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One-Stage Synthesis of Adamantyl-Containing α-Aminonitriles

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Abstract—Reactions of 2-adamantan-2-one, acetone cyanohydrin, and amine lead to the formation of substituted 2-amino-2-cyanoadamantanes. The reaction is of a general character as has been proved by examples on a series of ketones and amines and it proceeds through the formation from the acetone cyanohydrin and amines of 2-amino-2-cyanopropane derivatives reacting further with the carbonyl compounds.

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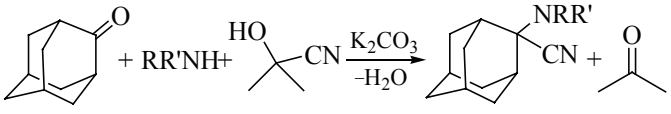
The research in the field of synthesis and studies of the biological activity of adamantine derivatives substituted in the position *2* are topical for these substances exhibt various kinds of biological action and some among them are used as drugs [1]. The search for the routes to the synthesis of new adamantane amino derivatives continues up till now. In particular, recently published results of investigations on the biological activity of hydroxyaminoalkyladamantanes substituted in the position *2* of the adamantly group, structural analogs of "rimantadine" pharmaceutical, showed their significant antiviral and other types of activity [2, 3]. Initial compounds for the synthesis of aminomethyl derivatives are the corresponding adamantyl-containing α-aminonitriles. The traditional methods of α-aminonitriles synthesis consist in the reaction of a carbonyl compound, amine, and hydrogen cyanide. As a source of the latter alkali metal cyanides [4] or silyl cyanide [5] are commonly used. The obvious disadvantage of this method is the application of highly toxic or fairly inaccessible reagents.

We formerly have developed a procedure for the preparation of adamantyl-containing aminonitriles underlain by the reaction of 2-cyano-2-hydroxyadamantane (adamantanone cyanohydrin) with ammonia, primary and secondary amines, and also with hydrazines [6]. For the synthesis of adamantyl-containing α-aminonitriles from low basic amines of aniline series another route was developed consisting in the reaction of the corresponding adamantylenimines with acetone cyanohydrin [7]. It was presumed that the one-stage synthesis of 2-amino-2-cyanoadamantane derivatives by the direct reaction of an amine, adamantan-2-one (**I**), and acetone cyanohydrin in suitable yields was impossible due to the side reaction of amine with acetone cyanohydrin with the formation of the respective 2-amino-2-cyanopropane derivatives [8]. A published information exists on the reactions of carbonyl compounds (benzaldehyde, valeraldehyde, cyclohexanone) with amines (benzylamine, ethylenediamine, piperidine, morpholine) and acetone cyanohydrin in water or organic solvent with product yields from 13 to 99% [9]. However the information on the possible synthesis with the use of ketones of polycyclic structure is absent.

We found that adamantyl-containing aminonitriles formed in yields 65–80% at mixing ketone **I**, the corresponding amine, and acetone cyanohydrin at 100–120°C without solvent in the presence of catalytic quantity of potassium carbonate. In the course of the reaction the calculated amount of acetone and water was distilled off.

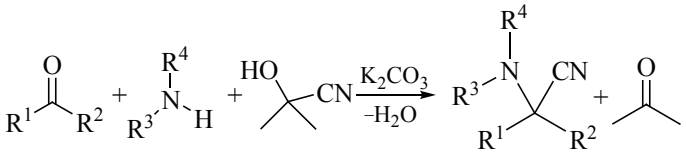


I **IIa–IIe**

R = H, R' = Cy (**a**), CH_2CH_2OH (**b**), Ph (**c**); R,R' = $(CH_2)_5$ (**d**), $(CH_2)_2O(CH_2)_2$ (**e**).

This reaction is suitable for the preparation both of

alkyl- and arylaminonitriles with an adamantyl moiety. The developed synthetic procedure for preparation of compounds **IIa–IIe** is convenient for it is a one-stage process, requires the use of slight excess of acetone cyanohydrin and amine, no solvent, and it provides a possibility to carry out one-pot process and to distill the product in the same reactor. We demonstrated that the reaction under study can be applied to the preparation of a wide range of α-aminonitriles by involving in the syntesis various initial ketones. In particular, the general character of the developed synthetic method was confirmed by the examples of reactions with methyl isobutyl ketone, cyclopentanone, and acetophenone, not described before [9].

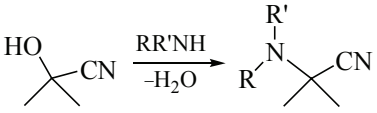


IIIa–IIIe

$R^1,R^2 = (CH_2)_4$, $R^3,R^4 = (CH_2)_2O(CH_2)_2$ (**a**); R^1 = Me, R^2 = *i*-Bu, $R^3,R^4 = (CH_2)_2O(CH_2)_2$ (**b**); R^1 = Me, R^2 = Ph, $R^3,R^4 = (CH_2)_5$ (**c**), $(CH_2)_2O(CH_2)_2$ (**d**); $R^1,R^2 = (CH_2)_4$, R^3 = H, R^4 = Ph (**e**).

The structure of compounds **IIIa, IIIb, IIId, IIIe** was confirmed by ^{1}H NMR spectra. In particular, the occurrence of this reaction is confirmed by the appearance of the signals of the protons from the introduced alkyl groups, and also of the protons of methine (methylene) groups at the nitrogen atom in the region 2.5–3.5 ppm. The properties of known compounds were in agreement with the published data [8].

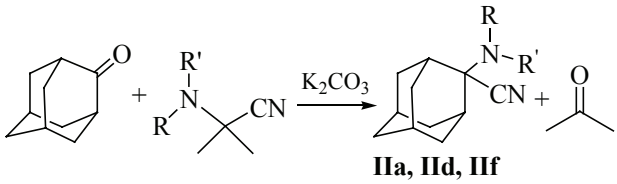
In [9] in various conditions the other products were detected: 2-amino-2-cyanopropane derivatives, imines, cyanohydrins of initial ketones. However, the optimum conditions of the formation of the target α-aminonitriles were not established. Aiming at discovering the mechanism of nitriles **IIa–IIe** formation we examined the possibility of proceeding of the presumed stage of the above reaction, namely, the reaction of ketone **I** with 2-amino-2-cyanopropane derivatives. To this end we synthesized α-aminonitriles **IVa–IVd** by the reaction between acetone cyanohydrin and some amines.



IVa–IVd

R,R' = piperidino (**a**), moppholino (**b**); R = H, R' = Cy (**c**), Bn (**d**).

Compounds **IVa–IVd** were purified by distillation, their structure was confirmed by ^{1}H NMR spectra, the properties of known compounds were in agreement with the published data [8]. The reaction of α-aminonitriles **IVa–IVd** with adamantanone (**I**) was carried out at a small excess of nitriles at heating in the presence of potassium carbonate. In the course of the reaction an equivalent amount of acetone was isolated.



IIa, IId, IIf

R = H, R' = Cy (a), R,R' = $(CH_2)_5$ (**d**); R = H, R'= CH_2Ph (**f**).

It was found that this reaction led to the formation of target nitriles **IIa, IId, IIf** in high yields. A similar reaction was described in [10] by an example of cyclohexanone and some aldehydes. At establishing its general character it can be regarded as a new modification of Strecker reaction.

The developed synthetic method can be used for the preparation of a series of 2-alkyl(aryl)amino-2-cyanoO-adamantanes whose hydrogenation can provide unsymmetrical amines containing 2,2-disubstituted adamantyl fragment, and the reaction with Grignard reagents can afford amino-containing adamantylated ketones interesting as potential biologically active substances.

EXPERIMENTAL

^{1}H NMR spectra of compounds obtained were registered on a spectrometer Varian Mercury-300 (300 MHz) in tetrachloromethane, internal references HMDS or TMS.

2-Cyano-2-cyclohexylaminoadamantane (IIa). *a*. A mixture of 5 g (0.033 mol) of 2-adamantanone (**I**), 4.7 g (0.055 mol) of acetone cyanohydrin, 5 g (0.05 mol) of cyclohexylamine, and 0.1 g of potassium carbonate were heated for 2 h in a round bottom flask equipped with a Liebig condenser. During the reaction at 70–75°C equimolar amount of water and acetone was distilled off. Then the residue was distilled in a vacuum from the same flask collecting the fraction of bp 224–227°C (20 mm Hg). Yield 6.9 g (81%), mp 93–94°C (mp 93–94°C [6]). ^{1}H NMR spectrum, δ, ppm: 0.68 s (1H, NH), 1.05–2.25 m (14H, 2,2-Ad; 10H, Cy), 2.62 m (1H, CHN).

b. A mixture of 3 g (0.02 mol) of compound **I**, 3.7 g

(0.022 mol) of 2-cyano-2-cyclohexylaminopropane, and 0.1 g of potassium carbonate were heated in a round bottom flask equipped with a Liebig condenser at 80–100°C within 30–40 min; therewith equimolar quantity of acetone was distilled off. The residue was distilled in a vacuum. Yield 3.5 g (67%), bp 225–28°C (20 mm Hg), mp 93–94°C (mp 93–94°C [6]).

Compounds **IIb–IIf, IIIa–IIIe** were obtained similarly.

2-(β-Hydroxyethylamino)-2-cyanoadamantane (IIb) was obtained along method *a* from 5 g (0.033 mol) of compound **I**, 4 g (0.047 mol) of acetone cyanohydrin, 2.6 g (0.043 mol) of 2-aminoethanol, and 0.1 g of potassium carbonate. Yield 5.7 g (79%), oily substance, bp 190–193°C (20 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.20 s (1H, NH), 1.43–2.24 m (14H, 2,2-Ad), 2.68 s (1H, OH), 3.01 t (2H, CH_2N), 3.59 t (2H, CH_2O). Found, %: C 70.88; H 9.07; N 12.69. $C_{13}H_{20}N_2O$. Calculated, %: C 70.91; H 9.09; N 12.73.

2-Phenylamino-2-cyanoadamantane (IIc) was obtained along method *a* from 5 g (0.033 mol) of compound **I**, 3.5 g (0.038 mol) of aniline, 4.3 g (0.05 mol) of acetone cyanohydrin, and 0.1 g of potassium carbonate. Yield 6.3 g (75%), mp 171–173°C (172–173°C [6]). ^{1}H NMR spectrum, δ, ppm: 1.53–2.30 m (14H, Ad), 3.48 s (1H, NH), 6.74–6.77 m (3H, Ph), 7.05–7.12 m (2H, Ph).

2-Piperidino-2-cyanoadamantane (IId). *a.* From 5 g (0.033 mol) of compound **I**, 4.3 g (0.05 mol) of piperidine, 5.1 g (0.06 mol) of acetone cyanohydrin, and 0.1 g of potassium carbonate was obtained 6.4 g (80%) of compound **IId**, bp 210–212°C (18 mm Hg), mp 77–78°C (mp 77–78°C [6]). ^{1}H NMR spectrum, δ, ppm: 1.35–2.32 m (20H, 2,2-Ad + 3 CH_2), 2.60 br.s (4H, $2CH_2N$).

***b*.** From 4 g (0.027 mol) of compound **I**, 5 g (0.032 mol) of 2-piperidino-2-cyanopropane, and 0.2 g of potassium carbonate was obtained 5.1 g (78%) of compound **IId**, mp 78–79°C, bp 211–213°C (18 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.35–2.34 m (20H, 2,2-Ad + 3 CH_2), 2.60 br.s (4H, $2CH_2N$).

2-Morpholino-2-cyanoadamantane (IIe). *a*. From 5 g (0.033 mol) of compound **I**, 3.5 g (0.04 mol) of morpholine, 4.3 g (0.05 mol) of acetone cyanohydrin, and 0.1 g of potassium carbonate was obtained 6.4 g (79%) of compound **IIe**, bp 170–180°C (15 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.38–2.13 m (14H, 2,2-Ad), 2.56 t [4H, $(CH_2)_2N$], 3.72 t [4H, $(CH_2)_2O$]. Found, %: C 73.20; H 8.92; N 11.42. $C_{15}H_{22}N_2O$. Calculated, %: C 73.17; H 8.94; N 11.38.

2-Benzylamino-2-cyanoadamantane (IIf). *b*. From 2 g (0.0133 mol) of adamantan-2-one and 2.4 g (0.0138 mol) of 2-benzylamino-2-cyanopropane was obtained 2.9 g (81%) of compound **IIf**, bp 215–217°C (20 mm Hg), mp 103–104°C (mp 104– 105°C [6]). ^{1}H NMR spectrum, δ, ppm: 1.60–1.85 m (12H, Ad), 2.52 s (1H, Ad), 3.01 s (1H, Ad), 4.38 s (2H, CH_2), 7.03–7.24 m (5H, Ph).

2-Morpholino-2-cyanocyclopentane (IIIa). *a***.** From 4.2 g (0.05 mol) of cyclopentanone, 5 g (0.058 mol) of morpholine, and 5 g (0.059 mol) of acetone cyanohydrin was obtained 4.86 g (54%) of compound **IIIa**, bp 145–147°C (20 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.64–1.69 m (2H, CH_2), 1.81 m (4H, $2CH_2$), 2.11 m (2H, CH_2), 2.48 t [4H, $(CH_2)_2N$], 3.56 t [4H, $(CH_2)_2O$]. Found, %: C 66.68; H 8.99; N 15.52. $C_{10}H_{16}N_2O$. Calculated, %: C 66.63; H 8.95; N 15.54.

b. From 4.2 g (0.05 mol) of cyclopentanone and 8.5 g (0.055 mol) of 2-morpholino-2-cyanopropane was obtained 5.3 g (69%) of compound **IIIa**, bp 152–154°C (20 mm Hg).

4-Methyl-2-morpholino-2-cyanopentane (IIIb). *a.* From 5.0 g (0.05 mol) of methyl isobutyl ketone, 5 g (0.058 mol) of morpholine, and 5 g (0.059 mol) of acetone cyanohydrin was obtained 6.56 g (68%) of compound **IIIb**, bp 153–154°C (20 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.67 t (3H, CH_3), 1.07 t (6H, $2CH_3$), 1.30 d (2H, CH_2), 1.55 m (1H, CH), 2.18 t (4H, CH_2N), 3.27 t (4H, CH_2O). Found, %: C 67.25; H 10.24; N 11.32. $C_{11}H_{20}N_2O$. Calculated, %: C 67.31; H 10.27; N 14.27.

b. From 5.0 g (0.05 mol) of methyl isobutyl ketone and 8.5 g (0.055 mol) of 2-morpholino-2-cyanopropane was obtained 6.4 g (65%) of compound **IIIb**, bp 152–154°C (20 mm Hg).

2-Piperidino-2-phenylpropionitrile (IIIc). *a*. From 4.8 g (0.04 mol) of acetophenone, 5.2 g (0.06 mol) of piperidine, 6 g (0.07 mol) of acetone cyanohydrin was obtained 5.2 g (0.024 mol, 60%) of compound **IIIc**, bp 159–161°C (20 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.39 s (3H, CH_3), 1.40–1.48 m (6H, $3CH_2$), 2.43 t (4H, CH_2N), 7.35 t (2H, Ph), 7.42 t (1H, Ph), 7.82 d (2H, Ph). Found, %: C 78.50; H 8.51; N 12.99. $C_{14}H_{18}N_2$. Calculated, %: C 78.46; H 8.47; N 13.07.

1-Morpholino-1-cyanocyclohexane (IIId). *b.* From 4.9 g (0.05 mol) of cyclohexanone and 9.1 g (0.06 mol)

of 2-morpholino-2-cyanopropane was obtained 6.0 g (88%) of compound **IIId**, bp 149–150°C (20 mm Hg) {bp 160–162°C (18 mm Hg) [11]}. ^{1}H NMR spectrum, δ, ppm: 1.20–1.61 m (6H, $3CH_2$), 1.70 m (2H, CH_2), 1.99 m (2H, CH_2), 2.48 t (4H, CH_2N), 3.58 t (4H, CH_2O).

1-Phenylamino-1-cyanocyclohexane (IIIe). *b*. From 2 g (0.02 mol) of cyclohexanone, 3.2 g (0.02 mol) of 2-phenylamino-2-cyanopropane and 0.05 g of potassium carbonate was obtained 2.76 g (69%) of compound **IIIe**, bp 166–168°C (15 mm Hg), mp 66–68°C (mp 71–75°C [12]). ^{1}H NMR spectrum, δ, ppm: 1.55 br.s (4H, $2CH_2$), 1.74 m (2H, CH_2), 2.05–2.15 m (2H, CH_2), 2.30–2.32 m (2H, CH_2), 3.78 br.s (1H, NH), 6.52 d (2H, Ph), 6.85 t (1H, Ph), 7.08 t (2H, Ph).

2-Piperidino-2-cyanopropane (IVa). A mixture of 8.5 g (0.1 mol) of piperidine and 8.5 g (0.1 mol) of acetone cyanohydrin was heated for 1 h at 100°C; after that the reaction mixture separated in two phases. The upper organic layer was distilled in a vacuum collecting the fraction of bp 114–115°C (20 mm Hg), {bp 93.5°C (6 mm Hg) [11]}. Yield 9.9 g (65%). ^{1}H NMR spectrum, δ, ppm: 1.33–1.47 m (2H, CH_2), 1.40 s (6H, $2CH_3$), 1.52 m (4H, $2CH_2$), 2.49 t [4H, $(CH_2)_2N$].

Compounds **IVb–IVd** were similarly obtained.

2-Morpholino-2-cyanopropane (IVb) was obtained from 8.6 g (0.1 mol) of morpholine and 8.5 g (0.1 mol) of acetone cyanohydrin. Yield 9.6 g (76%), bp 116–117°C (15 mm Hg) {bp 129–130°C (5 mm Hg) [11]}. ^{1}H NMR spectrum, δ, ppm: 1.38 s (6H, $2CH_3$), 2.49 t [4H, $(CH_2)_2N$], 3.57 t [4H, $(CH_2)_2O$].

2-Cyano-2-cyclohexylaminopropane (IVc) was obtained from 15 g (0.15 mol) of cyclohexylamine and 12 g (0.14 mol) of acetone cyanohydrin. Yield 17.0 g (73%), white crystals, mp 47–50°C, bp 119–120°C (20 mm Hg) {mp 56°C, bp 68°C (2 mm Hg) [11]}. ^{1}H NMR spectrum, δ, ppm: 1.03–1.15 m (4H, 2 CH_2), 1.21–1.32 m (2H, CH_2), 1.35 C (6H, 2 CH_3), 1.52 d (1H, NH), 1.64–1.71 m (2H, CH_2), 1.82–1.84 m (2H, CH_2), 2.58 m (1H, CHN).

2-Benzylamino-2-cyanopropane (IVd) was obtained from 5 g (0.047 mol) benzylamine and 5 g (0.059 mol) of acetone cyanohydrin. Yield 7.5 g (91%), bp 145–146°C (20 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.33 s (6H, $2CH_3$), 3.72 s (2H, CH_2), 7.04–7.22 m (5H, Ph). Found, %: C 75.78; H 8.12; N 16.10. $C_{11}H_{14}N_2$. Calculated, %: C 75.82; H 8.10; N 16.08.

REFERENCES

1. Morozov, I.S., Petrov, V.I., and Sergeeva, S.A., *Farmakologiya adamantanov* (Pharmacology of Adamantanes), Volgograd: Izd. Volgogr. Med. Akademii, 2001.
2. Zoidis, G., Kolocouris, N., Kelly, J.M., Prathalingam, S.R., Naesens, L., and Clercq, E.D., *Eur. J. Med. Chem*., 2010, vol. 45, p. 5022.
3. Fytas, Ch., Zoidis, G., Tzoutzas, N., Taylor, M.C., Fytas, G., and Kelly, J.M*., J. Med. Chem*., 2011, vol. 54, p. 5250.
4. Orere, D.M. and Reese, C.B., *J. Chem. Soc*., 1977, p. 280.
5. Evans, D.A., Truesdale, L.K., and Carroll, G.L., *J. Chem. Soc*., 1973, p. 55.
6. Popov, Yu.V., Mokhov, V.M., Tankabekyan, N.A., and Safronova, O.Yu., *Zh. Prikl. Khim*., 2012, vol. 85, p. 1474.
7. Popov, Yu.V., Mokhov, V.M., and Zimina, O.Yu., *Izv. Volgogr. Gos. Tekhn. Iniv*., 2008, vol. 5, p. 46.
8. Bucherer, H.Th. and Barsh, H., *J. Prakt. Chem.,* 1934, p. 151.
9. Galletti, P., Pori, M., and Giacomini, D., *Eur. J. Org. Chem.,* 2011, vols. 20–21, p. 3896.
10. Yanovskaya, L.A., Shachidayatov, Ch., Prokofiev, E.P., Andrianova, G.M., and Kucherov, V.F., *Tetrahedron*, 1968, vol. 24, p. 4477.
11. Shakhidayatov, Kh., *Zh. Org. Khim*., 1973, vol. 9, p. 1373.
12. Walter, V. and Hubner, U.. *J. Prakt. Chem.,* 1916, vol. 93, p. 119.