ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 4, pp. 476–479. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © R.I. Khusnutdinov, N.A. Shchadneva, L.F. Khisamova, 2015, published in Zhurnal Organicheskoi Khimii, 2015, Vol. 51, No. 4, pp. 495–497.

Synthesis of *N*-(Adamantan-1-yl)amides by Reaction of Carboxylic Acid Amides with 1-Bromo(chloro)adamantane Catalyzed by Manganese Compounds

R. I. Khusnutdinov, N. A. Shchadneva, and L. F. Khisamova

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences,
pr. Oktyabrya 141, Ufa, 450075 Bashkortostan, Russia
e-mail: ink@anrb.ru

Received January 17, 2015

Abstract—*N*-(Adamantan-1-yl)amides were synthesized in 70–90% yield by reaction of 1-bromoadamantane with carboxylic acid amides in the presence of manganese salts and complexes.

DOI: 10.1134/S107042801504003X

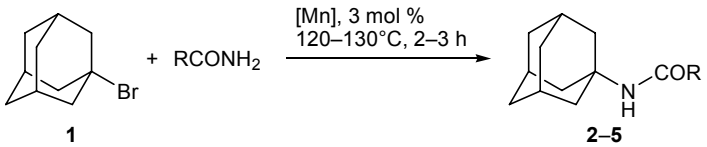
Adamantane and its derivatives are widely used in the synthesis of valuable chemical substances needed in various industries. An important field of application of adamantane derivatives is the synthesis of antiviral and neurotropic drugs. *N*-(Adamantan-1-yl) carboxylic acid amides are closest precursors of biologically active adamantanamines which exhibit antimicrobial activity and are used for the treatment and prophylactics of severe diseases such as influenza, herpes, pneumonia, etc. [1–3].

1-Bromoadamantane (**1**) is used most frequently in laboratory and large-scale syntheses of various *N*-(adamantan-1-yl)amides. Adamantyl cation is generated therefrom by the action of concentrated sulfuric [4] or nitric acid [5], oleum [6], equimolar mixture of trifluoroacetic acid and boron trifluoride–diethyl ether complex [7], or liquid bromine [8]. These reagents are taken in a large excess with respect to 1-bromoadamantane (**1**), which complicates the isolation of target products [9]. *N*-(Adamantan-1-yl)amides were also synthesized by reaction of 1-bromoadamantane (**1**) with formamide or acetamide at elevated temperature (185–195°C) [10] or in the presence of a stoichiometric amount of silver sulfate Ag_2SO_4 [11]. In both cases, the yield of adamantylamides did not exceed 45%.

Taking into account practical importance of *N*-(adamantan-1-yl)amides, we have developed a new efficient procedure for their preparation using metal-complex catalysts. The reaction of 1-bromoadamantane (**1**) with formamide in the presence of manganese catalysts [$MnCl_2$, $MnBr_2$, $Mn(OAc)_2$, $Mn(acac)_3$, $Mn_2(CO)_{10}$] was carried out by heating for 2–3 h at 120–130°C, the molar ratio 1-bromoadamantane–formamide–catalyst being 100:(200–300):(1–3). Under the optimal conditions, the conversion of 1-bromoadamantane (**1**) was complete, and the only product was *N*-(adamantan-1-yl)formamide (**2**). Other carboxylic acid amides, in particular acetamide, propionamide, *N*-methylformamide, and benzamide, also readily reacted with bromide **1** under the above conditions to afford *N*-(adamantan-1-yl)amides **3**–**5** in 78–100% yield. The nature of organic amide did not affect the reaction selectivity and yield.

The progress of the reaction was monitored by GLC. The optimal reactant concentrations and conditions for the synthesis of *N*-(adamantan-1-yl)amides **2**–

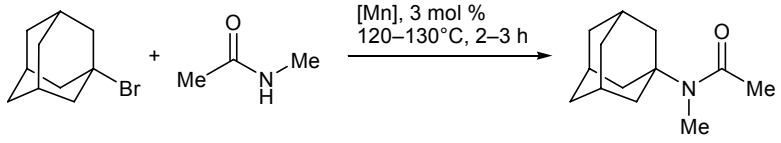
Scheme 1.



1 **2–5**

2, R = H; **3**, R = Me; **4**, R = Et; **5**, R = Ph.

Scheme 2.



1 **7**

7 were found. Carboxylic acid amides were taken in 2–3-fold excess since they acted simultaneously as reagent and solvent; the reactions with solid amides were carried out in melt.

Malonamide reacted with 1-bromoadamantane at one amide group. However, the yield of *N*-(adamantan-1-yl)propanediamide (**6**) did not exceed 10% even on prolonged heating (130°C, 8 h). Benzamide vigorously reacted with bromide **1** to produce *N*-(adamantan-1-yl)benzamide (**5**) in quantitative yield. The reaction of 1-bromoadamantane (**1**) with *N*-methylacetamide was fairly active, and *N*-(adamantan-1-yl)-*N*-methylacetamide (**7**) was formed in 75% yield (Scheme 2).

The reactivity of 1-chloroadamantane (**8**) in analogous reactions was similar to that of bromide **1**, and the reactions of **8** with amides afforded 45–90% of *N*-(adamantan-1-yl)amides **2**–**7** with high selectivity. The conversion of adamantyl halides **1** and **8** and the yields of amides **2**–**7** depended on the catalyst nature. Among the examined manganese compounds [$Mn_2(CO)_{10}$, $Mn(OAc)_2 \cdot 4H_2O$, $Mn(acac)_3$, $MnBr_2$, $MnCl_2$], $Mn_2(CO)_{10}$ turned out to be the best catalyst.

N-(Adamantan-1-yl)amides **2**–**7** were purified from concomitant impurities by silica gel column chromatography using hexane–ethyl acetate as eluent. Amides **2**–**7** were identified by spectral methods and by comparing their properties with those of authentic samples and with published data [12].

Thus, manganese-containing catalysts ensure amidation of 1-bromo- and 1-chloroadamantanes with aliphatic and aromatic carboxylic acid amides under solvent-free conditions (see table).

Synthesis of *N*-(adamantan-1-yl)amides **2**–**7** from 1-bromoadamantane (**1**) and carboxylic acid amides in the presence of manganese compounds

Initial amide	Catalyst	Molar ratio **1**–amide–Mn	Temperature, °C	Reaction time, h	Yield of amide **2**–**7**, %
$MeCONH_2$	$MnCl_2$	100:300:3	130	2	36
	$MnBr_2$	100:300:3	130	2	45
	$Mn(OAc)_2$	100:300:3	130	2	87
	$Mn(acac)_3$	100:300:3	130	2	80
	$Mn(acac)_3$	100:200:3	130	2	65
	$Mn(acac)_3$	100:300:2	130	2	72
	$Mn(acac)_3$	100:300:3	120	3	95
	$Mn_2(CO)_{10}$	100:300:3	130	2	96
	$Mn_2(CO)_{10}$	100:300:3	120	3	95
	$Mn_2(CO)_{10}$	100:200:3	120	3	93
	$Mn_2(CO)_{10}$	100:300:1	120	3	88
	$Mn_2(CO)_{10}$	100:300:2	120	3	90
$HCONH_2$	$Mn_2(CO)_{10}$	100:300:3	120	3	97
$EtCONH_2$	$Mn_2(CO)_{10}$	100:300:3	120	3	92
$PhCONH_2$	$Mn_2(CO)_{10}$	100:300:3	120	3	99
$CH_2(CONH_2)_2$	$Mn_2(CO)_{10}$	100:300:3	120	3	10
MeCONHMe	$Mn_2(CO)_{10}$	100:300:3	120	3	75

EXPERIMENTAL

The IR spectra were recorded in KBr or mineral oil on a Bruker Vertex 70V spectrometer. The ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 100.62 MHz from solutions in $CDCl_3$. The mass spectra were obtained on a Shimadzu GCMS-QP2010Ultra instrument (Supelco PTE-5 capillary column, 60 m×0.25 mm; carrier gas helium; oven temperature programming from 40 to 280°C at a rate of 8 deg/min; injector temperature 260°C; ion source temperature 200°C; electron imact, 70 eV). The elemental compositions were determined on a Carlo Erba 1106 elemental analyzer.

The progress of reactions and the purity of products were monitored by GLC on Shimadzu GC-9A and GC-2014 instruments (2 m×3-mm column, stationary phase 5% of SE-30 on Chromaton N-AW-HMDS; oven temperature programming from 50 to 270°C at a rate of 8 deg/min; carrier gas helium, 47 mL/min). The yields of amides **2**–**7** were determined by GLC analysis of the reaction mixtures using undecane as internal standard; the calibration factors for 1-bromoadamantane and *N*-(adamantan-1-yl)acetamide were 1.53 and 1.68, respectively.

Synthesis of *N*-(adamantan-1-yl)amides 2–7 (*general procedure*). A 17-mL stainless-steel high-pressure micro reactor or a glass ampule (the results of parallel runs differed insignificantly) was charged under argon with 0.3 mmol of manganese compound, 10 mmol of 1-bromoadamantane (**1**), and 30 mmol of the corresponding amide. The reactor was hermetically closed (the ampule was sealed), and the mixture was heated for 2–3 h at 120–130°C under continuous stirring. When the reaction was complete, the reactor (ampule) was cooled to room temperature and opened, and the mixture was washed with water and extracted with methylene chloride (3×5 mL). The solvent was removed under reduced pressure, and the residue was recrystallized.

***N*-(Adamantan-1-yl)formamide (2).** Yield 94%, mp 139–140°C (from MeOH). IR spectrum, ν, cm^{-1}: 3278 (N–H), 1643 (C=O), 1559 (δN–H). ^{13}C NMR spectrum, δ_C, ppm: 29.11 (C^3, C^5, C^7), 36.15 (C^4, C^6, C^{10}), 43.48 (C^2, C^8, C^9), 51.62 (C^1), 162.08 (C=O). Found, %: C 73.62; H 9.53; N 7.77. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.56; N 7.81.

***N*-(Adamantan-1-yl)acetamide (3).** Yield 91%, mp 147–148°C (from MeOH); published data [12]: mp 147–147.5°C. IR spectrum, ν, cm^{-1}: 3220 (N–H), 1645 (C=O), 1545 (δN–H). ^{13}C NMR spectrum, δ_C, ppm: 25.42 (CH_3), 30.85 (C^3, C^5, C^7), 36.42 (C^4, C^6, C^{10}), 41.54 (C^2, C^8, C^9), 51.62 (C^1), 160.86 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 193 (43) $[M]^+$, 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 74.60; H 9.88; N 7.18. $C_{12}H_{19}NO$. Calculated, %: C 74.56; H 9.91; N 7.25.

***N*-(Adamantan-1-yl)propanamide (4).** Yield 88%, mp 103.5–104°C (from MeOH); published data [12]: mp 104.2°C. IR spectrum, ν, cm^{-1}: 3300 (N–H), 1650 (C=O), 1550 (δN–H). ^{13}C NMR spectrum, δ_C, ppm: 22.32 (CH_3), 28.35 (CH_2), 29.18 (C^3, C^5, C^7), 36.12 (C^4, C^6, C^{10}), 41.29 (C^2, C^8, C^9), 51.73 (C^1), 172.21 (C=O). Found, %: C 78.95; H 10.68; N 7.09. $C_{13}H_{21}NO$. Calculated, %: C 79.13; H 10.73; N 7.10.

***N*-(Adamantan-1-yl)benzamide (5).** Yield 92%, mp 148–149°C (from MeOH); published data [4]: mp 149–150°C. IR spectrum, ν, cm^{-1}: 3440 (N–H), 1655 (C=O), 1650 (C=O), 1580 (C=C_{arom}), 1515 (δN–H). ^{13}C NMR spectrum, δ_C, ppm: 29.51 (C^3, C^5, C^7), 36.71 (C^4, C^6, C^{10}), 41.61 (C^2, C^8, C^9), 52.43 (C^1), 126.80, 128.42, 130.12, 135.88 (C_{arom}), 167.08 (C=O). Found, %: C 79.88; H 8.25; N 5.46. $C_{17}H_{21}NO$. Calculated, %: C 79.96; H 8.29; N 5.48.

***N*-(Adamantan-1-yl)propanediamide (6).** Yield 10%. IR spectrum, ν, cm^{-1}: 3300 (N–H), 1650 (C=O), 1550 (δN–H). ^{13}C NMR spectrum, δ_C, ppm: 28.82 (C^3, C^5, C^7), 36.03 (C^4, C^6, C^{10}), 40.94 (C^2, C^8, C^9), 43.80 (CH_2), 50.78 (C^1), 165.67 (C=O), 175.04 (C=O). Found, %: C 65.98; H 8.48; N 11.79. $C_{13}H_{20}N_2O_2$. Calculated, %: C 66.07; H 8.53; N 11.85.

***N*-(Adamantan-1-yl)-*N*-methylacetamide (7).** Yield 75%. IR spectrum, ν, cm^{-1}: 3270 (N–H), 1650 (C=O). ^{13}C NMR spectrum, δ_C, ppm: 23.05 (CH_3), 29.56 (CH_3), 30.76 (C^3, C^5, C^7), 37.08 (C^4, C^6, C^{10}), 39.84 (C^2, C^8, C^9), 54.95 (C^1), 171.87 (C=O). Found, %: C 75.25; H 10.18; N 6.69. $C_{13}H_{21}NO$. Calculated, %: C 75.32; H 10.21; N 6.76.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 14-03-97029r_povolzh'e-a) and by the program of the President of the Russian Federation for young scientists and post-graduate students engaged in promising researches and developments in the priority fields of modernization of the Russian economics (project no. SP-4810.2013.4 for 2013–2015).

REFERENCES

1. Bagrii, E.I., *Adamantany, poluchenie, svoistva, primenenie* (Adamantanes: Synthesis, Properties, and Application), Moscow: Nauka, 1989.
2. Fort, R.C., Jr., *Adamantane: The Chemistry of Diamond Molecules*, New York: Marcel Dekker, 1976, p. 385.
3. Gerasimova, N.P., Ermolaeva, V.V., Pashinin, A.N., Nozhnin, N.A., Moskvichev, Yu.A., and Alov, E.M., *Neftekhimiya*, 2005, vol. 45, p. 37.
4. Sasaki, T., Eguchi, E., and Toru, T., *Bull. Chem. Soc. Jpn*., 1968, vol. 41, p. 236.
5. Klimochkin, Yu.N., Bagrii, E.I., Dolgopolova, T.N., and Moiseev, I.K., *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1988, vol. 37, no. 4, p. 757.
6. Butenko, L.N. and Khardin, A.P., USSR Inventor's Certificate no. 491616, 1976.
7. Plakhotnik, V.M., Kovtun, V.Yu., and Yashunskii, V.G., *Zh. Org. Khim*., 1982, vol. 18, p. 1001.
8. Baklan, V,F., Khil'chevskii, A.N., and Kukhar', *Zh. Org. Khim*., 1984, vol. 20, p. 2238.
9. Moiseev, I.K., Makarova, N.V., and Zemtsova, M.N., *Russ. Chem. Rev*., 1999, vol. 68, no. 12, p. 1001.
10. Polis, Ya.Yu., USSR Inventor's Certificate no. 1609406, 1977.
11. Paulshock, M. and Watts, J.C., US Patent no. 3310469, 1967.
12. Khusnutdinov, R.I., Shchadneva, N.A., Mayakova, Yu.Yu., Khisamova, L.F., and Dzhemilev, U.M., *Russ. J. Org. Chem*., 2011, vol. 47, p. 1682.