Reactions of methyl esters of adamantane acids with acetonitrile*

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Methyl adamantane-1-carboxylate and methyl (1-adamantyl)acetate react with acetonitrile in the presence of sodium hydride to give 3-(1-adamantyl)-3-oxopropanenitrile and 4-(1-adamantyl)-3-oxobutanenitrile, respectively. Reaction involving methyl (1-adamantyl)-acetate produces also 2-(1-adamantyl)-*N*-(*E*-1-cyanoprop-1-ene-2-yl)acetamide; the structure of this side product was established by X-ray diffraction analysis.

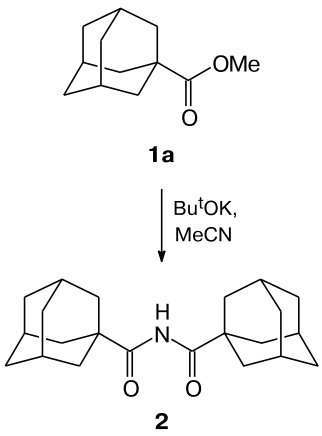
Key words: keto nitriles, esters, adamantane derivatives, condensation, acetonitrile.

Keto nitriles are valuable building blocks useful in the synthesis of different heterocycles, *e.g.*, aminopyrazoles,[1] aminoisoxazoles,[2] and 3,4-dihydroisoquinolines[3] possessing a wide range of biological activity. Adamantane derivatives have found broad applications as antiviral, antibacterial, and antiparkinsonian agents, immunostimulants and muscle relaxants.[4,5] Only two patents have claimed the applications of 3-(1-adamantyl)-3-oxopropanenitrile as an intermediate in the synthesis of photographic material[6] and antiasthmatic agent.[7] Moreover, spectral and physicochemical properties of this compound were published[8] only in 2015 despite the fact that this nitrile is a key intermediate in the synthesis of rimantadine analogs promising as new ion channel inhibitors of RNA viruses.[9,10] In the first patent,[6] 3-(1-adamantyl)-3-oxopropanenitrile was synthesized in 50% total yield by acylation of (*tert*-butyl)cyanoacetate with adamantane-1-carbonyl chloride in the presence of potassium *tert*-butoxide followed by acid hydrolysis and decarboxylation. The authors of the second patent[7] used the reaction sequence involving condensation of acetonitrile with ethyl adamantane-1-carboxylate on treatment with potassium 2-methylbutan-2-olate and subsequent transformation of the crude product into aminopyrazole. The good yield (68%) was achieved by authors of work[8] by using relatively complex protocol, namely, condensation of *N*-methyl-*N*-methoxyadamantane-1-carboxamide with acetonitrile in THF in the presence of MeLi—LiBr at −78 °C.

With the aim to study properties of keto nitriles of adamantane series, we elaborated a procedure for condensation of methyl adamantane-1-carboxylate (**1a**) and methyl (1-adamantyl)acetate (**1b**) with acetonitrile on treatment with different bases in toluene.

The attempt to employ sodium isopropoxide as a condensing agent failed leading only to the starting esters **1a**,**b** and the corresponding carboxylic acids. The use of potassium *tert*-butoxide also does not lead to the target keto nitriles. It is of note that along with the starting ester **1a**, the reaction produces bis(adamantane-1-carbonyl)imide (**2**) in 5% yield, the spectral properties of compound **2** is similar to whose of dipivaloyl imide[11] (Scheme 1).

Scheme 1



Keto nitriles **3a**,**b** were obtained in the yield not exceeding 17% by carrying out the reaction in a toluene—acetonitrile mixture (1 : 12.5) in the presence of sodium metal as a reagent (Scheme 2). The condensation of ester **1a** with acetonitrile on treatment with sodium hydride as a base affords keto nitrile **3a** in 75% yield. The yield of

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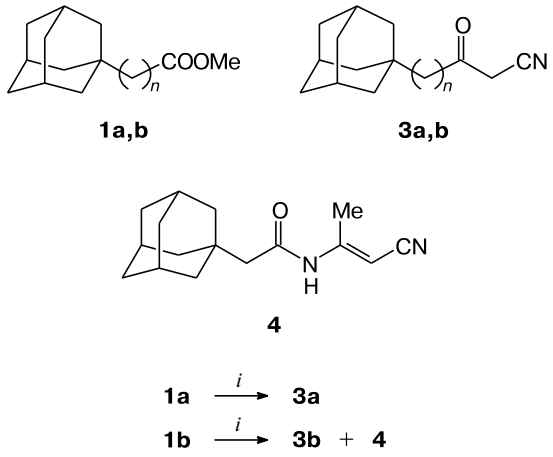
homologous keto nitrile **3b** was substantially lower (42%) due to formation of the second reaction product, compound **4**. The structure of compound **4** was established by X-ray diffraction analysis (Fig. 1, CCDC 1047447).[12]

Scheme 2

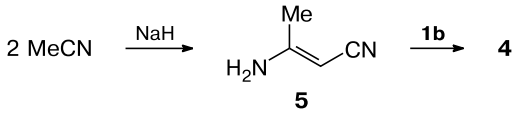


n = 0 (**1a**, **3a**), 1 (**1b**, **3b**)

i. NaH/MeCN, toluene.

Apparently, the strong base mediates the known self-condensation of acetonitrile[13,14] to give its dimer, 3-aminobut-2-enenitrile (**5**), the amino group of **5**, in turn, undergoes acylation with ester **1b** (Scheme 3).

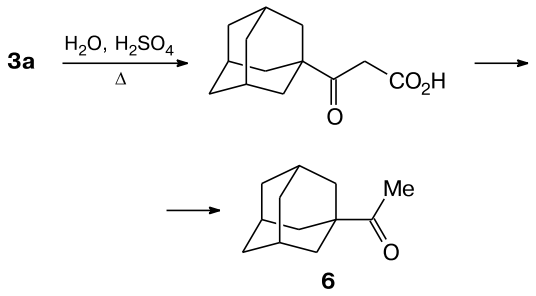
Scheme 3



A similar product was not detected in the reaction of methyl adamantane-1-carboxylate (**1a**) with acetonitrile. This fact can apparently be attributed to the high degree of steric shielding of the carbonyl group caused by the adamantane framework, which led to a decrease in the reaction rate of bulky nucleophile **5** with ester **1a** than in the case of ester **1b**.

Hydrolysis of keto nitrile **3a** with sulfuric acid gives 3-(1-adamantyl)-3-oxopropanoic acid, which further undergoes decarboxylation to yield the known 1-acetyladamantane (**6**) (Scheme 4).

Scheme 4



In summary, we developed a simple and versatile procedure towards keto nitriles of adamantane series and found a new direction of the sodium hydride-mediated condensation of acetonitrile with the ester.

Experimental

IR spectra were recorded on a SHIMADZU IR Affinity-1 Fourier-transform IR spectrophotometer (Japan) in the KBr pellets in the 400—4000 cm^{-1} range using the atmospheric correction function to remove water and carbon dioxide peaks. ^1H and ^{13}C NMR spectra were run with a JEOL ECX-400 instrument (Japan) at working frequencies of 400 and 100 MHz, respectively, in $CDCl_3$. Elemental analyses were performed with a EuroEA Elemental Analyzer (USA).

Bis(adamantane-1-carbonyl)imide (2). To a mixture of methyl adamantane-1-carboxylate (**1a**) (9.9 g, 51 mmol) in acetonitrile (50 mL), a preliminary prepared solution of potassium (2 g, 51 mmol) in *tert*-butanol (20 mL) and 18-crown-6 (0.5 g) were added. The reaction mixture was refluxed for 40 h. The

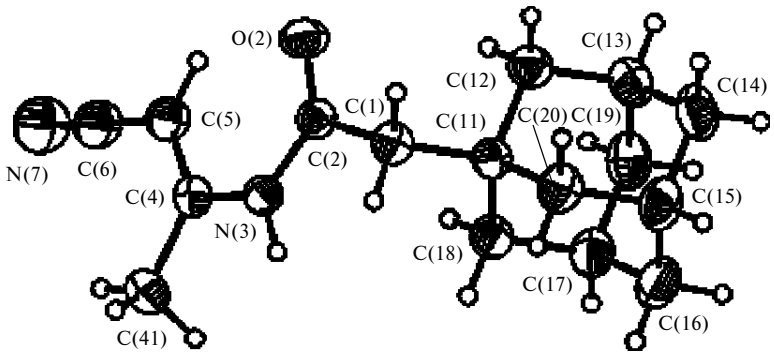


Fig. 1. Molecular structure of compound **4**. Nonhydrogen atoms are depicted at the 30% probability level; hydrogen atoms are shown as spheres of arbitrary radius.

resulting precipitate was collected by filtration, dissolved in water (20 mL), acidified with acetic acid to pH 5, and extracted with benzene. The extract was dried with sodium sulfate, the solvent was removed *in vacuo*. Recrystallization of the residue from water afforded compound **2** in the yield of 0.43 g (5%), colorless crystals, m.p. 234—236 °C. IR, ν/cm^{-1}: 3352 m (NH), 2901 v.s (C—H), 2580 v.s (C—H), 1736 v.s (C=O). ^{1}H NMR, δ: 1.67—1.79 (m, 12 H, Ad); 1.86—1.90 (m, 12 H, Ad); 2.06—2.10 (m, 6 H, Ad); 8.34 (s, 1 H, NH). ^{13}C NMR, δ,: 28.0 (Ad), 36.3 (Ad), 39.1 (Ad), 42.9 (Ad), 175.2 (C=O). Found (%): C, 77.42; H, 9.11; N, 4.03. $C_{24}H_{31}NO_2$. Calculated (%): C, 77.38; H, 9.15; N, 4.10.

3-(1-Adamantyl)-3-oxopropanenitrile (3a). To a mixture of methyl adamantane-1-carboxylate (**1a**) (3 g, 15 mmol), acetonitrile (9.5 mL, 179 mmol), toluene (25 mL), and NaH (a 60% dispersion in mineral oil, 0.725 g, 17.6 mmol) was added under argon. The stirred reaction mixture was refluxed for 8 h. The precipitate formed was collected by filtration, washed with 10% aqueous acetic acid (6 mL), and dried. Recrystallization from petroleum ether afforded compound **3a** in the yield of 2.35 g (75%), colorless crystals, m.p. 98—100 °C (*cf.* Ref. 8: m.p. 112 °C). IR, ν/cm^{-1}: 2909 v.s (C—H), 2851 v.s (C—H), 2261 w (CN), 1705 v.s (C=O). ^{1}H NMR, δ: 1.50—1.70 (m, 12 H, Ad); 2.00—2.10 (m, 3 H, Ad); 3.59 (s, 2 H, CH_2). ^{13}C NMR, δ: 27.2 ($\underline{C}H_2CN$), 27.7 (Ad), 36.2 (Ad), 38.0 (Ad), 46.9 (Ad), 114.4 (CN), 202.5 (C=O). Found (%): C, 76.89; H, 8.46; N, 6.82. $C_{13}H_{17}NO$. Calculated (%): C, 76.81; H, 8.43; N, 6.89.

4-(1-Adamantyl)-3-oxobutanenitrile (3b) and 2-(1-adamantyl)-*N*-(*E*-1-cyanoprop-1-ene-2-yl)acetamide (4). Compound **3b** was synthesized in the yield of 2.2 g (42%) similarly to compound **3a** from methyl (1-adamantyl)acetic acid (**1b**) (5 g, 24 mmol), colorless crystals, m.p. 44—45 °C (petroleum ether). IR, ν/cm^{-1}: 2905 v.s (C—H), 2851 v.s (C—H), 2257 w (CN), 1717 v.s (C=O). ^{1}H NMR, δ: 1.58—1.64 (m, 9 H, Ad); 1.65—1.72 (m, 3 H, Ad); 1.94—1.98 (m, 3 H, Ad); 2.30 (s, 2 H, Ad$C\underline{H}_2$); 3.43 (s, 2 H, CH_2CN). ^{13}C NMR, δ: 28.5 (Ad), 34.0 (CH_2), 34.5 (CH_2), 36.6 (Ad), 42.3 (Ad), 55.0 (Ad), 114.0 (CN), 196.9 (C=O). Found (%): C, 77.32; H, 8.87; N, 6.39. $C_{14}H_{19}NO$. Calculated (%): C, 77.38; H, 8.81; N, 6.45.

The insoluble residue on recrystallization from ethanol afforded amide **4** in the yield of 1.4 g (22%), yellow crystals, m.p. 175—176 °C. IR, ν/cm^{-1}: 3283 s (NH), 3209 m (NH), 3140 m (NH), 3090 m (NH), 3024 w (NH), 2901 v.s (CH), 2847 v.s (CH), 2218 v.s (CN), 1708 v.s (C=O), 1639 s (C=N), 1519 v.s (NH). ^{1}H NMR, δ: 1.55—1.75 (m, 12 H, Ad); 1.80—2.00 (m, 3 H, Ad); 2.03 (s, 2 H, Ad$C\underline{H}_2$); 2.15 (s, 3 H, CH_3); 6.44 (s, 1 H, CH); 7.49 (s, 1 H, NH). ^{13}C NMR, δ: 20.7 (CH_3), 28.6 (CH, Ad), 33.6 (C, Ad), 36.7 (CH_2, Ad), 42.5 (CH_2, Ad), 52.5 (Ad$\underline{C}H_2$), 80.9 ($\underline{C}HCN$), 119.0 (CN), 151.8 (C=NH), 171.1 (C=O). Found (%): C, 74.44; H, 8.63; N, 10.78. $C_{16}H_{22}N_2O$. Calculated (%): C, 74.38; H, 8.58; N, 10.84.

A single crystal of compound **4** was obtained by crystallization from ethanol. X-Ray diffraction experiment was carried out with a Enraf—Nonius CAD-4 diffractometer[15] (graphite monochromator, λ(Cu-Kα) = 1.5418 Å, temperature of 295 K, ω scan mode). Crystallographic parameters, details of the X-ray experiments, structure solution, and refinement parameters for compound **4** are summarized in Table 1. The absorption was accounted for using the experimental azimuthal scanning curves (T_{min}/T_{max}). The structure was solved by the direct method. Positions and displacement parameters for non-hydrogen atoms were refined by full matrix least-squares first isotropically, then anisotropically. Hydrogen atoms were placed in geometrically calculated positions. All calculations were performed employing SHELXL-2013 software.[16] Visualization of the molecule geometry was carried out with PLATON program package.[17]

Table 1. Crystallographic characteristics and selected parameters of X-ray diffraction experiment

Parameter	Value
Molecular formula	$C_{16}H_{22}N_2O$
Molecular weight	258.36
Crystal system	Monoclinic
Space group	*C*2/*c*
a/Å	24.578(4)
b/Å	10.2967(16)
c/Å	13.636(3)
β/deg	120.530(10)
V/Å^3	2972.5(10)
Z	8
d_{calc}/g cm^{-3}	1.155
μ/cm^{-1}	0.566
Scanning range	4.176 ≤ θ ≤ 74.889
Number of measured reflections (R_{int})	3062 (0.0745)
Number of reflections with $I > 2\sigma(I)$	2203
Number of refined parameters	178
R_1 ($I > 2\sigma(I)$)	0.0501
wR_2 (all data)	0.1447

In crystal, molecules of **4** are bound by classical N(3)—H(3)...N(7)^i H-bonds with the following parameters: N(3)—H(3) = = 0.882(19) Å, H(3)...N(7)^i = 2.07(2) Å, N(3)...N(7)^i = 2.944(2) Å, angle N(3)—H(3)...N(7)^i = 173.2(19)°. Symmetry operation (*i*) *x*, −*y*, *z* + × was applied to generate the coordinates of the N(7)^i from the N(7) atom.

1-Acetyladamantane (6). To a water—sulfuric acid mixture (1 : 1, 10 mL), 3-(1-adamantyl)-3-oxopropanenitrile (**3a**) (1.25 g, 7 mL) was added. The reaction mixture was heated at 140—145 °C for 5 h, and extracted with benzene. Steam distillation, filtration of the product from water layer, and drying afforded compound **6** in the yield of 0.6 g (55%), m.p. 53—54 °C (*cf.* Ref. 18: m.p. 54 °C).

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