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Synthesis of 3,5-Dimethyladamantan-1-ol by Reaction of 1,3-Dimethyladamantane with Bromotrichloromethane and Water in the Presence of Manganese Complexes

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Abstract—3,5-Dimethyladamantan-1-ol was synthesized in 79% yield by reaction of 1,3-dimethyladamantane with bromotrichloromethane and water in the presence of manganese salts and complexes activated by pyridine.

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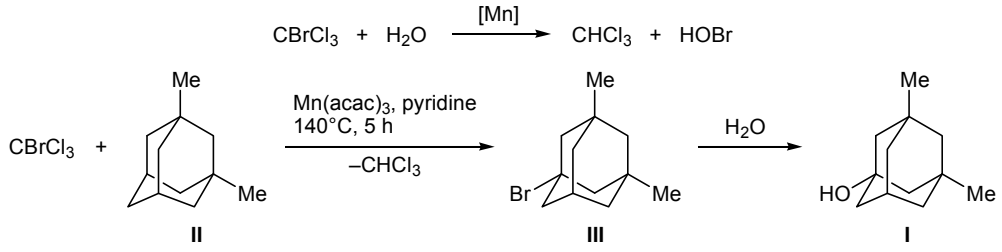
Adamantane and its derivatives are widely used for the preparation of valuable compounds needed for various branches of industry. Due to high thermal stability adamantane derivatives are used to obtain heat-resistant polymers. They are also starting materials in the manufacture of oils, hydraulic fluids, and antimicrobial additives for lubricants. An important field of application of adamantane and its derivatives is the synthesis of drugs with antiviral and neurotropic activity. A useful adamantane derivative is 3,5-dimethyladamantan-1-ol (**I**) which is a starting compound for the synthesis of 3,5-dimethyladamantan-1-amine, the active component of Memantine, an anti-Alzheimer drug also efficient in the treatment of other central nervous system disorders at early stages [1–4].

Most methods for the preparation of 3,5-dimethyladamantan-1-ol (**I**) are based on the bromination of 1,3-dimethyladamantane (**II**), followed by hydrolysis of 1-bromo-3,5-dimethyladamantane (**III**) thus formed in the presence of inorganic and organic bases [5–11]. These procedures are not free from such disadvantages as the use of aggressive concentrated inorganic acids, complex equipment due to high corrosivity of initial reactants, and formation of large amounts of acid wastes and wastewater to be disposed.

Taking into account practical importance of 3,5-dimethyladamantan-1-ol (**I**), we set ourselves the task of developing a new efficient one-pot procedure for the preparation of compound **I** using metal complex catalysis. In order to convert 1,3-dimethyladamantane (**II**) into alcohol **I**, we tried the system $CBrCl_3$–H_2O–[Mn] {where [Mn] = $Mn(OAc)_3 \cdot 4H_2O$, $Mn_2(CO)_{10}$, $Mn(acac)_3$}. As shown previously [12], such systems generate hypobromous acid HOBr.

GLC analysis of the reaction mixture showed that the formation of 3,5-dimethyladamantan-1-ol (**I**) in the reaction of 1,3-dimethyladamantane (**II**) with $CBrCl_3$ and water in the presence of $Mn(acac)_3$ is a stepwise process (Scheme 1). In the first step 1,3-dimethyladamantane (**II**) reacts with $CBrCl_3$ to give 1-bromo-

Scheme 1.



3,5-dimethyladamantane (**III**). Presumably, this reaction follows a radical mechanism and is initiated by hypobromous acid whose concentration was estimated by iodometric titration at 9.8 mg/mL in 2 h and 5.4 mg/mL in 5 h. Simultaneously, bromide **III** undergoes hydrolysis to alcohol **I**, and the concentrations of **I** and **III** in the reaction mixture become equal in 1 h after the reaction started. According to the GLC and GC/MS data, the reaction mixture also contained chloroform, which indicated participation of $CBrCl_3$ in the formation of bromide **III**. After 1 h, the concentrations of $CHCl_3$ and $CBrCl_3$ were comparable. No reaction occurred in the absence of $CBrCl_3$. To complete the hydrolysis of **III** to alcohol **I**, heating for a longer time (5 h) is necessary.

The conversion of 1,3-dimethyladamantane (**II**) and the yield of 3,5-dimethyladamantan-1-ol (**I**) depended on the catalyst nature. Among the examined manganese compounds, $Mn(acac)_3$ turned out to be the best catalyst whose highest activity was attained when pyridine was added to the reaction mixture. The role of pyridine is likely to bind hydrogen bromide, and the resulting pyridine hydrobromide can act as phase-transfer catalyst.

The optimal substrate-to-pyridine ratio (1 : 2) was determined experimentally. Higher concentration of pyridine strongly complicates isolation of compound **I** from the reaction mixture because of poor layer separation, so that the yield of the target product decreases. Apart from pyridine itself, alkylpyridines, cyanopyridines, and 2,2′-bipyridine are also capable of activating manganese complexes, but their activating effect is weaker. The reaction was not accompanied by bromination or hydroxylation of the methyl groups in 1,3-dimethyladamantane (**II**).

The reactions were carried out with 1,3-dimethyladamantane, $CBrCl_3$, $Mn(acac)_3$, H_2O, and substituted pyridine taken at a molar ratio of 100 : (125–150) : 5 : (6000–10000) : (200–400) at 130–150°C for 5–6 h. Under the optimal conditions using $Mn(acac)_3$–pyridine as catalytic system, the major product was 3,5-dimethyladamantan-1-ol (**I**) whose yield attained 79%, the conversion of 1,3-dimethyladamantane (**II**) being 97%. As by-products (~5%) we identified by GC/MS dibromo derivatives of 1,3-dimethyladamantane and isomeric diols. The results of the synthesis of 3,5-dimethyladamantan-1-ol (**I**) under different conditions are collected in Table 1. We have developed a procedure for quantitative determination of the yield of **I** by GLC analysis of the reaction mixture obtained from 1,3-dimethyladamantane (**II**), water, and $CBrCl_3$ in the presence of $Mn(acac)_3$; decane was used as internal standard.

Further experiments showed that compound **I** can also be synthesized using CBr_4 instead of $CBrCl_3$. Under the optimal conditions the conversion of 1,3-dimethyladamantane **II** was 65–70%, the yield of 3,5-dimethyladamantan-1-ol (**I**) was 35–40%, and 1- and 2-bromo-3,5-dimethyladamantanes were formed in 30% yield (Table 2). The optimal ratio CBr_4–**II** was

Table 1. Reaction of 1,3-dimethyladamantane (**II**) with bromotrichloromethane and water in the presence of manganese compounds (MnL_x) and substituted pyridines (Py)

Molar ratio MnL_x–**II**–$CBrCl_3$–H_2O–Py	MnL_x	Activator	Temperature, °C	Reaction time, h	Conversion of **II**, %	Yield of **I**, %
5 : 100 : 125 : 6000 : 200	$Mn(acac)_3$	Pyridine	140	5	96	79
5 : 100 : 125 : 10000 : 400	$Mn(acac)_3$	Pyridine	140	5	97	70
5 : 100 : 125 : 10000 : 200	$Mn(acac)_3$	Pyridine	140	5	98	65
5 : 100 : 125 : 10000 : 200	$Mn(acac)_3$	Pyridine	150	6	88	50
5 : 100 : 125 : 6000 : 400	$Mn(acac)_3$	2-Methylpyridine	140	5	76	32
5 : 100 : 125 : 6000 : 400	$Mn(acac)_3$	3-Methylpyridine	140	5	97	66
5 : 100 : 125 : 6000 : 400	$Mn_2(CO)_{10}$	Pyridine	140	5	74	43
5 : 100 : 125 : 6000 : 400	$Mn(OAc)_2 \cdot 4H_2O$	Pyridine	140	5	83	35
5 : 100 : 125 : 6000 : 400	$Mn_2(CO)_{10}$	3-Methylpyridine	140	5	97	52
5 : 100 : 125 : 6000 : 400	$Mn(acac)_3$	4-Methylpyridine	140	5	83	47
5 : 100 : 150 : 300 : 200	$Mn(acac)_3$	2,2′-Bipyridine	130	6	94	6
5 : 100 : 150 : 300 : 200	$Mn(acac)_3$	2-Cyanopyridine	130	6	96	10

Table 2. Synthesis of 3,5-dimethyladamantan-1-ol (**I**) by reaction of 1,3-dimethyladamantane (**II**) with carbon tetrabromide and water in the presence of $Mn(acac)_3$

Molar ratio $Mn(acac)_3$–**II**–CBr_4–H_2O–Py	Temperature, °C	Reaction time, h	Conversion of **II**, %	Yield of **I**, %
5:100:50:6000:0	140	6	53	40
5:100:50:6000:400	140	6	55	35
5:100:100:6000:0	140	6	60	28
5:100:50:6000:200	150	4	65	37
5:100:50:6000:0	150	4	67	34
5:100:100:6000:0	150	6	70	30
5:100:50:6000:0	140	8	57	40

1:2. Rise in the concentration of CBr_4 resulted in increased conversion of **II**, but the fraction of 1- and 2-bromo and dibromo derivatives of 1,3-dimethyladamantane increased simultaneously. Addition of pyridine and variation of the conditions had almost no effect on the reaction course.

Alcohol **I** was purified from impurities by column chromatography on silica gel using hexane–ethyl acetate as eluent.

EXPERIMENTAL

The IR spectra were recorded in KBr or mineral oil on a Bruker Vertex 79V spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance-400 instrument at 400.13 and 100.62 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The mass spectra were obtained on a Shimadzu GCMS-QP2010Ultra instrument (Supelco PTE-5 capillary column, 60 m×0.25 mm; carrier gas helium; injector temperature 260°C; oven temperature programming from 40 to 280°C at a rate of 8 deg/min; ion source temperature 200°C; electron impact, 70 eV). The elemental compositions were determined on a Carlo Erba 1108 analyzer. GLC analyses were carried out on a Carlo Erba GC 6000 Vega Series 2 chromatograph using a 3-m steel column packed with 15% of PEG-6000 on Chromaton N-AW-HMDS (oven temperature programming from 50 to 180°C at a rate of 8 deg/min; carrier gas helium, flow rate 47 mL×min^{-1}). Calibration factors of 1.01 and 1.41 (relative to decane used as internal standard) were found for 1,3-dimethyladamantane (**II**) and 3,5-dimethyladamantan-1-ol (**I**), respectively.

3,5-Dimethyladamantan-1-ol (I). *a*. A 17-mL high-pressure micro reactor was charged with 0.18 g (0.5 mmol) of $Mn(acac)_3$, 1.6 g (10 mmol) of 1,3-dimethyladamantane (**II**), 1.25 mL (12.5 mmol) of $CBrCl_3$, 10.8 mL (600 mmol) of water, and 1.6 mL (20 mmol) of pyridine. The reactor was tightly closed and heated for 5 h at 140°C. It was then cooled to 20°C and opened, and the mixture was washed with water and extracted with ethyl acetate (3×5 mL). The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel using hexane–ethyl acetate (first 9:1 and then 7:3) as eluent. Yield 80% (purity >98%), mp 95–97°C.

b. A 17-mL high-pressure micro reactor was charged with 0.18 g (0.5 mmol) of $Mn(acac)_3$, 1.6 g (10 mmol) of 1,3-dimethyladamantane (**II**), 1.66 g (0.5 mmol) of CBr_4, 10.8 mL (600 mmol) of water, and 5.3 mL (30 mmol) of CH_2Br_2. The reactor was tightly closed and heated for 6 h at 140°C. The mixture was then treated as described in *a*. Yield 40%. IR spectrum: ν 3394 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 0.86–0.92 m (6H, CH_3), 1.23–1.4 m (8H, 4-H, 8-H, 9-H, 10-H), 1.56–1.6 m (2H, 6-H), 1.96–1.98 m (1H, 7-H), 2.17–2.19 m (2H, 2-H), 2.69 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.02 (C^7), 29.98 (CH_3), 31.09 (C^3, C^5), 42.47 (C^8, C^{10}), 43.87 (C^6), 50.48 (C^2), 51.44 (C^4, C^9), 69.81 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 180 (26.0) $[M]^+$, 165 (11.5) $[M-15]^+$, 123 (100) $[M-57]^+$, 109 (95.1), 107 (29.0), 81(10.3), 67 (10.9), 55 (16.9), 43 (18.8), 41 (22.4). Found, %: C 79.91; H 11.15. $C_{12}H_{20}O$. Calculated, %: C 79.94; H 11.18. *M* 180.1515.

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