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The first one-pot synthesis of 1,3-dicarbonyl adamantanes from 1-bromoadamantanes

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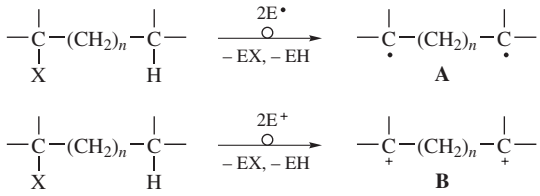
Treatment of 1-bromoadamantane and 1-bromo-3,5-dimethyladamantane with $CBr_4 \cdot 2AlBr_3$ under carbon monoxide atmosphere followed by quenching with nucleophiles affords 1,3-dicarbonyl adamantanes.

Replacement of labile atoms or groups by other functionalities is a powerful synthetic approach in modern organic chemistry.[1] Meanwhile, selective one-pot bifunctionalization involving the cleavage of both labile C–X and poorly reactive C_{sp^3}–H bonds with the formation of compounds containing two new functional groups is a considerable challenge. Principally, depending on the type of the initiating system, these transformations should proceed either through biradical (**A**) or dication (**B**) intermediates (Scheme 1).



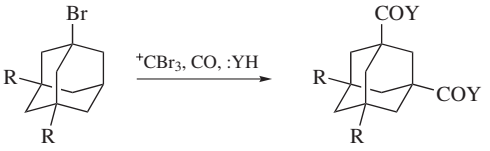
Scheme 1

Radical transformations can hardly be expected to be selective. At the same time, generation of species bearing two carbocationic centers would require the use of potent superelectrophiles. However, in their presence, cracking, isomerizations, and other by-processes are also difficult to be avoided.

Herein, we report a new approach to one-pot transformations of 1-bromoadamantanes which produce bifunctional derivatives with two new carbonyl-containing groups at the bridged-head position *via* cleavage of both C–Br and C_{sp^3}–H bonds.

Our strategy was based on the use of superelectrophile $CBr_4 \cdot 2AlBr_3$, which, as we found, can easily generate carbocations from alkanes[2] or even from monofunctionalized alkanes[3,4] leaving a functional group unaffected. Under CO atmosphere, these cations are converted into the corresponding acylium intermediates, which, in turn, upon *in situ* treatment with nucleophiles afford monofunctional[2] or bifunctional products,[3,4] respectively.

We found that carbonylation of 1-bromoadamantane **1a** and 1-bromo-3,5-dimethyladamantane **1b** in the presence of $CBr_4 \cdot 2AlBr_3$ followed by the *in situ* treatment of the resulting 1,3-dicarbonylation products with nucleophiles provides a convenient synthetic route to dicarbonyl adamantanes with two new functional groups at the bridged-head position.† In contrast to the reactions previously described,[3,4] where the original functionalities interacted with the superelectrophile reversibly and finally remained intact, the here studied labile Br atom was replaced by the carbonyl moiety either. These one-pot reactions



1a R = H
1b R = Me
:YH = H_2O, alcohol, amine, arene, heteroarene

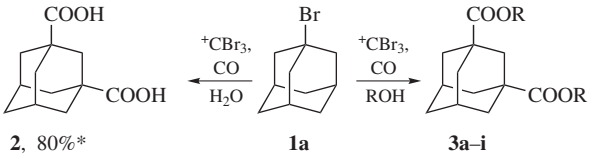
Scheme 2

proceeded selectively under very mild conditions and afforded the target dicarbonyl adamantanes in high yields (Scheme 2).

Carbonylation of **1a** was carried out in CH_2Br_2 at 0 °C under 1 atm of CO in the presence of 20–50% excess of superelectrophile $CBr_4 \cdot 2AlBr_3$ (E) for 3 h. The process can also be performed at room temperature for 45 min, however, in this case the selectivity is lower. The resulting carbonylation product was then treated with 1.5–4-fold molar excess of a nucleophile with respect to E strictly under CO atmosphere at 0 °C for *ca*. 30 min, with the exception of the reaction with water, which required a longer time. In case of various alcohols, the corresponding diesters **3a–i** were obtained (Scheme 3). According to GC, as a rule, conversion of **1a** was close to 100%. The product yields were determined by GC and NMR (with mesitylene as an internal standard), the yields of isolated products in the Schemes 3–5 are marked by asterisk.

Surprisingly, we found that if water and then solvent, such as diethyl ether or chloroform, were added to the product of carbonylation of **1a**, dimethyl or diethyl adamantane-1,3-carboxylates, respectively, were formed in good yields instead of the target diacid. Although the content of MeOH and EtOH impurities in Et_2O and $CHCl_3$, respectively, was no higher than 0.3–0.5%, and water was used in 50–100-fold molar excess with

† *Typical procedure*. At 0 °C under CO atmosphere (1 atm) bromoadamantane **1a** or **1b** (0.83 mmol) was added to the stirred solution of the complex $CBr_4 \cdot 2AlBr_3$ (E), freshly prepared from $AlBr_3$ (2.50 mmol) and CBr_4 (1.25 mmol) in anhydrous CH_2Br_2 (1.3 ml) at room temperature. A molar ratio [E]:[**1a**] = 1.2:1; [E]:[**1b**] = 1.5:1. After 3 h stirring at 0 °C under CO atmosphere, a nucleophile YH (molar ratio [YH]:[E] = 4:1) was added to the *in situ* prepared carbonylation intermediate. The mixture was left to warm up to 0 °C for 20–30 min. After that, 10 ml of water and 20 ml of $CHCl_3$ were carefully added under stirring, and organic layer was separated. The remaining aqueous layer was extracted with $CHCl_3$ (2×20 ml), combined organic extracts were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by crystallization or precipitation.

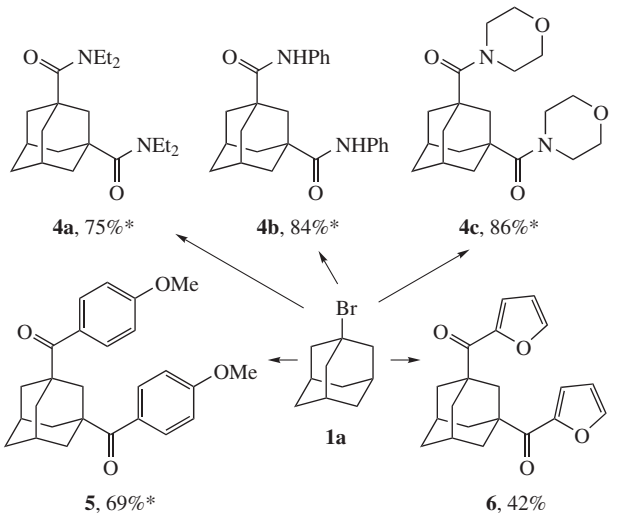


3a R = Me, 83%
3b R = Et, 81%
3c R = Pr^i, 97%
3d R = Bu^s, 84%
3e R = $(CH_2)_3Br$, 75%
3f R = $CH_2C{\equiv}CH$, 74%
3g R = CH_2CF_3, 92%
3h R = $CH_2CH(Me)CF_3$, 94%
3i R = $CH_2(CF_2)_2H$, 90%

Scheme 3

respect to the alcohols, the carbonylation product absorbed alcohols much quicker even from very diluted solutions.‡ The desired diacid was obtained only when quenching of the carbonylation intermediate with water was performed at room temperature for several hours (up to 48 h) in the solvent-free manner or at least with the use of alcohol-free solvent. Under these conditions, adamantane-1,3-dicarboxylic acid was isolated in 70–80% yield. These results show that the reactions of the carbonylation product with water proceeded much slower than those with alcohols.

The use of diethylamine, morpholine and aniline led to the corresponding dicarboxamides **4a**–**c**. In the case of anisole, diketone **5** was obtained in 69% yield, while very active furan provided only 42% yield of diketone **6** together with 1-bromo-3-(2-furylcarbonyl)adamantane as a by-product (Scheme 4).

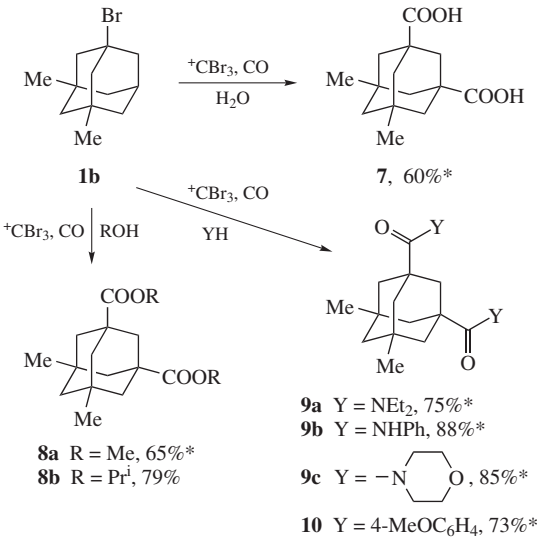


Scheme 4 *Reagents*: $CBr_4{\cdot}2AlBr_3$, CO, Et_2NH (for **4a**), $PhNH_2$ (for **4b**), morpholine (for **4c**), anisol (for **5**) or furan (for **6**).

1-Bromo-3,5-dimethyladamantane **1b** behaved similarly to form the corresponding dicarbonyl compounds (Scheme 5). The reactions with **1b** required somewhat higher excess of E than those with **1a** to achieve good selectivity and high yields of the products. It seems likely that the carbonylation product generated from **1b** is less stable in comparison with that prepared from **1a**, because donor methyl groups in acylium cations facilitate their decarbonylation.[6]

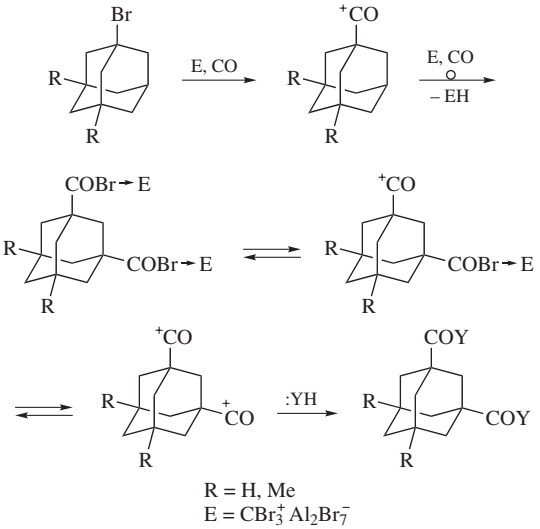
‡ In a special experiment, **1a** (1.07 mmol) was carbonylated in the presence of $CBr_4{\cdot}2AlBr_3$ (1.29 mmol) in CH_2Br_2 (1.4 ml) at 0 °C over 3 h. *In situ* treatment of the carbonylation product with 30 ml of hexane, containing 0.162 g (2.19 mmol) of Bu^sOH afforded the $Ad(COOBu^s)_2$ in 68% yield.

For experimental details, analytical and spectroscopic (^1H, ^{13}C, ^{19}F NMR and MS) data for obtained compounds, see Online Supplementary Materials.



Scheme 5

The suggested reaction path for **1a**,**b** (Scheme 6) involves the elimination of the Br atom by the superelectrophile. Evidently, this step occurs catalytically. The Ad^+ (or 1,3-Me_2Ad^+) adds CO to form more stable $AdCO^+$ (or 1,3-Me_2AdCO^+). The latter, in turn, undergoes the abstraction of hydride to give under CO atmosphere diacylium species which is a precursor for the formation of the final products.



Scheme 6

A great body of evidence accumulated in the last few decades shows that positively charged species are capable of further interaction with strong protic or aprotic superelectrophiles to produce highly active ditonic dications, *i.e.*, the species containing two cationic centers separated by one or several atoms, and even gistonic dications with two cationic centers located at two adjacent carbon atoms.[7] The ditonic 1,3-adamantanediyl dication containing two tertiary carbenium centers separated by a methylene group was shown by B3LYP/6-31G* quantum chemical calculation to have a minimum on the potential energy surface,[8] although attempts to prepare it in the superacid solution were unsuccessful.[9] Elucidation of the nature of the carbonylation products of 1-bromoadamantane will be the subject of our future work.

Many derivatives of adamantane carboxylic acids display promising biological activities.[5,10] Incorporation of the AdCO into polymers such as polyesters and polyamides enhances their thermal and chemical stability.[11] Other fields of application of

AdCO-containing compounds involve crown ethers,[12(a),(b)] peptide ionophores,[12(c)] *etc*.[13]

Important, carbonyl-containing groups in the prepared products can be easily transformed into a broad variety of other functionalities.[5] Therefore, one may expect that a new approach to selective one-pot synthesis of various bifunctional adamantanes from available bromoadamantanes would provide new ways to biological active compounds, polymers, and other valuable products.

Until now, one-pot synthesis of 1,3-dicarbonyl adamantanes has not been known. Previously reported syntheses[14] of such compounds are based on poorly available adamantane-1,3-dicarboxylic acid as the starting material and the use of oleum as the reaction medium, and do not provide good yields of the products.

The herein developed method seems to be rather common for the preparation of various 1,3-dicarbonyl adamantanes by using nucleophiles which are reluctant to superelectrophiles. In the case of very active nucleophiles, the corresponding compounds can be prepared by the known multi-step reactions starting from adamantanedicarboxylic acids, which could be obtained by our method using water as a nucleophile.

Many of the products prepared in this work are new. Their structures are consistent with ^{1}H and ^{13}C NMR, mass spectra and elemental analyses, which are available in Online Supplementary Materials.

In summary, the use of powerful superelectrophilic complex $CBr_4 \cdot 2AlBr_3$ allowed us to achieve selective one-pot bifunctionalization of 1-bromoadamantanes. Thus, a new simple one-pot synthesis of valuable 1,3-dicarbonyl adamantanes has been developed.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.09.009.

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