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Adamantylation of Carbonitriles with 1,3-Dehydroadamantane and Its Homologs

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Abstract—1,3-Dehydroadamantane and its methyl-substituted homologs react with carbonitriles at the α-carbon atom of the latter to give the corresponding α-adamantyl carbonitriles. This reaction provide a convenient one-step procedure for selective synthesis of branched nitriles which are difficult to obtain by traditional procedures.

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Adamantyl-containing nitriles are important intermediate products in the synthesis of some biologically active compounds. Their reduction gives the corresponding amines whose structural analogs exhibit antiviral and anti-Parkinson activity [1]. In molecules of most known adamantyl-containing nitriles, the adamantyl radical and cyano group are separated by one or more methylene groups. Published data on nitriles of the general formula 1-AdCH(CN)R, where the 1-adamantyl radical is attached to the α-carbon atom with respect to the cyano group, are few in number.

The first member of the series of such nitriles is 1-adamantylacetonitrile, which is obtained by reaction of 1-adamantylmethyl *p*-toluenesulfonate with potassium cyanide in DMF (24 h, 120°C [2]. The most widely used procedure for the synthesis of adamantyl-containing nitriles is based on dehydration of the corresponding carboxylic acid amides [3, 4] which are prepared in turn from acid chlorides. Phosphorus(III) chloride and thionyl chloride were used as dehydrating agents [5]. However, this procedure involves several steps, and its scope is seriously limited by accessibility of initial adamantyl-substituted carboxylic acids. The synthesis of such acids is often laborious. Only three adamantyl-containing carboxylic acids have been reported: adamantane-1-carboxylic, 1-adamantylacetic, and 3-(1-adamantyl)propionic [6, 7].

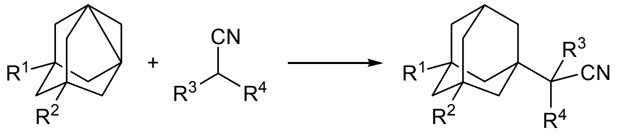
1-Adamantylacetonitrile was used to synthesize α-substituted nitriles of the general formula 1-AdCH(CN)R. Branched adamantyl-containing nitriles were obtained by reaction of 1-adamantylacetonitrile with methyl iodide [8] or ethyl iodide [9] in the presence of lithium diisopropylamide or butyllithium in anhydrous tetrahydrofuran at –78°C [yield 39 (R = Me) and 97% (R = Et)]. The reaction of 1-adamantylacetonitrile with 11-bromoundec-1-ene in the presence of lithium diisopropylamide at 0°C afforded 2-(adamantan-1-yl)tridec-12-enenitrile [10]. An attempt to accomplish electrochemical adamantylation of cinnamonitrile with 1-bromoadamantane resulted in the formation of an intractable mixture of different nitriles (yield 15–25%), including 2-(adamantan-1-yl)-3-phenylpropionitrile (15%) [11].

Thus, the existing methods for the synthesis of branched α-(adamantan-1-yl) carbonitriles are multistep and hence laborious.

Taking into account that the hydrogen atom in the α-position with respect to the cyano group possesses acidic properties, it was presumed that this position can be involved in reactions with bridged [3.3.1]-propellanes, including 1,3-dehydroadamantane (**Ia**) and its homologs, 3-methyl-1,3-dehydroadamantane (**Ib**) and 5,7-dimethyl-1,3-dehydroadamantane (**Ic**). We previously showed that propellane **Ia** reacts with a number of CH acids [12, 13], in particular with relatively weak ones [14, 15]. There are no published data on reactions of propellanes with aliphatic nitriles and structurally related compounds, except for the reaction of [1.1.1]propellane with cyanogen bromide, which involved cleavage of the C–Br bond [16].

In continuation of our studies on the chemical properties of bridged [3.3.1]propellanes, we have developed a new procedure for the synthesis of branched nitriles containing an adamantyl substituent on the α-carbon atom (Scheme 1).

Scheme 1.



Ia–Ic **IIa–IIh** **IIIa–IIIj**

I, R^1 = H, R^2 = H (**a**), Me (**b**); $R^1 = R^2$ = Me (**c**); **II**, R^3 = H, R^4 = H (**a**), Me (**b**), Et (**c**), Pr (**d**), *i*-Pr (**e**), Ph (**f**), 1-naphthyl (**g**); $R^3 = R^4$ = Me (**h**); **III**, $R^1 = R^2 = R^3$ = H, R^4 = H (**a**), Me (**b**), Et (**c**), Pr (**d**), *i*-Pr (**e**), Ph (**f**), 1-naphthyl (**g**); $R^1 = R^2$ = H, $R^3 = R^4$ = Me (**h**); R^1 = H, $R^2 = R^3 = R^4$ = Me (**i**), $R^1 = R^2$ = Me, R^3 = H, R^4 = *i*-Pr (**j**).

Initial nitriles **IIa**–**IIi** contained both donor (alkyl) and acceptor substituents (phenyl, 1-naphthyl), so that their CH acidity varied over a wide range. The reactions of 1,3-dehydroadamantane **Ia** with nitriles **IIa**–**IIi** were carried out using 3–10 equiv of the latter by heating the reactants for 8 h at 60–140°C. Reactions of nitriles with cycloalkanes were not reported. Addition to the α-carbon atom is typical only for reactive alkenes in the presence of strongly basic catalysts. High steric strain of the three-membered ring in propellanes **Ia**–**Ic** allows them to add to nitriles that are weak CH acids (pK_a 25–26 in water) in the absence of a catalyst under fairly mild conditions.

The yield of (adamantan-1-yl)acetonitrile (**IIIa**) was 30%, while the yield of 2-(adamantan-1-yl)-3-methylbutanenitrile (**IIIe**) was 92%. Relatively low yield of **IIIa** as compared to the addition products of some β-dicarbonyl compounds [13] or ketones [14] to compound **Ia** under analogous temperature conditions is likely to be determined by the lower CH acidity of acetonitrile. The direct dependence of the reactivity of nitriles on their CH acidity may be rationalized assuming ionic mechanism of the reaction, where the rate of addition is directly related to the rate of deprotonation of CH acid. The addition of **Ia** to high-boiling nitriles at 100–110°C was complete in 4–5 h with high yields (80–92%).

The low yield of (adamantan-1-yl)acetonitrile (**IIIa**) (pK_a of acetonitrile 25) compared to (adamantan-1-yl)phenylacetonitrile **IIIf** (pK_a of **IIf** 21.9 [17]), other conditions being similar, is also explained by the lower CH acidity of acetonitrile. Reduction of the yield in going from R^4 = Ph (**IIf**) to R^4 = 1-naphthyl (**IIg**) is likely to be determined by steric effect of bulkier α-naphthyl group which appreciably hinders attack on molecule **Ia**. No products of addition to the aromatic fragments of nitriles **IIf** and **IIg** were detected. Introduction of methyl groups into 1,3-dehydroadamantane molecule did not affect the reactivity of [3.3.1]propellanes **Ib** and **Ic** toward nitriles to an appreciable extent. Their reactions with nitriles **IIh** and **IIe** afforded 77–79% of α-adamantyl-substituted nitriles **IIIi** and **IIIj**.

The structure of compounds **IIIa**–**IIIj** was confirmed by their IR, ^{1}H NMR, and mass spectra. In the IR spectra of **IIIa**–**IIIj** the C≡N stretching vibration band was observed in the region 2232–2268 cm^{-1}. Protons in the adamantane fragment resonated in the ^{1}H NMR spectra as several signals at about δ 1.64 and 2.03 ppm, the α-CH signal appeared at δ 2.5 ppm, and the α-CH signal of **IIIf** was a singlet at δ 3.90 ppm.

Thus, the proposed procedure for the synthesis of adamantyl-containing nitriles from propellanes **Ia**–**Ic** is promising, for it ensures preparation of difficultly accessible branched nitriles with complex structure in one step and with high yields.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Varian Mercury-300 (300 MHz) and Bruker DRX-500 (500 MHz) spectrometers using hexamethyldisiloxane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS-30 instrument.

(Adamantan-1-yl)acetonitrile (IIIa). A solution of 2 g (0.015 mol) of 1,3-dehydroadamantane (**Ia**) in 20 mL of anhydrous diethyl ether was added to 6 g (0.14 mol) of anhydrous acetonitrile (**IIa**), the solvent was distilled off, and the mixture was heated for 8 h at 80–82°C. Excess acetonitrile was distilled off, and the residue was distilled under reduced pressure. Yield 0.8 g (0.0046 mol, 31%), mp 76–78°C; published data [5]: mp 78°C.

Compounds **IIIb**–**IIIj** were synthesized in a similar way.

2-(Adamantan-1-yl)propanenitrile (IIIb) was synthesized from 6 g (0.11 mol) of anhydrous propionitrile (**IIb**) and 2 g (0.015 mol) of propellane **Ia**; the mixture was heated at 95–97°C. Yield 2.3 g (0.014 mol, 82%), bp 120–122°C (2 mm). ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.20 t (3H, CH_3, J = 7.6 Hz), 1.52–2.10 m (15H, Ad), 2.31 s (1H, CH). Found, %:

C 82.44; H 9.98; N 7.21. $C_{13}H_{19}N$. Calculated, %: C 82.48; H 10.12; N 7.40.

2-(Adamantan-1-yl)butanenitrile (IIIc) was synthesized from 30 g (0.15 mol) of butyronitrile (**IIc** and 2 g (0.015 mol) of compound **Ia**; the mixture was heated at 118–120°C. Yield 2.66 g (0.013 mol, 89%), mp 51–53°C; published data [9]: mp 53–54°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.05 t (3H, CH_3, J = 8.7 Hz), 1.46–2.05 m (17H, Ad, CH_2), 2.40 s (1H, CH). Found, %: C 82.73; H 10.43; N 6.84. $C_{14}H_{21}N$. Calculated, %: C 82.70; H 10.41; N 6.89.

2-(Adamantan-1-yl)pentanenitrile (IIId) was synthesized from 12 g (0.15 mol) of valeronitrile (**IId**) and 2 g (0.015 mol) of compound **Ia**; the mixture was heated at 110–115°C. Yield 2.66 g (0.012 mol, 80%), bp 154–156°C (5 mm), mp 41–42°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.92 t (3H, CH_3, J = 14.5 Hz), 1.37–1.70 m (16H, Ad, CH_2), 12.03 s (3H, Ad), 2.39 s (1H, CH). Found, %: C 82.83; H 10.73; N 6.44. $C_{15}H_{23}N$. Calculated, %: C 82.89; H 10.67; N 6.44.

2-(Adamantan-1-yl)-3-methylbutanenitrile (IIIe) was synthesized from 5 g (0.06 mol) of isovaleronitrile (**IIe**) and 2 g (0.015 mol) of compound **Ia**; the mixture was heated at 130–140°C. Yield 2.27 g (0.014 mol, 92%), bp 151–153°C (5 mm), mp 38–39°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.80 t (6H, CH_3, J = 14.9 Hz), 1.50–2.40 m (16H, Ad, CH), 2.33 d (1H, CHCN, J = 15.8 Hz). Found, %: C 82.82; H 10.51; N 6.67. $C_{15}H_{23}N$. Calculated, %: C 82.89; H 10.67; N 6.44.

2-(Adamantan-1-yl)-2-phenylacetonitrile (IIIf) was synthesized from 10 g (0.085 mol) of phenylacetonitrile (**IIf**) and 4 g (0.03 mol) of compound **Ia**; the mixture was heated for 4 h at 70–80°C. Yield 6.77 g (0.027 mol, 90%), bp 173–175°C (3 mm), mp 118–120°C. ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.49–1.64 m (12H, Ad), 1.95 s (3H, Ad), 3.90 s (1H, CH), 7.20–7.40 m (5H, C_6H_5). Mass spectrum, m/z (I_{rel}, %): 251 $[M]^+$ (4), 176 (8), 167 (1), 135 $[Ad]^+$ (100), 107 (9), 93 (15), 79 (19). Found, %: C 85.94; H 8.35; N 5.61. $C_{18}H_{21}N$. Calculated, %: C 86.01; H 8.42; N 5.57. M 251.37.

2-(Adamantan-1-yl)-2-(naphthalen-1-yl)acetonitrile (IIIg) was synthesized from 10 g (0.06 mol) of (naphthalen-1-yl)acetonitrile (**IIg**) and 2 g (0.015 mol) of compound **Ia**; the mixture was heated for 4 h at 60–80°C; after vacuum distillation, the product was recrystallized from propan-2-ol. Yield 2.9 g (0.01 mol, 65%), bp 240–242°C (3 mm), mp 128–130°C. ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.64–2.36 m (15H, Ad), 4.15 s (1H, CH), 7.90–8.60 m (7H, $C_{10}H_7$). Found, %: C 87.44; H 7.95; N 4.61. $C_{22}H_{23}N$. Calculated, %: C 87.66; H 7.69; N 4.65.

2-(Adamantan-1-yl)-2-methylpropanenitrile (IIIh) was synthesized from 10 g (0.145 mol) of isobutyronitrile (**IIh**) and 2 g (0.015 mol) of compound **Ia**; the mixture was heated at 105–110°C. Yield 2.55 g (0.013 mol, 85%), bp 116–118°C (3 mm), mp 84–85°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.02 t (6H, CH_3, J = 12.6 Hz), 1.89–2.35 m (15H, Ad). Found, %: C 82.65; H 10.26; N 6.94. $C_{14}H_{21}N$. Calculated, %: C 82.70; H 10.41; N 6.89.

2-(3-Methyladamantan-1-yl)-2-methylpropanenitrile (IIIi) was synthesized from 10 g (0.145 mol) of nitrile **IIh** and 2.7 g (0.018 mol) of compound **Ib**; the mixture was heated at 100–105°C. Yield 3.4 g (0.014 mol, 79%), bp 154–156°C (5 mm), mp 75–77°C. ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.80 s (3H, CH_3), 1.19 s (6H, CH_3), 1.28–1.62 m (12H, Ad), 2.05 s (2H, Ad). Found, %: C 82.92; H 10.62; N 6.46. $C_{15}H_{23}N$. Calculated, %: C 82.89; H 10.67; N 6.44.

2-(3,5-Dimethyladamantan-1-yl)-3-methylbutanenitrile (IIIj) was synthesized from 10 g (0.121 mol) of nitrile **IIe**) and 3 g (0.018 mol) of compound **Ic**; the mixture was heated at 105–110°C. Yield 3.4 g (0.014 mol, 77%), bp 160–161°C (5 mm), mp 44–46°C. ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.80 s (6H, CH_3), 1.05–1.12 m (6H, CH_3), 1.25–2.39 m (12H, Ad), 1.45 s (1H, Ad), 1.73 m (1H, CH), 2.13 s (1H, CHCN). Found, %: C 83.13; H 11.11; N 5.76. $C_{17}H_{27}N$. Calculated, %: C 83.20; H 11.09; N 5.71.

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