence of CO, R^+ is transformed into the much more stable acyl cation RCO^+. The latter, in turn, can be converted into carbonyl-containing functionalized hydrocarbons RCOY upon addition of HY nucleophiles. In this manner, we have obtained a variety of carbonyl-containing compounds directly from saturated hydrocarbons RH, CO, and YH (alcohols; aliphatic, cyclic, heterocyclic and aromatic amines; tetraorganosilanes; aromatics; heteroaromatics; tetrahydrofuran; etc.) in the presence of $CX_4{\cdot}2AlBr_3$ in a one-pot procedure (Scheme 1).[5]

The obtained results[5] prompted us to propose that the same strategy based on electrophilic C–H activation might be suitable for the synthesis of bifunctional products from hydrocarbons already bearing one functional group. However, further functionalization of an already monosubstituted hydrocarbon seemed to be a more challenging task for the following two reasons. First, the presence of an electron-withdrawing group on the substrate is expected to destabilize the generated carbocation. Second, lone electron pairs on the already present functional group were expected to interact with the superelectrophile, resulting in diminished reactivity.

Monofunctional adamantanes 1-AdCOX, where X = NH_2 (**I**), NEt_2 (**II**), or OMe (**III**), were chosen as substrates on the basis of the

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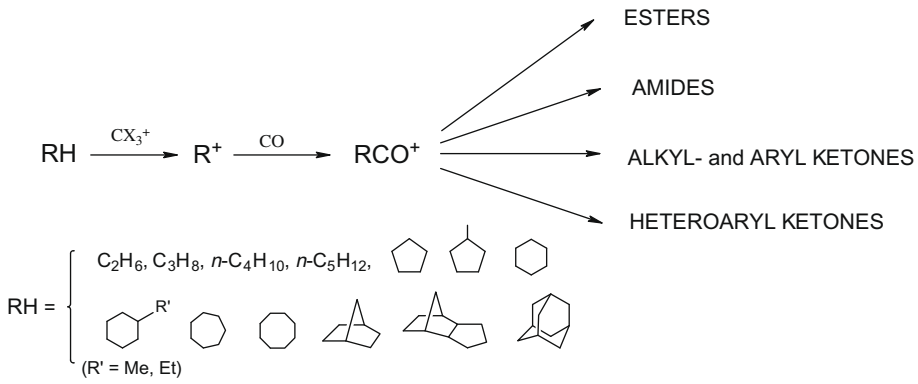


Scheme 1. Examples of one-pot alkane functionalizations.

following considerations. First, 1-substituted adamantanes such as amides and esters of 1-adamantanecarboxylic acid are commercially available. Second, these molecules contain three relatively reactive CH–bonds in the bridgehead positions. The projected transformation would lead to 1,3-bifunctional adamantanes that could be useful in the synthesis of new biologically active compounds,[6,7] thermal and chemical stable polymers,[8] novel crown ethers, peptide ionophores,[9] and other valuable fine chemicals.[6] Finally, the $CONR_2$ and COOMe groups already present, and those to be introduced, can be easily transformed into a broad range of other functionalities, including COOH, CN, CH_2NR_2, COOR′, and CON(OH)R′.[6c]

Thus the development of simple and efficient methods to synthesize 1,3-dicarbonyl-containing adamantanes directly from readily available monosubstituted starting materials is expected to open new methods for the preparation of novel biologically active compounds, polymers, and other valuable products.

In this work, we report that the use of the powerful superelectrophile $CBr_4{\cdot}2AlBr_3$ in a 30–50% excess allows the effective carbonylation of monofunctional adamantanes 1-AdCOX (**I**, **II**, and **III**), and as a result, the preparation of various 1,3-bifunctional adamantanes in high yields and with good selectivity (Scheme 2).

The carbonyl group is clearly a much stronger nucleophile than an sp^3 C–H bond. However, while interactions of the superelectrophile with the carbonyl group are reversible, C–H bond cleavage followed by acylium cation formation in the presence of CO is virtually irreversible. As a result, the less nucleophilic center can still react with the superelectrophile, even in the presence of much stronger CO donors.

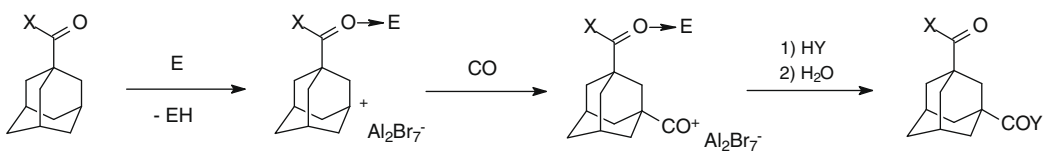
The carbonylation of **I**, **II**, and **III** under atmospheric CO pressure in the presence of polyhalomethane superelectrophiles was studied in detail in the temperature range 0 °C to −20 °C. The $CX_4{\cdot}nAlCl_3$ (X = Cl, Br, n = 1–2), $CCl_4{\cdot}nAlBr_3$ (n = 1–2), and $CBr_4{\cdot}nAlBr_3$ (n = 1–3) systems were tested as superelectrophiles (E) in CH_2X_2 (X = Br, Cl). The dependence of the results on the nature and molarity of the superelectrophile, the temperature, and duration of the reaction was studied. In situ treatment of the resultant carbonylated product was carried out under the optimal conditions found, namely, with 2–4 equiv of various HY nucleophiles with respect to **I**, at −20 °C to 0 °C; 0.5 h (depending on the nature of the nucleophile). The following nucleophilic substrates HY were used: alcohols, amines (diethylamine, pyrrolidine, piperidine, morpholine, and aniline), aromatics, and aromatic heterocycles (anisole, pyrrole, thiophene, and furan), and ethylene.

For the carbonylation of 1-$AdCONH_2$ (**I**), the molar ratio [**I**]:[E], the reaction time, and the molarity of E ranged from 1:1 to 1:3, from 1 to 20 h, and from 0.38 to 1.17 M, respectively. Comparison of the $CBr_4{\cdot}2AlBr_3$ and $CCl_4{\cdot}2AlCl_3$ systems under the same conditions ([**I**]:[E] = 1, 0 °C, 4 h) showed that, in both cases, the same products were formed and the conversions of **I** were very similar, but the selectivities of these reactions were different. Indeed, the yields of 1,3-Ad($CONH_2$)($COOPr^i$) were 65% and 36%, and those of the by-product 1,3-Ad($CONH_2$)Br amounted to 23% and 50%, respectively. Using the $CBr_4{\cdot}2AlBr_3$ system under different conditions ([**I**]:[E] = 1:1; 10 °C; 3 h, treatment with pyrrole) resulted in a 24% yield of the pyrrole acylation product and a 51% yield of the 1,3-Ad($CONH_2$)Br by-product.

Thus, the selectivity of the formation of 1,3-bifunctional adamantanes was not high in equimolar reactions at 0 °C to −20 °C even with the most potent $CBr_4{\cdot}2AlBr_3$ superelectrophile. However, at 0 °C for 2.5–4 h in the presence of 30–50% excess of $CBr_4{\cdot}2AlBr_3$, the carbonylation of amide **I** became the main process. This enabled the preparation of acylation products in high yield, and as a rule, with high selectivity. Two by-products were formed in small amounts in these reactions: the bromide 1,3-Ad($CONH_2$)Br and alkylation 1,3-Ad($CONH_2$)Y products. In most cases, their amounts ranged from 0–6% and 0–15%, respectively.

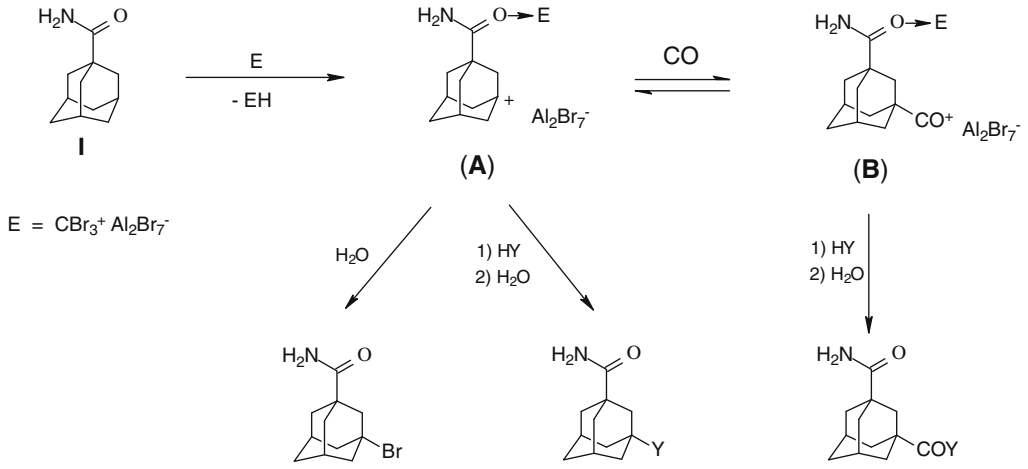
The observed results are shown in Scheme 3.

The proposed mechanistic scheme includes the generation of cation **A** from amide **I** coordinated with the superelectrophile. This cation can either add Br^- from the solvating $Al_2Br_7^-$ anion or a neutral CO molecule. The addition of Br^- occurs more easily, as intramolecular transformations of cations proceed more readily than intermolecular examples.[10] Increasing the temperature favors



E = CBr_3^+ $Al_2Br_7^-$; X = NH_2 (**I**), NEt_2 (**II**), OMe (**III**)

Scheme 2. One-pot synthesis of 1,3-bifunctional adamantanes.



Scheme 3. Reactions of 1-AdCONH$_2$ (**I**) with CO and HY nucleophiles in the presence of CBr_4·2$AlBr_3$.

decarbonylation of the acyl salt and, consequently, the formation of the above-mentioned by-products becomes more significant. At 0 °C under CO and in the presence of excess superelectrophile, the formation of bromide most probably represents a reversible process. It is likely that acylium salt **B** is more stable at 0 °C under the CO atmosphere, in comparison with $AdCO^+$, because acceptor groups in RCO^+ stabilize the acylium salts against decarbonylation.[11] Therefore, the bromide is a minor product under the optimal conditions.

Although both carbonylation and the subsequent reactions with nucleophiles were carried out under a strict CO atmosphere, 1,3-Ad(CONH$_2$)Y alkylation products were still formed in some cases. Their formation indicates the existence of an equilibrium between **A** and **B** even at 0 °C in the presence of CO. Although this equilibrium is shifted toward **B**, and cation **A** is probably present in the solution in only a small amount, the alkylation proceeds faster than the acylation. Contrary to bromide formation, the processes yielding the 1,3-Ad(CONH$_2$)Y alkylation products are irreversible.

Functionalization of **I** with CO and piperidine proceeded less selectively than with other nucleophiles, producing noticeable amounts of the alkylation product 1,3-Ad(CONH$_2$)($C_5H_{10}N$).

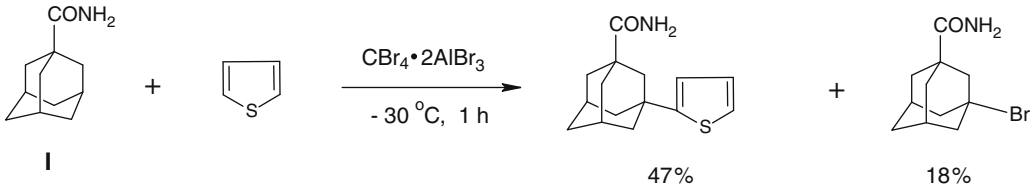
We showed that in the presence of CBr_4·2$AlBr_3$, the alkylation of **I** with a nucleophile could be carried out in moderate yield if the nucleophile was added to the reaction mixture in the absence of CO. Indeed, when thiophene was added to **I** at −30 °C in the presence of CBr_4·2$AlBr_3$, an exothermic reaction was observed giving 1,3-Ad(CONH$_2$)Y and 1,3-Ad(CONH$_2$)Br in 47% and 18% yields, respectively, with full conversion of **I** in 1 h (Scheme 4).

Under the optimal conditions, the yields of the desired 1,3-bifunctional products were 67–90% with conversions of **I** being close to 100%.

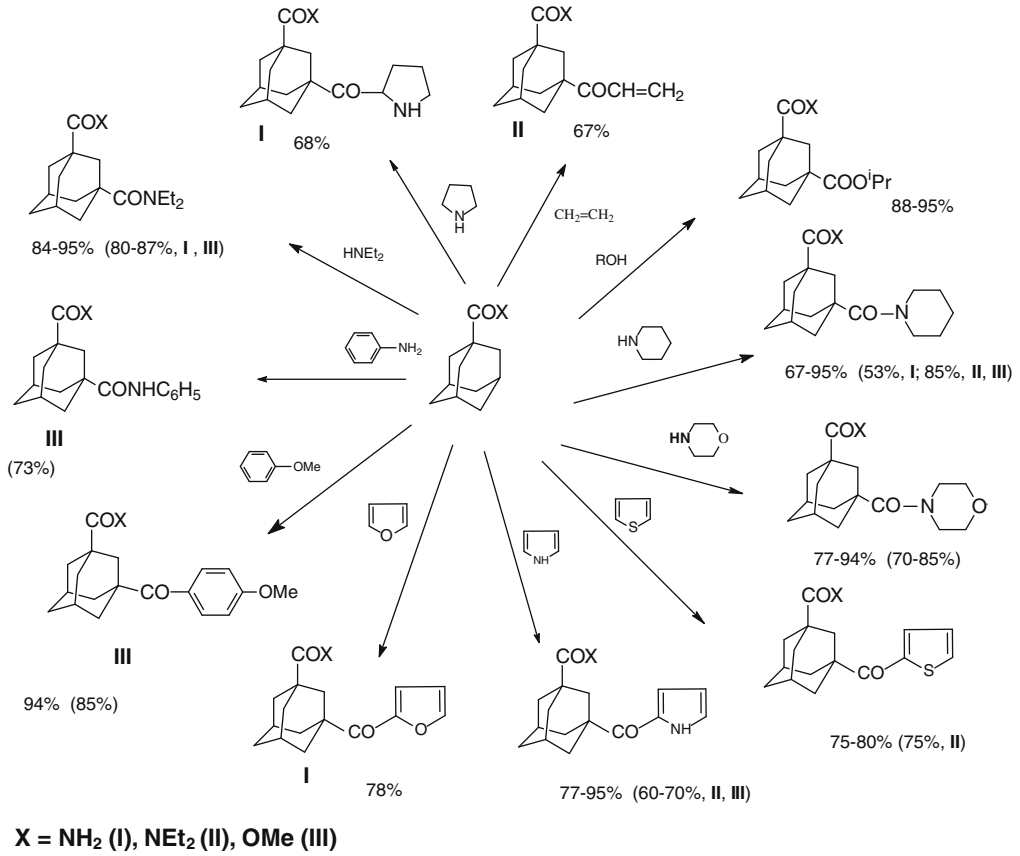
Under the above conditions (0 °C, 2.5–4 h), amide 1-AdCONEt$_2$ (**II**) and methyl 1-adamantanecarboxylate 1-AdCOOMe (**III**) also reacted readily with CO at atmospheric pressure in the presence of 30–50% excess of the CBr_4·2$AlBr_3$ superelectrophile to form the acylation products selectively and in high yields. These reactions usually proceeded more selectively than those with I. In most cases, the desired products were obtained in 81–96% yields, with the conversions being almost 100%. No alkylation products were produced in these reactions. It is worth noting that these 1,3-bifunctional adamantanes can be prepared, as a rule, more easily in an analytically pure state from II and III than from I. In most cases, it was sufficient to just wash the crude products with pentane.

The reactions of ethylene with the acyl salts generated in situ from **II** and **III** were nonselective. At −40 °C, after 1 h, the reaction of ethylene (1 atm) with 1,3-Ad(CONEt$_2$)CO^+ generated in situ from **II** (0 °C, 4 h) produced 1,3-Ad(CONEt$_2$)COCH=CH_2 (30%) together with 1,3-Ad(CONEt$_2$)$COCH_2CH_2Br$ (10%) and 1,3-Ad(CONEt$_2$)CO-CH_2CH_2OH (9%). At −20 °C, this reaction yielded 1,3-Ad(CONEt$_2$)-COCH=CH_2 (67%) and 1,3-Ad(CONEt$_2$)$COCH_2CH_2Br$ (10%). By contrast, at −20 °C or at 0 °C, the reaction of the acyl salt generated from **III** with ethylene led to alkylation products with Ad(COOMe)-CH_2CH_2Br as the main product.

The previously described methods for the preparation of 1,3-dicarbonyl-containing adamantanes are based on 1,3-adamantane-dicarboxylic acid as the starting material.[6–9,12,13] The disadvantages of these methods include the limited availability of the diacid, the necessity to use strong protic acids such as oleum, and a multistep synthesis involving carbonylation of adamantane or its derivatives (1-AdCOOH or 1-AdBr) into 1,3-Ad(COOH)$_2$,[12] followed by conversion into 1,3- Ad(COCl)$_2$ and transformation into the desired final product. In some cases, this reaction sequence resulted in poor selectivities and low yields (often below 30% even for the final step).[13] Furthermore, these methods are not simple routes for synthesizing adamantanes with two different functional groups. By contrast, our new method offers a number of advantages, including simplicity (one-pot procedure), high selectivities, and good yields of a wide range of products bearing identical or different substituents at the 1 and 3 positions.



Scheme 4. The alkylation and bromination of **I** in the absence of CO.



Scheme 5. The starting adamantanes **I**–**III** were used to generate all the products with the exception of those cases specifically marked (for example, **III** means that only compound **III** was used in that particular reaction). The yields were determined by GC and NMR-methods, the yields of isolated products are given in brackets.

The products obtained are presented in Scheme 5.

The structures of the products were proved from elemental analysis, ^{1}H and ^{13}C NMR and mass spectroscopy. The products of the in situ treatment of the carbonylation products **II** and **III** with ethylene were characterized by GC–MS only.

Almost all the products obtained are new compounds. Their melting points, elemental analyses, mass spectra, and ^{1}H and ^{13}C NMR spectra are provided as Supplementary data. The assignment of the chemical shifts was made mostly on the basis of calculated values obtained with the Program ACD/HCNMR DB.

In summary, an 'alkane-like' strategy has been successfully demonstrated for the selective one-pot synthesis of novel 1,3-bifunctional adamantanes with the same or different functional groups, from readily available derivatives of 1-adamantanecarboxylic acid, CO, and various nucleophiles. We believe that this approach can be extended to the preparation of other 1,3-disubstituted adamantanes bearing desired functional groups. We are currently working on the application of this concept to the synthesis of bifunctionalized hydrocarbons from monofunctionalized alkanes.

2. Typical experimental procedure

At 0 °C under atmospheric CO pressure, **I**, **II,** or **III** was added with stirring to freshly prepared $CBr_4{\cdot}2AlBr_3$ (E) in anhydrous CH_2Br_2 at room temperature. Molar ratio [**I**] (**II** or **III**):E = 1:(1.3–1.5); [E] ~ 1 M). The mixture was stirred for 2.5–4 h. The reaction mixture was cooled to −20 °C and the nucleophilic substrate (2–4 equiv with respect to **I**, **II,** or **III**) was added under atmospheric CO. The mixture was allowed to warm to 0 °C and then cold $CHCl_3$ (~10 mL per 0.2 g of the starting adamantane) and H_2O (20 mL) were carefully added under cooling. The organic extract was separated and the aqueous solution was extracted again with $CHCl_3$ (10 mL). The combined $CHCl_3$ extracts were washed with H_2O and dried over $MgSO_4$. After removing the solvent under reduced pressure, the product was precipitated from minimal amounts of toluene (benzene, ether, dioxane, and acetone) with pentane or hexane, or washed with pentane or hexane. The product of reaction **III,** CO and anisole was purified by crystallization from petroleum. Conversions of **I**, **II,** or **III** were determined by GC, yields of products were measured by GC or NMR (with 1,3,5-tribromobenzene as an internal standard). If the elemental analysis of a product was not satisfactory, the above-mentioned procedure for the purification was repeated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.022.

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