ISSN 1070-4280, *Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 11, pp. 1682–1685. © Pleiades Publishing, Ltd., 2011.*
Original Russian Text © R.I. Khusnutdinov, N.A. Shchadneva, Yu.Yu. Mayakova, L.F. Khisamova, U.M. Dzhemilev, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 11, pp. 1650–1653

Ritter Reaction of Organic Nitriles with 1-Bromo- and 1-Hydroxyadamantanes Catalyzed by Manganese Compounds and Complexes

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Received February 8, 2011

Abstract—Manganese compounds and complexes [$MnCl_2$, $MnBr_2$, $Mn(OAc)_2$, $Mn(acac)_2$, $Mn(acac)_3$, $Mn_2(CO)_{10}$] catalyze Ritter reaction of organic nitriles with 1-bromo- and 1-hydroxyadamantanes. The reaction proceeds in water environment in the absence of acids at 100–130°C over 3–5 h and affords *N*-(adamantan-1-yl)amides in 75–100% yields.

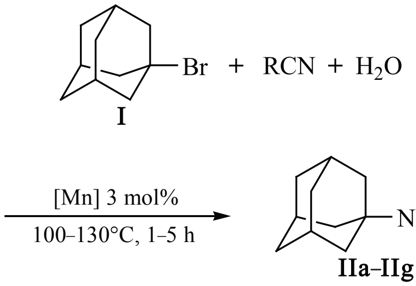
DOI: 10.1134/S1070428011110042

The transformations of adamantane and its derivatives under the conditions of Ritter reaction have been fairly wide studied since the arising *N*-(adamantan-1-yl)amides are the nearest precursors of the biologically active aminoadamantanes possessing antimicrobial and antiviral activity and used in the treatment and prophylaxis of severe diseases (influenza, herpes, pneumonia etc.) [1, 2].

The laboratory and industrial synthesis of various *N*-(adamantan-1-yl)amides using 1-bromoadamantane (**I**) is most common; the generation from compound **I** of adamantan-1-yl carbocation occurs under the action of concn. sulfuric [3] and acetic acids [4], oleum [5], equimolar mixture of trifluoroacetic acid and boron trifluoride etherate [6], liquid bromine [7] which are taken in a large excess with respect to 1-bromoadamantane (**I**) hampering the isolation of the target amide [8].

We carried out Ritter reaction of 1-bromoadamantane (**I**) with acetonitrile and the other nitriles in the presence of manganese-containing catalysts like $MnCl_2$, $MnBr_2$, $Mn(OAc)_2$, $Mn(acac)_2$, $Mn(acac)_3$, $Mn_2(CO)_{10}$ where the best were $Mn_2(CO)_{10}$ and manganese(III) acetylacetonate. The reaction proceeded in water at the molar ratio of reagents and catalyst [Ad-Br] : [CH_3CN] : [H_2O] : [Mn] = 100 : 300–500 : 100 : 1–3.

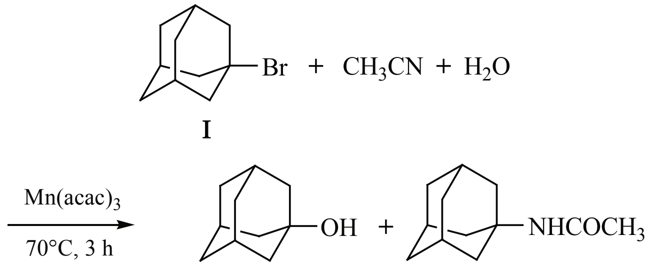
Under the optimum conditions (100°C, 3 h or 130°C, 1 h) at the complete conversion of 1-bromoadamantane (**I**) the only reaction product was N-(adamantan-1-yl) acetamide (**IIa**). Other nitriles also are actively involved into the reaction: propanenitrile, benzonitrile, 4-methylbenzonitrile, acrylonitrile, malononitrile, 1,6-hexanedinitrile that under the given conditions in the presence of Mn-containing catalysts furnish the corresponding N-(adamantan-1-yl)amides **IIb–IIg** in 75–100% yield. The nature and the structure of the organic nitrile do not notably affect the selectivity and the yield of amides.



R = CH_3 (**a**), C_2H_5 (**b**), Ph (**c**), 4-CH_3Ph (**d**), CH_2=CH (**e**), CH_2CN (**f**), $(CH_2)_4$CN (**g**).

The reaction progress was monitored by GLC. We established the optimum reagents concentrations, the desired conditions for the synthesis of *N*-(adamantan-1-yl)amides **IIa–IIg**. Liquid nitriles (acetonitrile, propanenitrile, benzonitrile, acrylonitrile) were used in excess for they served the reagent and the solvent simultaneously. The reaction with solid nitriles (malononitrile, 4-methylbenzonitrile) was carried out in dichloromethane.

In the study of the effect of conditions on the course of the reaction between 1-bromoadamantane (**I**) and acetonitrile in the presence of Mn-containing catalysts in the reaction mixture at 70–80°C adamantan-1-ol (**III**) was found which apparently formed by hydrolysis of initial 1-bromoadamantane (**I**).



I

III, 84% **IIa**, 16%

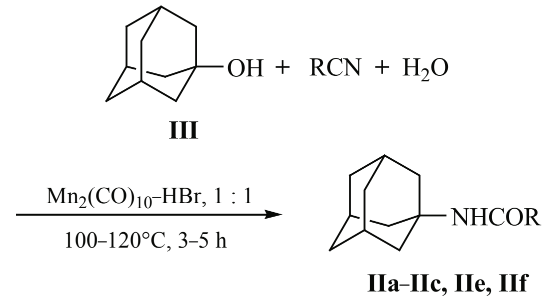
Assuming that the amidation reaction proceeded through the stage of adamantan-1-ol (**III**) formation we attempted to perform its amidation with CH_3CN in the presence of Mn-containing catalyst. However, amide **IIa** did not form even under severe conditions (175°C, 45 h) and initial adamantan-1-ol (**III**) was recovered intact. We succeeded to bring alcohol **III** into the reaction with acetonitrile by activating manganese-containing catalysts [Mn(acac)$_2$, Mn(acac)$_3$, Mn(OAc)$_2$, Mn$_2$(CO)$_{10}$] with hydrobromic acid. In the presence of the catalytic system [Mn]–HBr adamantan-1-ol (**III**) reacted with acetonitrile in water environment at 100–120°C within 3–5 h. In the absence of the manganese catalyst in the other identical conditions ([1-AdOH] : [CH_3CN] : [H_2O] : [HBr] = 100 : 300–500 : 100 : 3) adamantan-1-ol (**III**) was recovered intact. The best molar ratio of reagents was [1-AdOH] : [CH_3CN] : [H_2O] : [Mn] : [HBr] = 100 : 300–500 : 100 : 3 : 3. Under the optimum conditions the yield of *N*-(adamantan-1-yl)acetamide (**IIa**) reached 100%.

The other nitriles (propanenitrile, benzonitrile, acrylonitrile, malononitrile) also showed a high activity

Experimental results of the synthesis of *N*-(adamantan-1-yl)acetamide from 1-bromoadamantane or adamantan-1-ol (1-AdX) and acetonitrile in water in the presence of manganese-containing catalysts

Catalyst	1-AdX	Molar ratio [1-AdX] : [CH_3CN] : [H_2O] : [Mn] : [HBr]	*T*, °C	Reaction time, h	Conversion of 1-AdX, %	Amide **IIa** yield, %
MnCl$_2$	1-AdBr (**I**)	100 : 300 : 100 : 3 : 0	130	2	82	100
MnCl$_2$	1-AdBr	100 : 300 : 100 : 3 : 0	130	2	85	100
MnBr$_3$	1-AdBr	100 : 300 : 100 : 3 : 0	130	2	89	100
Mn(OAc)$_2$	1-AdBr	100 : 300 : 100 : 3 : 0	130	1	91	100
Mn(OAc)$_2$	1-AdBr	100 : 300 : 100 : 3 : 0	110	3	95	100
Mn(acac)$_2$	1-AdBr	100 : 300 : 100 : 3 : 0	110	3	97	99
Mn(acac)$_3$	1-AdBr	100 : 300 : 100 : 3 : 0	110	2	99	100
Mn$_2$(CO)$_{10}$	1-AdBr	100 : 300 : 100 : 3 : 0	110	3	100	100
Mn(acac)$_3$	1-AdBr	100 : 300 : 100 : 3 : 0	110	2	100	100
Mn(acac)$_3$	1-AdBr	100 : 300 : 100 : 3 : 0	130	1	99	100
Mn(acac)$_3$	1-AdBr	100 : 300 : 100 : 3 : 0	100	3	100	100
Mn(acac)$_3$	1-AdOH	100 : 500 : 100 : 1 : 0	120	6	0	–
Mn(acac)$_3$	1-AdOH	100 : 400 : 100 : 3 : 0	120	6	0	–
Mn(acac)$_3$	1-AdOH	100 : 500 : 100 : 3 : 1	120	6	52	100
Mn(acac)$_3$	1-AdOH	100 : 300 : 100 : 1 : 3	120	6	78	100
Mn(OAc)$_2$	1-AdOH	100 : 300 : 100 : 1 : 3	120	6	83	100
Mn$_2$(CO)$_{10}$	1-AdOH	100 : 300 : 100 : 1 : 3	100	5	87	100
Mn$_2$(CO)$_{10}$	1-AdOH	100 : 300 : 100 : 3 : 3	120	5	99	100
No catalyst	1-AdOH	100 : 300 : 100 : 0 : 3	120	6	0	–

in the reaction with adamantan-1-ol (**III**) in the presence of $Mn_2(CO)_{10}$–HBr.



R = CH_3 (**a**), C_2H_5 (**b**), Ph (**c**), CH_2=CH (**e**), CH_2CN (**f**).

Thus Mn-containing catalysts make it possible to carry out Ritter reaction of 1-bromoadamantane (**I**) and adamantan-1-ol (**III**) with organic nitriles in one stage in water without the presence of strong acids (see the table).

The structure of amides **IIa–IIg** was established by spectral methods comparing the data with those of authentic samples and published data.

EXPERIMENTAL

IR spectra in the range 550–3600 cm^{-1} were recorded on a spectrophotometer Bruker Vertex 70V from pellets with KBr or mulls in mineral oil. ^{13}C NMR spectra were registered on a spectrometer Bruker Avance-400 at operating frequency 100.62 MHz from solutions in $CDCl_3$. Mass spectra were taken on a GC-MS instrument Shimadzu QP-2010 Plus, capillary column Supelko PTE-5 (30 m × 0.35 mm). Elemental composition of the reaction products was measured on an analyzer Carlo Erba 1106.

The reaction progress was monitored and the purity of compounds obtained was checked by GLC on a chromatograph Chrome-5, flame-ionisation detectors, columns 1.2 and 3 m long, diameter 3 mm; stationary phase silicone SE-30 (5%) on the carrier Chromaton-N-HMDS (0.125–0.160 mm), ramp from 50 to 280°C at a rate 8 deg/min), carrier gas helium (50 ml/min).

Amidation of 1-bromoadamantane (I) with organic nitriles. Into a small pressure reactor of stainless steel (*V* 20 ml) or in a glass ampoule (the results of parallel runs were practically identical) under an argon atmosphere was charged 0.3 mmol of manganese-containing catalyst, 10 mmol of 1-bromoadamantane (**I**), 30 mmol of organic nitrile, 10 mmol of water, 2 ml of dichloromethane (for solid nitriles). The reactor was air-tight closed (the ampoule was sealed), and the reaction mixture was heated at 100°C for 5 h with stirring. On completion of the reaction the reactor (ampoule) was cooled to room temperature, opened, the organic layer was separated, the reaction products were extracted from the water layer into dichloromethane (3 × 5 ml), the solvent was distilled off from the combined organic solutions, the residue was recrystallized.

Amidation of adamantan-1-ol (III) with organic nitriles. Into a small pressure reactor of stainless steel (*V* 20 ml) or in a glass ampoule (the results of parallel runs were practically identical) under an argon atmosphere was charged 0.3 mmol of manganese-containing catalyst, 0.3 mmol of hydrobromic acid, 10 mmol of adamantan-1-ol (**III**), 20 mmol of organic nitrile, 10 mmol of water or 2 ml of dichloromethane for solid nitriles. The reactor was air-tight closed (the ampoule was sealed), and the reaction mixture was heated at 100°C for 5 h with stirring. On completion of the reaction the workup and isolation of the products were carried out as described above.

***N*-(Adamantan-1-yl)acetamide (IIa).** Yield 98%, mp 147–147.5°C (methanol) {147–149°C (hexane) [9]}. IR spectrum, ν, cm^{-1}: 3220 (NH), 1645 (C=O), 1545 (NH). ^{13}C NMR spectrum, δ, ppm: 25.40 (CH_3), 30.85 ($C^{3,5,7}$), 36.42 ($C^{4,6,10}$), 41.50 ($C^{2,8,9}$), 51.61 (C^{1}), 160.86 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 193 $[M]^+$ (43), 192 (9), 150 (7), 137 (8), 136 (100), 135 (24), 134 (25), 100 (8), 94 (45), 93 (18), 92 (16), 91 (17), 79 (15), 77 (14), 58 (8), 55 (7), 43 (31), 42 (12), 41 (21), 39 (14). Found, %: C 74.61; H 9.88; N 7.19. $C_{12}H_{19}NO$. Calculated, %: C 74.56; H 9.91; N 7.25.

***N*-(Adamantan-1-yl)propaneamide (IIb).** Yield 98%, mp 104.2°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1650 (C=O), 1550 (NH). ^{13}C NMR spectrum, δ, ppm: 22.30 (CH_3), 28.35 (CH_2), 29.18 ($C^{3,5,7}$), 36.12 ($C^{4,6,10}$), 41.29 ($C^{2,8,9}$), 51.73 (C^{1}), 172.21 (C=O). Found, %: C 78.87; H 10.65; N 7.11. $C_{13}H_{21}NO$. Calculated, %: C 79.13; H 10.73; N 7.10.

***N*-(Adamantan-1-yl)benzamide (IIc).** Yield 98%, mp 148.5–149°C (hexane) (149–150°C [3]). IR spectrum, ν, cm^{-1}: 3440 (NH), 1655 (amide I), 1580 (C=C, aromatic), 1515 (amide II). ^{13}C NMR spectrum, δ, ppm: 29.51 ($C^{3,5,7}$), 36.71 ($C^{4,6,10}$), 41.61 ($C^{2,8,9}$), 52.43 (C^{1}), 126.80, 128.42, 130.12, 135.88 (arom), 167.09 (C=O). Found, %: C 79.82; H 8.25; N 5.48. $C_{17}H_{21}NO$. Calculated, %: C 79.96; H 8.29; N 5.48.

***N*-(Adamantan-1-yl)-4-methylbenzamide (IId).** Yield 75%, mp 147.5–148°C (hexane). IR spectrum, ν, cm^{-1}: 3440 (NH), 1655, 1580, 1515. ^{13}C NMR spectrum, δ, ppm: 21.66 (CH_3), 29.68 ($C^{3,5,7}$), 36.07 ($C^{4,6,10}$), 41.66 ($C^{2,8,9}$), 52.26 (C^{1}), 122.23, 130.03, 133.09, 142.64 (arom), 171.15 (C=O). Found, %: C 79.98; H 8.36; N 5.11. $C_{18}H_{31}NO$. Calculated, %: C 80.25; H 8.60; N 5.20.

***N*-(Adamantan-1-yl)acrylamide (IIe).** Yield 95%, mp 147–147.5°C (methanol) (145–147°C [9]). IR spectrum, ν, cm^{-1}: 3440 (NH), 1670, 1630 (C=C), 1520. ^{13}C NMR spectrum, δ, ppm: 29.17 ($C^{3,5,7}$), 36.11 ($C^{4,6,10}$), 41.26 ($C^{2,8,9}$), 51.75 (C^{1}), 125.03 (=CH_2), 132.07 (CH=), 164.42 (C=O). Found, %: C 75.89; H 9.26; N 6.77. $C_{13}H_{19}NO$. Calculated, %: C 76.05; H 9.33; N 6.82.

***N*-(Adamantan-1-yl)-2-cyanoethanamide (IIf).** Yield 85%, mp 146–146.5°C (methanol) (147–148°C [3]). IR spectrum, ν, cm^{-1}: 3440 (NH), 2280 (C≡N), 1690, 1530. ^{13}C NMR spectrum, δ, ppm: 26.80 (CH_2), 29.34 ($C^{3,5,7}$), 36.12 ($C^{4,6,0}$), 41.22 ($C^{2,8,9}$), 53.28 (C^{1}), 115.09 (CH≡N), 159.38 (C=O). Found, %: C 71.33; H 8.15; N 12.79. $C_{13}H_{18}N_2O$. Calculated, %: C 71.52; H 8.31; N 12.83.

***N*-(Adamantane-1-yl)-5-cyanopentanamide (IIg).** Yield 78%, mp 199–200°C (methanol). IR spectrum, ν, cm^{-1}: 3260 (NH), 2240 (C≡N), 1650, 1560. ^{13}C NMR spectrum, δ, ppm: 15.68 (CH_2), 24.15 (CH_2), 29.51 ($C^{3,5,7}$), 36.28 (CH_2), 36.71 ($C^{4,6,10}$), 41.61 ($C^{2,8,9}$), 54.70 (C^{1}), 114.54 (CH≡N), 171.71 (C=O). Found, %: C 73.56; H 9.18; N 10.74. $C_{16}H_{24}N_2O$. Calculated, %: C 73.80; H 9.29; N 10.76.

ACKNOWLEDGMENTS

The study was carried out under the financial support of the Federal agency on science and innovations (State contract no. 02.740.11.0631).

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