ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 9, pp. 1532–1539. © Pleiades Publishing, Ltd., 2020.
Russian Text © The Author(s), 2020, published in Zhurnal Organicheskoi Khimii, 2020, Vol. 56, No. 9, pp. 1353–1362.

Selective Nitroxylation of Adamantane Derivatives in the System Nitric Acid–Acetic Anhydride

Yu. N. Klimochkin[a], E. A. Ivleva[a,*], and I. K. Moiseev[†a]

[a] *Samara State Technical University, Samara, 443100 Russia*

**e-mail: elena.a.ivleva@yandex.com*

Received May 15, 2020; revised May 26, 2020; accepted May 28, 2020

Abstract—A number of new nitroxyadamantanes have been synthesized by nitroxylation of the corresponding substrates with nitric acid in acetic anhydride. High electrophilicity and reduced acidity of the system HNO_3–Ac_2O increases the stability of nitrates and significantly decreases the probability of formation of alcohols. In some cases, nitrolysis and oxidation of functional groups in the substrate are observed.

Keywords: nitroxylation, fuming nitric acid, acetic anhydride, nitrolysis, nitrates, adamantane

DOI: 10.1134/S1070428020090055

Functional adamantane derivatives are basic structural units of physiologically active compounds and advanced materials [1–12]. Over the past decades, the problem of activation of C–H bonds in cage compounds has been important [13] in view of searching for readily accessible starting materials for the synthesis of compounds with a high degree of molecular complexity and structural diversity. Nitroxy derivatives of the adamantane series are among such functional derivatives. They are used to obtain carboxylic acids by the Koch–Haaf [14, 15] and Bott reactions [16], 1-adamantylarenes by the Friedel–Crafts reaction [17, 18], alcohols [19, 20], and other compounds containing an adamantane fragment [21–25]. Nitroxyadamantanes are intermediate products in the synthesis of cage alcohols [26] and amines [27, 28]. Some adamantane derivatives with a nitroxy group in the bridgehead position exhibit biological activity [29] or are precursors to biologically active compounds [30–33]. Polynitroxyadamantanes have found application as a new class of energetic materials [34–36].

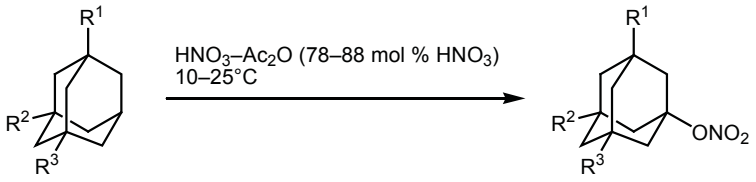
The main procedure for the introduction of a nitroxy group into the bridgehead position of adamantane molecule is based on nitroxylation with fuming nitric acid [37–41]. However, side formation of alcohols in this reaction inevitably reduces the yield of nitroxy derivatives. Furthermore, this method is inapplicable to a number of substrates in which functional groups are unstable toward nitric acid. Therefore, there is a necessity of searching for a more selective nitroxylation system which could provide the possibility of not only extending the series of available nitroxyadamantane derivatives with various substituents but also improving the yield of already known compounds due to minimization of side processes.

The system nitric acid–acetic anhydride meets the above requirements. Its efficiency is determined by the following two factors. First, the system HNO_3–Ac_2O is characterized by a considerably lower protonating power and almost zero equilibrium concentration of water, so that the fraction of alcohols in the products is low. Second, when the system contains more than 50 mol % of nitric acid, the concentration of acetyl nitrate decreases, and highly electrophilic nitric anhydride is formed in the reaction mixture; at an acetic anhydride concentration of lower than 18 mol %, the equilibrium concentration of nitronium cations sharply increases [42], and fast nitroxylation is observed even with substrates containing electron-withdrawing substituents.

Several examples of successful application of the system HNO_3–Ac_2O for the synthesis of some nitroxy derivatives of polycyclic hydrocarbons have been reported [43–45]. In some cases, reactions of the same substrate with nitric acid and its mixture with acetic anhydride gave different products. In particular, 2-mono- and 2,2-disubstituted adamantane derivatives reacted with 100% HNO_3 to give adamantan-2-one regardless of the substituent nature, whereas no nitrolysis of functional groups was observed in HNO_3–Ac_2O [46, 47]. In the present work we extended the scope of application and experimentally proved selec-

† Deceased.

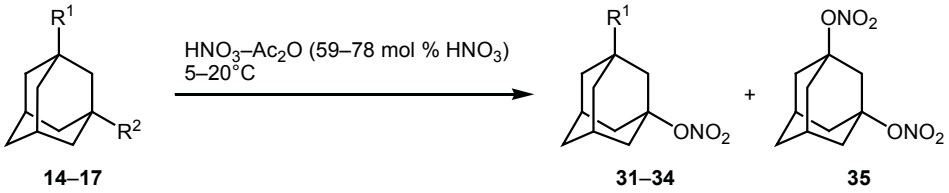
Scheme 1.



1–13 **18–30**

1, R^1 = MeCH(OH), $R^2 = R^3$ = H; **2**, $R^1 = R^2$ = $HOCH_2$, R^3 = H; **3**, **20**, R^1 = Ac, $R^2 = R^3$ = H; **4**, **21**, R1 = EtC(O), $R^2 = R^3$ = H; **5**, **22**, R1 = *i*-PrC(O), $R^2 = R^3$ = H; **6**, **23**, R^1 = HOC(O), $R^2 = R^3$ = H; **7**, **24**, R^1 = HOC(O), R^2 = Me, R^3 = H; **8**, **25**, R^1 = HOC(O), R^2 = Et, R^3 = H; **9**, **26**, R^1 = HOC(O), $R^2 = R^3$ = Me; **10**, **27**, R^1 = $HOC(O)CH_2$, $R^2 = R^3$ = H; **11**, **28**, R^1 = O_2N, $R^2 = R^3$ = Me; **12**, **29**, R^1 = N≡C, $R^2 = R^3$ = H; **13**, **30**, R^1 = AcNH, $R^2 = R^3$ = H; **18**, R^1 = $MeCH(ONO_2)$, $R^2 = R^3$ = H; **19**, $R^1 = R^2$ = $MeOC(O)CH_2$, R^3 = H.

Scheme 2.



14–17 **31–34** **35**

14, R^1 = H, R^2 = F; **31**, R^1 = H; **15**, $R^1 = R^2$ = F; **32**, R^1 = F; **16**, $R^1 = R^2$ = Cl; **33**, R^1 = Cl; **17**, $R^1 = R^2$ = Br; **34**, R^1 = Br.

tivity of the system HNO_3–Ac_2O by using a wide series of adamantane substrates containing electron-withdrawing substituents in the bridgehead positions.

The substrates were alcohols **1** and **2**, ketones **3**–**5**, carboxylic acids **6**–**10**, nitrogen-containing compounds **11**–**13**, and halogen derivatives **14**–**17**. The reactions were carried out in a mixture of nitric acid and acetic anhydride containing 59–78 mol % of HNO_3 at 5–25°C (Schemes 1, 2). The detailed conditions of the synthesis of nitroxy derivatives **18**–**34** are collected in Table 1. In

Table 1. Reaction of adamantane derivatives **1**–**4** and **6**–**17** with nitric acid in acetic anhydride

Substrate no.	HNO_3, equiv	Concentration of HNO_3 in a HNO_3–Ac_2O mixture, mol %	Temperature, °C	Reaction time, h	Yield, %
1	30	78	10	2	84[a]
2	90	78	20	15	86
3	40	78	10	2	67
4	40	78	10	2	87
6	40	88	20	5	94
7	45	88	25	5	91
8	50	88	20	5	87
9	60	88	25	6	89
10	40	78	20	1	81
11	25	78	10	3	43
12	40	78	10	4	47
13	25	78	10	3	42
14	25	78	10	3	57[b]
15	20	78	20	1	59[c]
16	25	78	5	2	46[d]
17	10	59	5	1	21[e]

[a] Compound **20** (7%) was also isolated.
[b] Compound **35** (33%) was also isolated.
[c] Compound **35** (12%) was also isolated.
[d] Compound **35** (23%) was also isolated.
[e] Compound **35** (22%) was also isolated.

Table 2. Reaction of adamantane derivatives **1**, **3**–**5**, **7**–**9**, and **13** with nitric acid

Substrate no.	HNO_3, equiv	Temperature, °C	Reaction time, h	Product	Yield, %
1	40	–5	1	**3** **23**	85 7
3	70	20	3	**23**	87
4	40	20	3	**21** **23**	46 22
5	40	20	3	**22**	92
7	70	20	2	**24**	70
8	70	20	2	**25**	68
9	70	20	2	**26**	67
13	50	15	5	**30**	66

parallel, compounds **1**, **3**–**5**, **7**–**9**, and **13** were reacted with nitric acid in the absence of acetic anhydride (for details, see Table 2).

In fact, 1-(adamantan-1-yl)ethanol (**1**) and (adamantane-1,3-diyl)dimethanol (**2**) differently reacted with nitric acid and its mixture with acetic anhydride. The reaction of **1** with nitric acid involved mainly oxidation to 1-acetyladamantane (**3**), and minor 3-nitroxyadamantane-1-carboxylic acid (**23**) was also isolated (yield 7%). Nitroxy derivative **18** was formed in the reaction of **1** with HNO_3–Ac_2O; however, oxidation processes could not be suppressed completely. Diol **2** in the system HNO_3–Ac_2O was converted to 3,5-bis(acetoxymethyl)adamantan-1-yl nitrate (**19**), whereas only 1,3-bis(nitroxymethyl)adamantane was formed in 98% HNO_3, in keeping with the data reported previously [48].

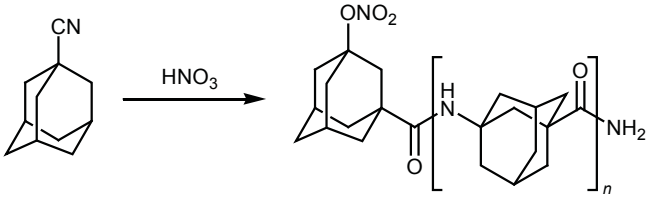
The nature of products formed in the reactions of adamantyl alkyl ketones **3**–**5** with nitric acid is determined by the relative rates of nitroxylation and enolization of initial ketone. The latter process is the limiting step of oxidation of ketones, and its rate increases with rise in the acidity of the medium [49]. Fairly readily enolizable 1-acetyladamantane (**3**) in nitric acid is completely converted to nitroxy carboxylic acid **23**, and only the use of HNO_3–Ac_2O makes it possible to obtain nitroxy ketone **20** in 67% yield. 1-Adamantyl ethyl ketone (**4**) reacted with HNO_3 to give a mixture of nitroxylation and oxidation products **21** and **23**, respectively. No oxidation occurred in the system HNO_3–Ac_2O, and keto nitrate **21** was obtained in 87% yield. It should be noted that 1-adamantyl isopropyl ketone (**5**) is quite stable in 100% HNO_3 and is smoothly nitroxylated to keto nitrate **22**. Such effect of the substrate structure on the reaction direction suggests increased steric hindrances to enolization in ketones **4** and **5**.

Carboxylic acids **6**–**10** were converted into the corresponding nitroxy derivatives **23**–**27** in both nitric acid and its mixture with acetic anhydride. The yields of **23**–**26** in the system HNO_3–Ac_2O were higher on the average by 20% than in nitric acid where hydroxy acids were formed as by-products. The yield of 3-nitroxyadamantane-1-carboxylic acid (**23**) in the reaction of **6** with HNO_3 was 71% [43]. The yields of 2-(3-nitroxyadamantan-1-yl)acetic acids (**27**) in HNO_3–Ac_2O in HNO_3 were comparable (80 and 81%) [40].

It was previously found [43] that 1-nitroadamantane in the reaction with nitric acid undergoes slow nitrolysis with the formation of adamantan-1-yl nitrate and that the corresponding nitro nitrate is formed in HNO_3–Ac_2O. In fact, the reaction of 3,5-dimethyl-1-nitroadamantane (**11**) with nitric acid in acetic anhydride afforded 43% of 3,5-dimethyl-7-nitroadamantan-1-yl nitrate (**28**).

Electrophilically induced oligomerization of adamantane-1-carbonitrile (**12**) in 98% nitric acid led to

Scheme 3.



12 *n* = 1–3

the formation of a mixture of poorly soluble high-melting amide oligomers containing 2 to 4 cage fragments (according to spectral data; Scheme 3). It seemed interesting to obtain in this way a polyamide with a higher molecular weight. Nitrile **12** in HNO_3–Ac_2O was converted to cyano nitrate **29**, whereas no Ritter reaction was observed.

N-(Adamantan-1-yl)acetamide (**13**) in 100% HNO_3 underwent nitroxylation to 3-acetamidoadamantan-1-yl nitrate (**30**). In addition, minor nitrolysis products, adamantan-1-yl nitrate (**31**) and adamantane-1,3-diyl dinitrate (**35**) were detected (Scheme 2). The reaction of **13** with HNO_3–Ac_2O gave 42% of **30**.

Nitrate **31** and dinitrate **35** were formed as the only products in the reactions of both 1-fluoroadamantane (**14**) and 1-bromo- and 1-chloroadamantanes with both HNO_3 and HNO_3–Ac_2O [43]. 1,3-Dihaloadamantanes were expected to exhibit a lower reactivity. In fact, 1,3-dihaloadamantanes **15**–**17** in the system HNO_3–Ac_2O gave rise to the corresponding haloadamantyl nitrates **32**–**34** in addition to dinitrate **35**. The highest yield was observed for fluoro nitrate **32**, whereas the yield of bromo nitrate **34** was as low as 21% even under mild nitrolysis conditions.

Nitroxy derivatives **18**–**34** were isolated in 21–94% yield. In the ^{13}C NMR spectra of **18**–**34**, the quaternary carbon atom bearing the ONO_2 group resonated at δ_C 86– 90 ppm.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR Affinity-1 spectrometer (Japan). The ^1H and ^{13}C NMR spectra were recorded on a JEOL NMR-ECX400 spectrometer (Japan) at 400 and 100 MHz, respectively, using tetramethylsilane as internal standard. The melting points were measured in capillaries on an MPM-H2 melting point apparatus (Germany) and are uncorrected. The elemental analyses were carried out with a EuroVector 3000 EA analyzer (Italy) using L-cystine as standard. 1-(Adamantan-1-yl)ethanol (**1**) [50], (adamantane-1,3-diyl)dimethanol (**2**) [29], 1-(adamantan-1-yl)ethanone (**3**) [51], 1-(adamantan-1-yl)propan-1-one (**4**) and 1-(adamantan-1-yl)-2-methylpropan-1-one (**5**) [52], adamantane-1-carbonitrile (**12**) [53], *N*-(adamantan-1-yl)acetamide (**13**) [54], 1,3-dichloroadamantane (**16**) [55], and 1,3-dibromoadamantane (**17**) [56] were synthesized according to reported procedures. Carboxylic acids **6**–**10** were taken from the collection of chemicals at the Organic Chemistry Department of the Samara State Technical University. Compounds **14** and **15** were provided by A.M. Aleksandrov (Kukhar' Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine).

3,5-Dimethyl-1-nitroadamantane (11). 1,3-Dimethyladamantane, 15 mL (0.08 mol), was heated to the boiling point, 3.4 mL (0.085 mol) of 100% nitric acid was slowly added dropwise, and the mixture was heated at 200°C for 1.5 h until nitrogen oxides no longer evolved. After cooling, the solidified material was treated with 50 mL of diethyl ether, the solution was dried over solid sodium hydroxide and evaporated, and the residue was purified by chromatography using pentane as eluent; the first fraction was collected. Yield 6.65 g (39%), bp 125–127°C (5 torr); published data [57]: bp 114–115°C (2 torr).

General procedure for the oxidation of compounds 1–4 and 6–17 in the system HNO_3–Ac_2O. Compound **1**–**4** or **6**–**17**, 0.01 mol, was added to a mixture of 98% nitric acid and acetic anhydride. The mixture was kept under the conditions indicated in Table 1 and poured onto crushed ice. Compounds **18**–**21** and **31**–**34** were extracted with diethyl ether (3×10 mL), the combined extracts were washed with a solution of sodium hydrogen carbonate and water until neutral washings, dried over sodium sulfate, and evaporated. Compounds **23**–**30** precipitated and were filtered off, washed with water until neutral washings, and dried.

1-(3-Nitroxyadamantan-1-yl)ethyl nitrate (18) was obtained from alcohol **1** and was purified by column chromatography using hexane as eluent. Yield 84%, n_D^{20} = 1.5125. IR spectrum, ν, cm^{-1}: 1628, 1285 (ONO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.51 d (3H, CH_3, J = 6.5 Hz), 1.35–2.50 m (14H, Ad), 5.52 q (1H, CH, J = 6.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 17.7 (CH_3), 30.2 (CH), 37.0 (CH_2), 38.8 (CH_2), 41.3, 42.1 (CH_2), 43.4 (CH_2), 85.6 (CH), 89.1. Found, %: C 50.41; H 6.40; N 9.85. $C_{12}H_{18}N_2O_6$. Calculated, %: C 50.35; H 6.34; N 9.79.

In addition, 3-acetyladamantan-1-ylnitrate (**20**) was isolated by column chromatography. Yield 7%, n_D^{20} = 1.5113. IR spectrum, ν, cm^{-1}: 1705 (C=O), 1625, 1290 (ONO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.70–2.55 m (14H, Ad), 2.11 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.3 (CH_3), 27.4 (CH), 34.4 (CH_2), 37.0 (CH_2), 40.1 (CH_2), 42.9, 48.7 (CH_2), 88.6, 210.7. Found, %: C 60.30; H 7.22; N 5.92. $C_{12}H_{17}NO_4$. Calculated, %: C 60.24; H 7.16; N 5.85.

3,5-Bis(acetoxymethyl)adamantan-1-yl nitrate (19) was obtained from diol **2** and was purified by

column chromatography using carbon tetrachloride–ethyl acetate (4:1) as eluent. Yield 86%, n_D^{20} = 1.5177. IR spectrum, ν, cm^{-1}: 1740 (C=O), 1625, 1270 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20–2.44 m (13H, Ad), 2.06 s (6H, CH_3), 3.78 s (4H, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.9 (CH_3), 29.9 (CH), 37.3, 37.4 (CH_2), 38.6 (CH_2), 39.9 (CH_2), 40.9 (CH_2), 72.0 (CH_2), 89.7, 171.0. Found, %: C 56.36; H 6.86; N 4.17. $C_{16}H_{23}NO_7$. Calculated, %: C 56.30; H 6.79; N 4.10.

3-Acetyladamantan-1-yl nitrate (20) was obtained from 1-acetyladamantane (**3**). Yield 67%, n_D^{20} = 1.5113. The spectral characteristics were identical to those given above.

3-Propanoyladamantan-1-yl nitrate (21) was obtained from ketone (**4**) and was purified by column chromatography using pentane as eluent. Yield 87%, n_D^{20} = 1.5025. IR spectrum, ν, cm^{-1}: 1715 (C=O), 1625, 1290 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 t (3H, CH_3, J = 7.1 Hz), 1.55–2.45 (14H, Ad), 2.50 q (2H, CH_2, J = 7.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 8.7 (CH_3), 26.9 (CH), 32.9 (CH_2), 34.4 (CH_2), 37.6 (CH_2), 40.6 (CH_2), 41.7, 49.1 (CH_2), 88.1, 213.4. Found, %: C 61.70; H 7.62; N 5.59. $C_{13}H_{19}NO_4$. Calculated, %: C 61.64; H 7.56; N 5.53.

3-Nitroxyadamantane-1-carboxylic acid (23) was obtained from acid **6**. Yield 94%, mp 135–137°C (from hexane); published data [44]: mp 145–147°C.

5-Methyl-3-nitroxyadamantane-1-carboxylic acid (24) was obtained from acid **7**. Yield 91%, mp 85–87°C (from hexane); published data [48]: mp 85–86°C.

5-Ethyl-3-nitroxyadamantan-1-carboxylic acid (25) was obtained from acid **8**. Yield 87%, mp 88–90°C (from hexane); published data [48]: mp 88–89°C.

3,5-Dimethyl-7-nitroxyadamantane-1-carboxylic acid (26) was obtained from acid **9**. Yield 89%, mp 98–100°C (from hexane); published data [48]: mp 99–100°C.

2-(3-Nitroxyadamantan-1-yl)acetic acid (27) was obtained from acid **10**. Yield 81%, mp 123–125°C (from hexane); published data [40]: mp 136–138°C.

3,5-Dimethyl-7-nitroadamantan-1-yl nitrate (28) was obtained from 3,5-dimethyl-1-nitroadamantane (**11**). Yield 43%, mp 89–90°C (from hexane). IR spectrum, ν, cm^{-1}: 1630 (ONO_2), 1540 (NO_2), 1365 (NO_2), 1280 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.08 s (6H, CH_3), 1.28–2.54 m (12H, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.8 (CH_3), 35.2, 41.3 (CH_2), 44.3 (CH_2), 45.7 (CH_2), 48.7 (CH_2), 86.3, 89.2. Found, %: C 53.39; H 6.78; N 10.42. $C_{12}H_{18}N_2O_5$. Calculated, %: C 53.33; H 6.71; N 10.36.

3-Cyanoadamantan-1-yl nitrate (29) was synthesized from nitrile **12**. Yield 47%, mp 86–88°C (from hexane). IR spectrum, ν, cm^{-1}: 2225 (CN), 1615, 1280 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.72–2.46 m (14H, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 29.5 (CH), 33.0, 33.9 (CH_2), 38.1 (CH_2), 38.4 (CH_2), 41.3 (CH_2), 86.3, 122.7. Found, %: C 59.52; H 6.42; N 12.69. $C_{11}H_{14}N_2O_3$. Calculated, %: C 59.45; H 6.35; N 12.61.

3-Acetamidoadamantan-1-yl nitrate (30) was obtained from acetamide **13**. Yield 42%, mp 130–132°C (from hexane). IR spectrum, ν, cm^{-1}: 3180 (NH), 1635, 1555 (C=O), 1615, 1275 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.70 s (3H, CH_3), 1.55–2.35 m (14H, Ad), 7.55 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 24.2 (CH_3), 30.5 (CH), 34.7 (CH_2), 38.6 (CH_2), 40.1 (CH_2), 43.1 (CH_2), 54.2, 89.4, 169.5. Found, %: C 56.75; H 7.20; N 11.09. $C_{12}H_{18}N_2O_4$. Calculated, %: C 56.68; H 7.14; N 11.02.

Adamantan-1-yl nitrate (31) was obtained from 1-fluoroadamantane (**14**) and was purified by column chromatography using hexane as eluent. Yield 57%, mp 102–104°C [43]). In addition, adamantane-1,3-diyl dinitrate (**35**) was isolated. Yield 33%, mp 114–115°C [43].

3-Fluoroadamantan-1-yl nitrate (32) was obtained from 1,3-difluoroadamantane (**15**) and was purified by column chromatography using hexane as eluent. Yield 59%, mp 68–70°C (from MeOH). IR spectrum, ν, cm^{-1}: 1620, 1280 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.65–2.37 m (14H, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 31.2 (CH), 34.1 (CH_2), 38.2 (CH_2), 41.2 (CH_2), 44.9 (CH_2), 89.6, 92.4 (J = 203 Hz). Found, %: C 55.89; H 6.63; N 6.58. $C_{10}H_{14}FNO_3$. Calculated, %: C 55.81; H 6.56; N 6.51. In addition, dinitrate **35** was isolated in 12% yield.

3-Chloroadamantan-1-yl nitrate (33) was obtained from 1,3-dichloroadamantane (**16**) and was purified by column chromatography using hexane as eluent. Yield 46%, mp 41–42°C (from MeOH). IR spectrum, ν, cm^{-1}: 1625, 1275 (ONO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.61–2.59 m (14H, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 32.4 (CH), 34.2 (CH_2), 38.3 (CH_2), 46.2 (CH_2), 49.3 (CH_2), 66.4, 89.2. Found, %: C 51.90; H 6.16; N 6.13. $C_{10}H_{14}ClNO_3$. Calculated, %: C 51.84; H 6.09; N 6.05. In addition, dinitrate **35** was isolated in 23% yield.

3-Bromoadamantan-1-yl nitrate (34) was obtained from 1,3-dibromoadamantane (**17**) and was purified by column chromatography using hexane as eluent. Yield 21%, mp 36–38°C (from MeOH). IR spectrum, ν, cm^{-1}: 1620, 1275 (ONO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.65–2.67 m (14H, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 32.9 (CH_2), 33.7 (CH), 37.8 (CH_2), 47.2 (CH_2), 50.3 (CH_2), 60.9, 88.6. Found, %: C 43.58; H 5.19; N 5.14. $C_{10}H_{14}BrNO_3$. Calculated, %: C 43.50; H 5.11; N 5.07. In addition, dinitrate **35** was isolated in 22% yield.

General procedure for the oxidation of compounds 1, 3–5, 7–9, and 13 with fuming nitric acid. Compound **1**, **3**–**5**, **7**–**9**, or **13**, 0.01 mol, was added in portions to 98% nitric acid. The mixture was kept under the conditions indicated in Table 2 and poured onto crushed ice. Compounds **3**, **21**, and **2** were extracted with diethyl ether (3×10 mL), the combined extracts were washed with a 10% solution of sodium hydroxide and with water until neutral washings, dried over sodium sulfate, and evaporated. Compounds **23**–**26** and **30** precipitated and were filtered off, washed with water until neutral washings, and dried.

1-(Adamantan-1-yl)ethanone (3) was obtained from alcohol **1**. Yield 85%, mp 50–51°C; published data [49]: mp 53–54°C. Acidification of the alkaline extract with concentrated aqueous HCl gave 3-nitroxyadamantane-1-carboxylic acid (**23**), yield 7%.

3-Nitroxyadamantane-1-carboxylic acid (23) was obtained from ketone **3**. Yield 87%.

3-Propanoyladamantan-1-yl nitrate (21) was obtained from ketone **4**. Yield 46%. Its spectral characteristics were identical to those given above. Acidification of the alkaline extract with concentrated aqueous HCl gave 22% of acid **23**.

3-(2-Methylpropanoyl)adamantan-1-yl nitrate (22) was obtained from ketone **5** and was purified by column chromatography using pentane as eluent. Yield 92%, n_D^{20} = 1.4958. IR spectrum, ν, cm^{-1}: 1725 (C=O), 1625, 1290 (ONO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.37 d (6H, CH_3, J = 6.5 Hz), 1.55–2.55 m (14H, Ad), 4.82 sept (1H, CH, J = 6.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.2 (CH_3), 26.9 (CH), 34.4 (CH_2), 35.7 (CH), 38.4 (CH_2), 40.0 (CH_2), 40.8, 49.6 (CH_2), 88.1, 217.1. Found, %: C 62.97; H 7.98; N 5.31. $C_{14}H_{21}NO_4$. Calculated, %: C 62.90; H 7.92; N 5.24.

3-Acetamidoadamantan-1-yl nitrate (30) was obtained from acetamide **13** in 66% yield. Its spectral characteristics were identical to those given above.

5-Methyl-3-nitroxyadamantane-1-carboxylic acid (24) was obtained from acid **7** in 70% yield.

5-Ethyl-3-nitroxyadamantane-1-carboxylic acid (25) was obtained from acid **8** in 68% yield.

3,5-Dimethyl-7-nitroxyadamantane-1-carboxylic acid (26) was obtained from acid **9** in 67% yield.

CONCLUSIONS

The system nitric acid–acetic anhydride has been proposed for nitroxylation of adamantane derivatives and shown to ensure better selectivity than nitric acid. In some cases, the proposed system suppressed nitrolysis and oxidation of functional groups that are unstable to nitric acid. In addition, the formation of alcohols as by-products is minimized due to lower degree of protonation of the nitroxy group and binding of liberated water.

ACKNOWLEDGMENTS

This study was performed using the facilities of the "Physicochemical Properties of Substances and Materials" joint center of the Sanara State Technical University.

FUNDING

This study was performed under financial support by the Ministry of Science and Higher Education of the Russian Federation (project part of state assignment no. 0778-2020-0005). The study of nitroxylation of haloadamantane derivatives was financially supported by the Russian Foundation for Basic Research (project no. 20-03-00869).

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

REFERENCES

1. Schoedel, A. and Rajeh, S., *Top. Curr. Chem*., 2020, vol. 378, p. 19. https://doi.org/10.1007/s41061-020-0281-0
2. Li, X., Guo, J., Tong, R., Topham, P.D., and Wang, J., *React. Funct. Polym*., 2018, vol. 130, p. 126. https://doi.org/10.1016/j.reactfunctpolym.2018.06.008
3. Nasrallah, H. and Hierso, J.-C., *Chem. Mater*., 2019, vol. 31, p. 619. https://doi.org/10.1021/acs.chemmater.8b04508
4. Chen, D., Fu, Y., Yu, W., Yu, G., and Pan, C., *Chem. Eng. J*., 2018, vol. 334, p. 900. https://doi.org/10.1016/j.cej.2017.10.133

5. Trandafir, M.M., Pop, L., Hădade, N.D., Florea, M., Neațu, F., Teodorescu, C.M., Duraki, B., van Bokhoven, J.A., Grosu, I., Pârvulescu, V.I., and Garcia, H., *Catal. Sci. Technol*., 2016, vol. 6, p. 8344. https://doi.org/10.1039/C6CY01631F
6. Lamoureux, G. and Artavia, G., *Curr. Med. Chem*., 2010, vol. 17, p. 2967. https://doi.org/10.2174/092986710792065027
7. Štimac, A., Šekutor, M., Mlinarić-Majerski, K., Frkanec, L., and Frkanec, R., *Molecules*, 2017, vol. 22, p. 297. https://doi.org/10.3390/molecules22020297
8. Wanka, L., Iqbal, K., and Schreiner, P.R., *Chem. Rev*., 2013, vol. 113, p. 3516. https://doi.org/10.1021/cr100264t
9. Spilovska, K., Zemek, F., Korabecny, J., Nepovimova, E., Soukup, O., Windisch, M., and Kuca, K., *Curr. Med. Chem*., 2016, vol. 23, p. 3245. https://doi.org/10.2174/0929867323666160525114026
10. Klimochkin, Y.N., Shiryaev, V.A., and Leonova, M.V., *Russ. Chem. Bull., Int. Ed*., 2015, vol. 64, p. 1473. https://doi.org/10.1007/s11172-015-1035-y
11. Shokova, E.A. and Kovalev, V.V., *Pharm. Chem. J*., 2016, vol. 50, p. 63. https://doi.org/10.1007/s11094-016-1400-7
12. Pham, V.H., Phan, T.P.D., Phan, D.C., and Vu, B.D., *Molecules*, 2020, vol. 25, p. 324. https://doi.org/10.3390/molecules25020324
13. Konovalov, A.I., Antipin, I.S., Burilov, V.A., Madzhidov, T.I., Kurbangalieva, A.R., Nemtarev, A.V., Solovieva, S.E., Stoikov, I.I., Mamedov, V.A., Zakharova, L.Ya., Gavrilova, E.L., Sinyashin, O.G., Balova, I.A., Vasilyev, A.V., Zenkevich, I.G., Krasavin, M.Yu., Kuznetsov, M.A., Molchanov, A.P., Novikov, M.S., Nikolaev, V.A., Rodina, L.L., Khlebnikov, A.F., Beletskaya, I.P., Vatsadze, S.Z., Gromov, S.P., Zyk, N.V., Lebedev, A.T., Lemenovskii, D.A., Petrosyan, V.S., Nenaidenko, V.G., Negrebetskii, V.V., Baukov, Yu.I., Shmigol', T.A., Korlyukov, A.A., Tikhomirov, A.S., Shchekotikhin, A.E., Traven', V.F., Voskresenskii, L.G., Zubkov, F.I., Golubchikov, O.A., Semeikin, A.S., Berezin, D.B., Stuzhin, P.A., Filimonov, V.D., Krasnokutskaya, E.A., Fedorov, A.Yu., Nyucohev, A.V., Orlov, V.Yu., Begunov, R.S., Rusakov, A.I., Kolobov, A.V., Kofanov, E.R., Fedotova, O.V., Egorova, A.Yu., Charushin, V.N., Chupakhin, O.N., Klimochkin, Yu.N., Osyanin, V.A., Reznikov, A.N., Fisyuk, A.S., Sagitullina, G.P., Aksenov, A.V., Aksenov, N.A., Grachev, M.K., Maslennikova, V.I., Koroteev, M.P., Brel', A.K., Lisina, S.V., Medvedeva, S.M., Shikhaliev, Kh.S., Suboch, G.A., Tovbis, M.S., Mironovich, L.M., Ivanov, S.M., Kurbatov, S.V., Kletskii, M.E., Burov, O.N., Kobrakov, K.I., and Kuznetsov, D.N., *Russ. J. Org. Chem*., 2018, vol. 54, p. 157. https://doi.org/10.1134/S107042801802001X
14. Moiseev, I.K. and Doroshenko, R.I., *Zh. Org. Khim*., 1983, vol. 19, p. 1117.
15. Moiseev, I.K., Bagrii, E.I., Klimochkin, Yu.N., Dolgopolova, T.N., Zemtsova, M.N., and Trakhtenberg, P.L., *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1985, vol. 34, p. 1983. https://doi.org/10.1007/BF00953951
16. Moiseev, I.K., Stulin, N.V., Yudashkin, A.V., and Klimochkin, Yu.N., *Zh. Obshch. Khim*., 1985, vol. 55, p. 1655.
17. Moiseev, I.K. and Doroshenko, R.I., *Zh. Org. Khim*., 1982, vol. 18, p. 1233.
18. No, B.I., Butov, G.M., and Ledenev, S.M., *Zh. Org. Khim*., 1994, vol. 30, p. 315.
19. Klimochkin, Yu.N., Leonova, M.V., Korzhev, I.R., Moiseev, I.K., Vladyko, G.V., Korobchenko, L.V., Boreko, E.I., and Nikolaeva, S.N., *Pharm. Chem. J*., 1992, vol. 26, p. 616. https://doi.org/10.1007/BF00777145
20. Barabanova, N.V., Medzhinskii, V.L., and Golod, E.L., *Russ. J. Org. Chem*., 1997, vol. 33, p. 1079.
21. Yurchenko, R.I. and Peresypkina, L.P., *Zh. Obshch. Khim*., 1991, vol. 61, p. 1019.
22. Ulomskii, E.N., Deev, S.L., Tkachev, A.V., Moiseev, I.K., and Rusinov, V.L., *Russ. J. Org. Chem*., 2002, vol. 38, p. 272. https://doi.org/10.1023/A:1015538322029
23. Saraev, V.V., Kanakina, T.P., Pevzner, M.S., Golod, E.L., Ugrak, B.I., and Kachala, V.V., *Chem. Heterocycl. Compd*., 1996, vol. 32, p. 928. https://doi.org/10.1023/A:1015538322029
24. Klimochkin, Yu.N., Tilli, T.S., and Moiseev, I.K., *Zh. Org. Khim*., 1988, vol. 24, p. 1780.
25. Klimochkin, Yu.N. and Moiseev, I.K., *Zh. Org. Khim*., 1991, vol. 27, p. 1795.
26. Klimochkin, Yu.N., Yudashkin, A.V., Zhilkina, E.O., Ivleva, E.A., Moiseev, I.K., and Oshis, Ya.F., *Russ. J. Org. Chem*., 2017, vol. 53, p. 971. https://doi.org/10.1134/S1070428017070028
27. Leonova, M.V., Skomorokhov, M.Yu., Moiseev, I.K., and Klimochkin, Yu.N., *Russ. J. Org. Chem*., 2015, vol. 51, p. 1703. https://doi.org/10.1134/S1070428015120064
28. Ivleva, E.A. and Klimochkin, Yu.N., *Org. Prep. Proced. Int*., 2017, vol. 49, p. 155. https://doi.org/10.1080/00304948.2017.1291004
29. Liu, Z., Yang, S., Jin, X., Zhang, G., Guo, B., Chen, H., Yu, P., Sun, Y., Zhang, Z., and Wang, Y., *Med. Chem. Commun*., 2017, vol. 8, p. 135. https://doi.org/10.1039/c6md00509h
30. Stulin, N.V., Yudashkin, A.V., Shiryaev, A.K., Moiseev, I.K., and Petrov, A.S., *Pharm. Chem. J*., 1984, vol. 18, p. 337. https://doi.org/10.1007/BF00766669

31. Cheng, H., Hoffman, J., Le, P., Nair, S.K., Cripps, S., Matthews, J., Smith, C., Yang, M., Kupchinsky, S., Dress, K., Edwards, M., Cole, B., Walters, E., Loh, C., Ermolieff, J., Fanjul, A., Bhat, G.B., Herrera, J., Pauly, T., Hosea, N., Paderes, G., and Rejto, P., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 2897. https://doi.org/10.1016/j.bmcl.2010.03.032
32. Klimochkin, Yu.N., Moiseev, I.K., Boreko, E.I., Vladyko, G.V., and Korobchenko, L.V., *Pharm. Chem. J*., 1988, vol. 23, p. 304. https://doi.org/10.1007/BF00758419
33. Klimochkin, Yu.N., Moiseev, I.K., Leonova, M.V., Nikolaeva, S.N., and Boreko, E.I., *Pharm. Chem. J*., 2017, vol. 51, p. 13. https://doi.org/10.1007/s11094-017-1548-9
34. Ling, Y., Ren, X., Lai, W., and Luo, J., *Eur. J. Org. Chem*., 2015, vol. 2015, p. 1541. https://doi.org/10.1002/ejoc.201403449
35. Klapötke, T.M., Krumm, B., and Widera, A., *ChemPlusChem*, 2018, vol. 83, p. 61. https://doi.org/10.1002/cplu.201700542
36. Skare, D. and Suceska, M., *Croat. Chem. Acta*, 1998, vol. 71, p. 765.
37. Fridman, A.L., Zalesov, V.S., Kon'shina, L.O., Kolobov, N.A., Dolbilkin, K.V., Moiseev, I.K., Mratkhuzina, T.A., and Belyaev, P.G., *Chem. Pharm. J*., 1976, vol. 10, p. 454. https://doi.org/10.1007/BF00757834
38. Moiseev, I.K., Bagrii, E.I., Klimochkin, Yu.N., Dolgopolova, T.N., Zemtsova, M.N., and Trakhtenberg, P.L., *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1985, vol. 34, no. 9, p. 1980. https://doi.org/10.1007/ BF00953950
39. Klimochkin, Yu.N. and Moiseev, I.K., *Zh. Org. Khim*., 1988, vol. 24, p. 557.
40. Yurchenko, R.I., Peresypkina, L.P., Miroshnichenko, V.V., and Yurchenko, A.G., *Russ. J. Gen. Chem*., 1993, vol. 63, p. 1072.
41. Gavrilova, V.S., Ivleva, E.A., Gnusarev, D.I., Osyanin, V.A., and Klimochkin, Yu.N., *Russ. J. Org. Chem*., 2015, vol. 51, p. 1382. https://doi.org/10.1134/S1070428015100048
42. Marcus, R.A. and Fresco, J.M., *J. Chem. Phys*., 1957, vol. 27, p. 564. https://doi.org/10.1063/1.1743769
43. Moiseev, I.K., Klimochkin, Yu.N., Zemtsova, M.N., and Trakhtenberg, P.L., *Zh. Org. Khim*., 1984, vol. 20, p. 1435.
44. Klimochkin, Yu.N., Zhilkina, E.O., Abramov, A.V., and Moiseev, I.K., *Zh. Org. Khim*., 1993, vol. 29, p. 1358.
45. Krasutsky, P.A., Likhotvorik, I.R., Dubinina, T.V., Nesterenko, V.V., and Jones, M., Jr., *Tetrahedron Lett*., 1995, vol. 36, p. 3079. https://doi.org/10.1016/0040-4039(95)00468-R
46. Klimochkin, Yu.N., Leonova, M.V., Moiseev, I.K., and Aleksandrov, A.M., *Russ. J. Org. Chem*., 1997, vol. 33, p. 340.
47. Klimochkin, Yu.N., Leonova, M.V., and Moiseev, I.K., *Russ. J. Org. Chem*., 1998, vol. 34, p. 494.
48. Ivleva, E.A., Pogulyaiko, A.V., and Klimochkin, Yu.N., *Russ. J. Org. Chem*., 2018, vol. 54, p. 1294. https://doi.org/10.1134/S107042801809004X
49. Becker, H., *Einführung in die Elektronentheorie organisch–chemischer Reaktionen*, Berlin: Wissenschaften, 1974, 3rd ed.
50. Hoang, H.N., Nagashima, Y., Mori, S., Kagechika, H., and Matsuda, T., *Tetrahedron*, 2017, vol. 73, p. 2984. https://doi.org/10.1016/j.tet.2017.04.024
51. Stetter, H. and Rauscher, E., *Chem. Ber*., 1960, vol. 93, p. 2054. https://doi.org/10.1002/cber.19600930922
52. Grava, I.Ya., Polis, Ya.Yu., Lidak, M.Yu., Liepin'sh, E.E., Shatts, V.D., Dipan, I.V., Gavars, M.P., and Sekatsis, I.P., *Zh. Org. Khim*., 1981, vol. 17, p. 778.
53. Owens, P.H., Gleicher, G.J., and Smith, L.M., *J. Am. Chem. Soc*., 1968, vol. 90, p. 4122. https://doi.org/10.1021/ja01017a036
54. Klimochkin, Y.N., Bagrii, E.I., Dolgopolova, T.N., and Moiseev, I.K., *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1988, vol. 37, p. 757. https://doi.org/10.1007/BF01455495
55. McKervey, M.A., Grant, D., and Hamill, H., *Tetrahedron Lett*., 1970, vol. 11, no. 23, p. 1975. https://doi.org/10.1016/S0040-4039(01)98131-6
56. Degtyarenko, A.S., Handke, M., Krämer, K.W., Liu, S.-X., Decurtins, S., Rusanov, E.B., Thompson, L.K., Krautscheid, H., and Domasevitch, K.V., *Dalton Trans*., 2014, vol. 43, p. 8530. https://doi.org/10.1039/c4dt00174e
57. Schneider, A. and Hills, O., BE Patent no. 666904, 1966; *Chem. Abstr*., 1966, vol. 65, p. 7077f.