Synthesis of Adamantane Derivatives. I. Application of the Ritter Reaction to 1-Bromoadamantane

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(Received May 15, 1967)

The Ritter reaction is known to be an excellent method for the preparation of amides from tertiary alcohols, tertiary halides, or olefins.[1] Recently adamantane derivatives have attracted much attention, for the practical purpose of their pharmacological activity[2] and for their theoretical interest for organic chemists.[3] Stetter *et al.* have used the Ritter reaction to prepare *N*-1-adamantylacetamide from 1-bromoadamantane and acetonitrile[4]; more recently Haaf has reported a modified procedure, in which adamantane has been directly amidated in the presence of tertiary carbonium ions with hydrogen cyanide.[5] From our repetition of the above two methods, we found that Haaf's method always gave many by-products, which caused a lowering of the yield of the main product, and that, furthermore, the procedure of Haaf's method was more complicated than that of Stetter's. From these reasons we chose 1-bromoadamantane, easily obtainable from adamantane,[6] as the starting material.

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[1] a) J. Ritter and P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948); b) J. Ritter and J. Kalish, *ibid.*, **70**, 4048 (1948); c) F. Benson and J. Ritter, *ibid.*, **71**, 4128 (1949); d) L. Hartzel and J. Ritter, *ibid.*, **71**, 4130 (1949); e) R. Lusskin and J. Ritter, *ibid.*, **72**, 5577 (1950).

[2] For example, K. Gerson, E. Krumkalns, R. Brindle, F. Marshall and M. Root, *J. Med. Chem.*, **6**, 760 (1963).

[3] For a recent review, see R. Fort, Jr., and P. von R. Schleyer, *Chem. Revs.*, **64**, 277 (1964).

[4] H. Stetter, J. Mayer, M. Schwarz and K. Wulff, *Chem. Ber.*, **93**, 226 (1960).

[5] W. Haaf, *ibid.*, **97**, 3234 (1964).

[6] H. Stetter, M. Schwarz and A. Hirschhorn, *ibid.*, **92**, 1629 (1959).

Results and Discussion

The formation of amides by the Ritter reaction of 1-bromoadamantane can be explained by the following reaction scheme:

$$\underset{\text{I}}{\text{Ad-Br}} + H_2SO_4 \rightleftarrows \underset{\text{II}}{\text{Ad}^{\oplus}HSO_4^{\ominus}} + HBr \qquad (a)$$

$$\underset{\text{II}}{\text{Ad}^{\oplus}HSO_4^{\ominus}} + RCN \rightleftarrows \underset{\text{III}}{\text{Ad-N=C}^{\oplus}\text{-R}\cdot HSO_4^{\ominus}} \qquad (b)$$

$$\underset{\text{III}}{\text{Ad-N=C}^{\oplus}\text{-R}\cdot HSO_4^{\ominus}} + H_2O \rightarrow \underset{\text{IV}}{\text{AdNHCOR}} \qquad (c)$$

Consequently, it might be expected that the formation of an intermediate adamantyl immonium ion complex, III, is a key factor in carrying

TABLE 1. *N*-1-ADAMANTYLAMIDES FROM THE REACTION OF 1-BROMOADAMANTANE WITH VARIOUS NITRILES[a]

Run No.	Nitrile	Molar ratio of RCN to AdBr	Solvent	React. time	Product	Yield[c] %
1	CH_3CN	30	None	12 hr	$AdNHCOCH_3$[d]	90
2	$(CH_3)_2CHCN$	10	None	17	$AdNHCOCH(CH_3)_2$	78
3	$CH_3(CH_2)_2CN$	10	None	42	$AdNHCO(CH_2)_2CH_3$	56
4	$CH_2{=}CHCN$[b]	1	AcOH	48	$AdNHCOCH{=}CH_2$	84
5	C_6H_5CN	30	None	6	$AdNHCOC_6H_5$	66.5
6	$NCCH_2CO_2C_2H_5$	10	*n*-Bu_2O	48	$AdNHCOCH_2CO_2C_2H_5$	53
7	$NCCH_2CN$	10	*n*-Bu_2O & AcOH (1 : 2)	20	$AdNHCOCH_2CN$	64
8	$NC(CH_2)_2CN$	10	*n*-Bu_2O & AcOH (1 : 2)	48	$AdNHCO(CH_2)_2CN$	20
9	H_2NCH_2CN	5	*n*-Bu_2O & AcOH (1 : 1)	62	Not isolated	
10	$NH{=}\underset{\overset{\mid}{NH_2}}{C}NHCN$	10	*n*-Bu_2O & AcOH (4 : 1)	62	Not isolated	
11	$NCCH_2CONH_2$	5	*n*-Bu_2O & AcOH (2 : 3)	11 days	Not isolated	

a) Reactions were carried out at room temperature (about 20°C) in the presence of 6 mol of conc. H_2SO_4 except where otherwise noted.
b) The reaction was carried out at 40°C in the presence of 1 mol of conc. H_2SO_4 and 1 mol of BF_3-Et_2O.
c) The yields were calculated on the products recrystallized once.
d) See Ref. 4.

TABLE 2. PROPERTIES OF *N*-1-ADAMANTYLAMIDES

Amide (mp, °C)	IR(KBr), cm⁻¹ ν_{NH}	Amide-I & II		Formula		Anal. % C	H	N
$AdNHCOCH(CH_3)_2$	3250	1640		$C_{14}H_{23}ON$	Found	75.76	10.82	6.37
(147)		1550			Calcd	75.97	10.47	6.33
$AdNHCO(CH_2)_2CH_3$	3300	1650		$C_{14}H_{23}ON$	Found	75.62	10.84	6.51
(119—120)		1550			Calcd	75.97	10.47	6.33
$AdNHCOCH{=}CH_2$	3440	1670	1630[a]	$C_{13}H_{19}ON$	Found	75.12	9.41	6.84
(155—156)		1520			Calcd	76.05	9.33	6.82
$AdNHCOC_6H_5$	3440	1655	1580[b]	$C_{17}H_{21}ON$	Found	80.13	8.38	5.33
(149—150)		1515			Calcd	79.96	8.29	5.49
$AdNHCOCH_2CO_2C_2H_5$	3360	1670	1720[c]	$C_{15}H_{23}O_3N$	Found	67.93	8.79	5.26
(103—104)		1550			Calcd	67.89	8.74	5.28
$AdNHCOCH_2CN$	3440	1690	2280[d]	$C_{13}H_{18}ON_2$	Found	71.29	8.52	12.84
(147—148)		1530			Calcd	71.52	8.31	12.83
$AdNHCO(CH_2)_2CN$	3260	1650	2240[e]	$C_{14}H_{20}ON_2$	Found	72.45	8.01	12.60
(194—195)		1560			Calcd	72.38	8.68	12.06

a) $\nu_{C=C}$ b) Phenyl $\nu_{C=C}$ c) Ester $\nu_{C=O}$ d, e) $\nu_{C\equiv N}$

out the Ritter reaction successfully. However, it is known that 1-bromoadamantane is less reactive than other nonbridged tertiary halides because of the difficulty of forming the carbonium ion, II.⁷⁾ Since both reactions, (a) and (b), are thought to be reversible, the use of excess concentrated sulfuric acid and nitrile seems to favor the formation of II and, therefore, of III. In order to carry out the reaction homogeneously, liquid nitriles such as *n*-butyronitrile, isobutyronitrile, and benzonitrile were used as the solvents, but when nitriles could not be used as the solvents because of the solid state or low solubility of 1-bromoadamantane, *n*-butyl ether, glacial acetic acid or their mixture was used as the solvent. All of the results, including the products, are summarized in Table 1. From this table it may be seen that most amides were prepared in good yields, but the reactions with some nitriles which have strong electron-withdrawing groups, such as dicyandiamide, cyanoacetamide, and acetaminonitrile, were not successful. This fact can be explained by the lowered electron density of the nitrile group and, thus, the smaller affinity with the adamantyl carbonium ions. When 1-bromoadamantane was treated with acrylonitrile in concentrated sulfuric acid, many side reactions were observed involving polymerizations, from which none of the expected acrylamide derivatives could be separated. However, when the reaction was carried out in acetic acid by using a mixture of concentrated sulfuric acid and boron trifluoride etherate as a catalyst at 40°C, the desired *N*-1-adamantylacrylamide was obtained in a yield of 84%.

Experimental

The microanalyses were performed on a Yanagimoto C. H. N. Corder, Model MT-1, while the IR spectra were obtained on a JASCO Model IR-S infrared spectrophotometer. All the melting points were measured on a Yanagimoto micromelting-point apparatus and are uncorrected.

General Procedure of the Ritter Reaction. The reaction was carried out at room temperature by using an excess of nitrile and of concentrated sulfuric acid to 1-bromoadamantane. After making sure by the thin-layer chromatography that no more 1-bromoadamantane existed in the reaction mixture, the mixture was poured onto cracked ice-water and the product was extracted with ether. The ether layer was dried over anhydrous sodium sulfate and evaporated to dryness to give a crude amide. Crude amide was usually purified by recrystallization from aqueous methanol, and in some cases by chromatography on a silica-gel column. The results are summarized in Table 1. Table 2 shows the analytical and some physical properties of these products.

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7) P. von R. Schleyer and R. Nicholas, *J. Am. Chem. Soc.*, **83**, 2700 (1961).