ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 6, pp. 820–822. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © R.I. Khusnutdinov, N.A. Shchadneva, L.F. Mukhametshina, 2010, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 6, pp. 828–830.

Synthesis of 1-Acetyladamantane by Reaction of 1-Bromoadamantane with Vinyl Acetate and Ethylidene Diacetate Catalyzed by $Mn_2(CO)_{10}$

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Received November 26, 2009

Abstract—A procedure has been developed for the synthesis of 1-acetyladamantane in 95% yield by reaction of 1-bromoadamantane with vinyl acetate or ethylidene diacetate in the presence of manganese complexes.

DOI: 10.1134/S1070428010060084

1-Acetyladamantane is one of the key adamantane derivatives that are used in the synthesis of substituted adamantanes possessing biological activity. In particular, 1-acetyladamantane is a starting material in the preparation of efficient anti-influenza drug Rimantadine [1]. Most known methods for the preparation of 1-acetyladamantane include a number of steps and are based on synthetic transformations of 1-substituted adamantanes 1-AdR (R = Br, OH, CN, COOH, COCl, etc.) [2–4]. We previously found [5] that 1-acetyladamantane may be obtained by reaction of vinyl acetate with 1,3-dibromoadamantane in the presence of rhodium complexes; the reaction was accompanied by evolution of hydrogen bromide. Obviously, the use of more accessible 1-bromoadamantane (**I**) instead of 1,3-dibromoadamantane would be more promising from the viewpoint of development of a simpler procedure for the synthesis of 1-acetyladamantane.

Our preliminary experiments showed that effective catalysts for the formation of 1-acetyladamantane (**II**) from 1-bromoadamantane (**I**) and vinyl acetate may be manganese compounds and complexes and that ethylidene diacetate can also be taken as acylating agent. The results characterizing the effect of the nature of manganese compound and ligand structure on the reaction course and the yield and composition of products are presented in Table 1. Complex composition of the reaction products should be noted (run nos. 5–7, 14, 15); apart from the target compound **II**, the reaction mixtures contained 1-adamantyl acetate (**III**) and adamantan-1-ol (**IV**) (Scheme 1). Presumably, the latter are formed with participation of decomposition products of excess vinyl acetate, acetic acid, acetic anhydride, and water [6].

With a view to reduce the consumption of vinyl acetate and minimize side processes, we tried to find an optimal solvent. The reaction of 1-bromoadamantane (**I**) with vinyl acetate in alcohols (methanol, ethanol) gave adamantan-1-ol (**IV**) as the major product. The yield of 1-acetyladamantane (**II**) in halomethanes (methylene chloride, chloroform, carbon tetrachloride) was 35–45%, but the use of these solvents was undesirable, for they promoted side transhalogenation of 1-bromoadamantane (**I**) with formation of less reactive 1-chloroadamantane. Among the examined solvents, the best was acetonitrile. However,

Scheme 1.

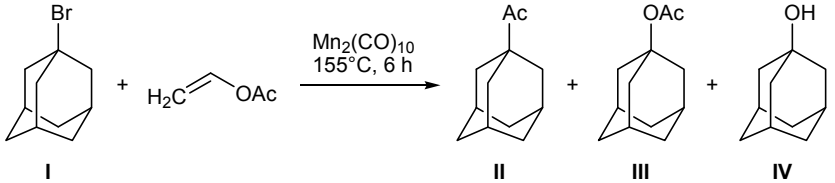


Table 1. Reaction of 1-bromoadamantane (**I**) with vinyl acetate (VA) in the presence of manganese compounds; molar ratio MnX_2 : **I** : VA = 1 : 100 : 200, 155°C, 6 h

Run no.	Catalyst	Ligand	Substrate conversion, %	Product composition, %			
				II	**III**	**IV**	oligomers
1	$MnCl_2$	–	15	100			
2	$MnBr_2$	–	21	100			
3	$Mn(C_{17}H_{35}CO_2)_2$[a]	–	18	80		20	
4	$Mn(C_7H_5CO_2)_2$[b]	–	48	60		40	
5	$Mn(OAc)_2$	–	56	72	10	18	
6	$Mn(acac)_2$	–	62	45	18	37	
7	$Mn(acac)_3$	–	60	50	10	40	
8	$Mn_2(CO)_{10}$	–	68	80	20		
9	$Mn_2(CO)_{10}$	Pyridine	32	100			
10	$Mn_2(CO)_{10}$	2,2′-Bipyridine	35	100			
11	$Mn_2(CO)_{10}$	Et_3N	0				
12	$Mn_2(CO)_{10}$	Morpholine	42	90		10	
13	$Mn_2(CO)_{10}$	$P(OPh)_3$	70				
14	$Mn_2(CO)_{10}$	PPh_3	60	80			20
15	$Mn_2(CO)_{10}$	$Ph_2PCH_2CH_2PPh_2$	85	50			50

[a] Manganese stearate.
[b] Manganese 2-ethylhexanoate.

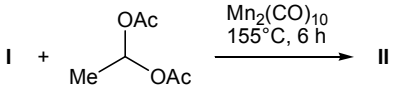
Table 2. Reaction of 1-bromoadamantane (**I**) with vinyl acetate (VA) in acetonitrile in the presence of $Mn_2(CO)_{10}$

Run no.	Molar ratio $Mn_2(CO)_{10}$: **I** : VA : MeCN	Temperature, °C	Reaction time, h	Substrate conversion, %	Product composition, %	
					II	oligomers
1	1 : 100 : 100 : 300	100	6	18	100	
2	1 : 100 : 200 : 300	100	6	25	100	
3	1 : 100 : 200 : 300	120	6	47	100	
4	1 : 100 : 200 : 300	140	6	68	100	
5	1 : 100 : 200 : 300	150	6	85	100	
6	1 : 100 : 300 : 500	150	6	90	100	
7	2 : 100 : 300 : 500	150	3	95	90	10
8	2 : 100 : 300 : 500	150	6	100	50	50

in this case 2–3-fold excess of vinyl acetate was necessary to attain the maximal yield of target compound **II** (Table 2).

The most favorable conditions included the use of $Mn_2(CO)_{10}$ (2 mol %) as catalyst and 3 equiv of vinyl acetate. The latter was found to be rapidly converted into ethylidene diacetate. Under these conditions, the yield of vinyl acetate oligomers in acetonitrile at 150°C in 3 h did not exceed 10%. Prolonged reaction is undesirable because of increased yield of oligomers. Taking into account formation of ethylidene diacetate from vinyl acetate during the reaction, we performed a series of experiments aimed at elucidating the role of ethylidene diacetate in the transformations under study. We found that ethylidene diacetate is a more effective

Scheme 2.



acylating agent than vinyl acetate. The reaction of compound **I** with ethylidene diacetate in acetonitrile in the presence of $Mn_2(CO)_{10}$ at 155°C in 6 h afforded 95% of 1-acetyladamantane (**II**), and no by-products were detected.

EXPERIMENTAL

The purity of the products was checked, and the composition of the reaction mixtures was determined, by GLC on a Khrom-5 chromatograph equipped with a 1.2-m×3-mm column packed with 5% of SE-30 on Chromaton N-AW-HMDS; oven temperature programming from 50 to 280°C at a rate of 8 deg/min; carrier gas helium. The IR spectra were recorded on a Specord IR-75 spectrometer from samples dispersed in mineral oil. The ^{13}C NMR spectra were measured from solutions in $CDCl_3$ on a Jeol FX 90Q instrument (22.5 MHz); the chemical shifts were determined relative to tetramethylsilane. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT-112S instrument (ion source temperature 220°C). The elemental compositions were determined on a Carlo Erba 1106 analyzer.

Reactions of 1-bromoadamantane (I) with ethylidene diacetate. A 10-ml glass ampule was charged under argon with 29 mg (0.3 mmol) of $Mn_2(CO)_{10}$, 0.54 g (10 mmol) of 1-bromoadamantane (**I**), 1.25 ml (30 mmol) ethylidene diacetate, and 0.26 ml (30 mmol) of the corresponding solvent. The ampule was sealed, placed into a stainless-steel high-pressure microreactor, and heated for 6 h at 155°C under stirring. When the reaction was complete, the reactor and the ampule therein were cooled to room temperature, the ampule was opened, the solvent was distilled off, and the residue was distilled under reduced pressure or recrystallized from hexane or ethanol. The yields were calculated on the reacted 1-bromoadamantane (**I**) (GLC, internal standard technique; Table 1). The products were identified by comparing their physical constants with those of authentic samples or with reference data.

1-Acetyladamantane (II). mp 53.2–53.5°C (from ethanol); published data [4]: mp 54°C (from methanol). IR spectrum: ν 1720 cm^{-1} (C=O). ^{13}C NMR spectrum, δ_C, ppm: 24.30 (CH_3), 27.20 (C^3, C^5, C^7), 35.84 (C^4, C^6, C^{10}), 37.43 (C^2, C^8, C^9), 45.51 (C^1), 212.17 (C=O).

1-Adamantyl acetate (III). Sublimes at 97°C (10 mm) [7]. ^{13}C NMR spectrum, δ_C, ppm: 22.52 (CH_3), 30.76 (C^3, C^5, C^7), 36.17 (C^4, C^6, C^9), 41.28 (C^2, C^8, C^{10}), 80.12 (C^1), 170.19 (C=O).

Adamantan-1-ol (IV). mp 282–283°C (sublimes); published data [8]: mp 283–284°C (from methanol, sublimes). ^{13}C NMR spectrum, δ_C, ppm: 30.85 (C^3, C^5, C^7), 36.15 (C^4, C^6, C^{10}), 45.32 (C^2, C^8, C^9), 67.90 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 152 (24) $[M]^+$, 109 (5), 96 (7), 95 (100), 94 (14), 79 (5), 77 (7), 55 (5), 43 (15), 41 (12), 39 (10), 29 (7).

This study was performed under financial support by the Russian Foundation for Basic Research and the Government of Bashkortostan Republic (project no. 08-03-97005-Povolzh'e) and by the Federal Science and Innovation Agency of the Russian Federation (State contract no. 02.740.11.0631).

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