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LETTERS TO THE EDITOR

Amidation of 1-Bromo-3,5-dimethyladamantane Catalyzed with Manganese Compounds and Complexes

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One of the most important compounds containing adamantane moiety are amides like 1-acetamido-3,5-dimethyladamantane, whose deprotection gives 1-amino-3,5-dimethyladamantane, the constituent of Memantine drug. Memantine is unique pharmaceutical preparation effective for the treatment of Alzheimer's disease and other CNS disorders at an early stage. It helps to normalize the psychic activity of human: it improves memory and ability to concentrate, reduces fatiguability, depression symptoms, and restores neuromuscular system disorders [1–5].

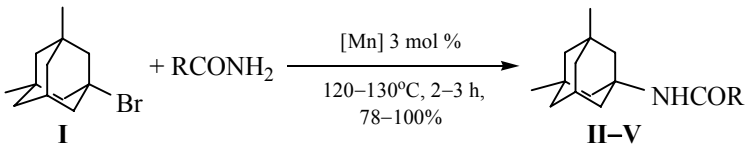
Typically 1-bromo-3,5-dimethyladamantane **I** is used for laboratory and industrial synthesis of various *N*-(adamant-1-yl)amides by Ritter method [6, 7]. Known methods for producing *N*-(adamant-1-yl)acylamides include reacting 1-bromoadamantane with formamide and acetamide at elevated temperature (185±195°C) [8], or in the presence of the stoichiometric amount of silver sulfate as the catalyst [9]. Yields of amides in both cases do not exceed 45%.

Considering the practical importance of *N*-(3,5-dimethyladamantane-1-yl)amides, we aimed at developing a new effective method for their preparation using metal complex catalysts. We have recently shown that the Mn-catalyzed reaction of 1-bromoadamantane with carboxylic acid amides produced *N*-(adamantan-1-yl)-amides in yields of 70–90% [10].

In the present work, we found that manganese compounds and complexes catalyzed amidation of 1-bromo-3,5-dimethyladamantane **I** with carboxylic acid amides. The reactions were carried out as described previously [10]. The interaction of 1-bromo-3,5-dimethyladamantane **I** with formamide, acetamide, propionamide, and benzamide in the presence of $Mn_2(CO)_{10}$ [or $MnCl_2$, $MnBr_2$, $Mn(OAc)_2$, $Mn(acac)_3$] resulted in the formation of the corresponding *N*-(3,5-dimethyladamant-1-yl)amides **II**–**V** in 78–99% yield. At the same time the nature and the structure of the organic amide had no significant effect on the selectivity of the reaction and the yield of adamantylamide (Scheme 1).

In summary, the Mn-containing catalysts made it possible to perform amidation of 1-bromo-3,5-dimethyladamantane **I** with organic amides in a single step in a solvent-free conditions.

Scheme 1.



I **II–V**

[Mn] = $MnCl_2$, $MnBr_2$, $Mn(OAc)_2$, $Mn(acac)_3$, $Mn_2(CO)_{10}$; R = H (**II**), CH_3 (**III**), C_2H_5 (**IV**), Ph (**V**).

The structure of *N*-(3,5-dimethyladamant-1-yl)acylamides **II**–**V** was confirmed by the IR and NMR spectroscopy methods.

General procedure for the synthesis of *N*-(3,5-dimethyladamant-1-yl)acetamides. The stainless steel pressure microreactor (V = 17 mL) or glass vial was charged under argon with 0.3 mmol of manganese-containing catalyst, 10 mmol of 1-bromo-3,5-dimethyladamantane **I**, and 30 mmol of amide. The reaction mixture was heated at 120–130°C for 3–4 h with stirring. After the reaction completed, the rector (vial) was cooled to room temperature and opened. The reaction mixture was washed with water, and then the reaction product was extracted with methylene chloride (3 × 5 mL). The solvent was removed under a reduced pressure, and the residue was recrystallized. *N*-(3,5-Dimethyladamant-1-yl)amides **II**–**V** were purified by column chromatography (silica gel, eluent – hexane–ethyl acetate).

***N*-(3,5-Dimethyladamantan-1-yl)formamide (II).** Yield 78%, mp 69–70°C (hexane). Physico-chemical constants and NMR spectral data correspond to the literature data [7].

***N*-(3,5-Dimethyladamantan-1-yl)acetamide (III).** Yield 99%, mp 109.5–110°C (hexane). Physico-chemical constants and NMR spectral data correspond to the literature data [11].

***N*-(3,5-Dimethyladamant-1-yl)propanamide (IV).** Yield 98%, mp 102–103°C (ethanol). IR spectrum, ν, cm^{-1}: 1550 (NH), 1650 (C=O), 3300 (NH). ^{13}C NMR spectrum, δ_C, ppm: 22.32 (CH_3), 29.07 ($C^{3,5}$), 29.46 (C^7), 29.97 (CH_3), 31.48 (CH_2), 41.59 ($C^{6,9}$), 42.66 (C^8), 44.68 ($C^{2,10}$), 49.54 (C^4), 51.73 (C^1), 172.21 (C=O). Found, %: C 76.49; H 10.68; N 5.89. $C_{15}H_{25}NO$. Calculated, %: C 76.55; H 10.71; N 5.95. M 235.36.

***N*-(3,5-Dimethyladamant-1-yl)benzamide (V).** Yield 97%, sublimation point 80°C (10 mmHg). IR spectrum, ν, cm^{-1}: 1515 (amide II), 1580 (C=C, arom.), 1650 (C=O), 1655 (amide I), 3440 (NH). ^{13}C NMR spectrum, δ_C, ppm: 29.82 (C^7), 30.09 ($C^{3,5}$), 30.19 (CH_3), 40.37 ($C^{6,9}$), 42.68 (C^8), 45.15 ($C^{2,10}$), 47.61 (C^4), 50.62 (C^1), 126.72, 128.67, 131.06, 135.92 (arom.), 166.78 (C=O). Found, %: C 80.48; H 8.85; N 4.92. C19H25NO. Calculated, %: C 80.52; H 8.89; N 4.94.

The reaction progress was monitored by gas-liquid chromatography on a Shimadzu GC-9A instrument, GC-2014 [column 2 m × 3 mm, stationary phase Silicone SE-30 (5%) supported on Chromaton N-AW-HMDS, ramp from 50 to 270°C at a heating rate of 8 deg/min, carrier gas helium (47 mL/min)].

The IR spectra were recorded on a Bruker-Vertex 70V spectrometer from KBr pellets or slurry in mineral oil. ^{13}C NMR spectra were registered in $CDCl_3$ on a Bruker Avance-400 spectrometer operating at 100.62 MHz. Elemental analysis was performed on a Carlo Erba 1106 analyzer.

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