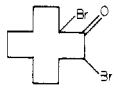
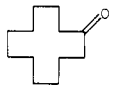
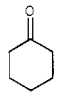
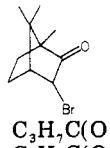
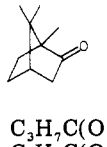
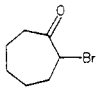
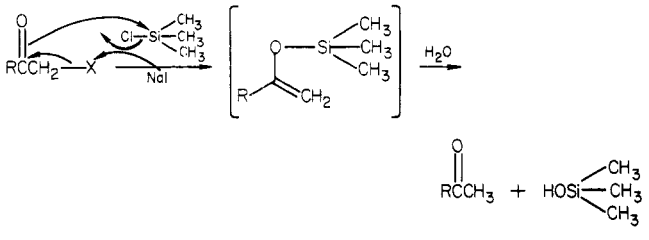
Table I. Reduction of α-Halo Ketones with Sodium Iodide/Chlorotrimethylsilane

substrate	ketone	amount (mmol) of reagent[c] ClSi-$(CH_3)_3$	NaI	t, h/ temp[d]	yield,[a,b] %	mp or bp/ torr, °C	lit.[5,6] mp or bp/torr, °C
$PhC(O)CH_2Br$	$PhC(O)CH_3$	15	15	5/rt	91	82/12	79/10
$PhC(O)CHBrPh$	$PhC(O)CH_2Ph$	15	15	3/rt	94	60.2	60-61
$PhC(O)CH_2Cl$	$PhC(O)CH_3$	15	15	4/rt	89	80-82/12	79/10
p-$PhPhC(O)CH_2Br$	p-$PhPhC(O)CH_3$	15	15	3/rt	93	120.5	120-121
		40	60	12/rt 2/reflux	98 98	60.7	59-61
		20	30	48/rt 3/reflux	75 78	128-129/760	130/760
		20	30	48/rt 3/reflux	72 78	48-49/15	47/15
		20	30	12/rt 2/reflux	89 87	176.8	175-179
$C_3H_7C(O)CH(Cl)C_3H_7$	$C_3H_7C(O)CH_2C_3H_7$	15	15	10/rt	85	50-52/15	70/26
$C_3H_7C(O)CH(Br)C_3H_7$	$C_3H_7C(O)CH_2C_3H_7$	15	30	8/rt	88	50-52/15	70/26
		20	30	8/rt	88	31-32/0.28	180/760

[a] Yields of the isolated products of ≥99% purity as determined by TLC (benzene as eluent) and IR and NMR spectroscopy. [b] All physical data including IR and NMR spectra were consistent with the literature data. [c] In every case 10 mmol of substrate was used. [d] rt is room temperature.

Scheme I



Experimental Section

(A) General Procedure for Reduction of α-Halogenated Aliphatic Ketones. To a solution of corresponding α-halo ketone (10 mmol) in dry acetonitrile (15 mL) is added a solution of sodium iodide (15 mmol) dissolved in acetonitrile (15 mL) at room temperature, and the mixture is stirred for 5 min. A solution of chlorotrimethylsilane (15 mmol) in acetonitrile (5 mL) is then added to the above mixture, and this is stirred at room temperature until the reaction is completed (monitored by TLC and NMR spectroscopy). The reaction mixture is then poured into a 10% aqueous solution of sodium thiosulfate, which removes the iodine liberated in the reaction and discharges the brown color of the solution. The colorless mixture is extracted with ether (3 × 25 mL), washed with water (2 × 25 mL) followed by brine (15 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent under vacuum gives almost pure reduced product, which is further purified by distillation or recrystallization and identified by physical and spectral characteristics.

General Procedure for Reduction of α-Halogenated Cycloalkyl Ketones. To a magnetically stirred solution of the corresponding α-halocycloalkyl ketone (10 mmol) in dry acetonitrile is added a solution of sodium iodide (30 mmol) in acetonitrile (20 mL), and the mixture is stirred for 5 min. A solution of chlorotrimethylsilane (20 mmol) in acetonitrile (5 mL) is then added to the above mixture while stirring is continued at room temperature until completion of the reaction. The workup is done according to the same procedure as that described previously for α-halogenated aliphatic ketones.

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Registry No. 2-Bromoacetophenone, 70-11-1; 2-bromo-2-phenylacetophenone, 1484-50-0; 2-chloroacetophenone, 532-27-4; 2-bromo-4′-phenylacetophenone, 135-73-9; 2,12-dibromocyclododecanone, 24459-40-3; 2-chlorocyclopentanone, 694-28-0; 2-chlorocyclohexanone, 822-87-7; 3-bromo-2-bornanone, 76-29-9; 5-chloro-4-octanone, 24251-73-8; 5-bromo-4-octanone, 61539-87-5; 2-bromocycloheptanone, 766-65-4; acetophenone, 98-86-2; 2-phenylacetophenone, 451-40-1; 4′-phenylacetophenone, 92-91-1; cyclododecanone, 830-13-7; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; camphor, 76-22-2; 4-octanone, 589-63-9; cycloheptanone, 502-42-1; sodium iodide, 7681-82-5; chlorotrimethylsilane, 75-77-4.

Synthetic Methods and Reactions. 86.[1] Novel Synthesis of *N*-(1-Adamantyl)amides from Adamantane

George A. Olah* and B. G. Balaram Gupta

Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90007

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Recently we reported[2] a convenient and mild Ritter-type synthesis of amides from alkyl(arylalkyl) halides using $NO^+PF_6^-$ as the halide-abstracting reagent in the presence of nitriles. A similar reaction has been reported to take

(1) For part 85, see G. A. Olah, M. Arvanaghi, and Y. D. Vankar, *J. Org. Chem.*, previous paper in this issue.

(2) G. A. Olah, B. G. B. Gupta, and S. C. Narang, *Synthesis*, 274 (1979). Also see B. G. Balaram Gupta, Ph.D. Thesis, University of Southern California, 1979.

0022-3263/80/1945-3532$01.00/0

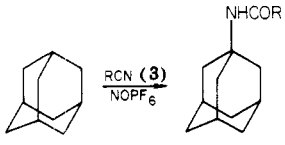
Table I. Conversion of Adamantane to the Corresponding *N*-(1-Adamantyl)amides with Various Nitriles

nitrile 3	yield of amide 2,[a] %	mp, °C found[b]	mp, °C lit.[2]
CH_3CN	98	147	148-149
C_2H_5CN	80	104.8	102.5-104.5
n-C_3H_7CN	78	120.5	119.1-120
C_6H_5CN	70	147.9	144-146
$C_6H_5CH_2CN$	82	177.1	177.1

[a] Yield of isolated, pure product. Purity was checked by TLC and IR and NMR spectroscopy. [b] The products were purified by recrystallization with hexane/chloroform as solvent.

place with nitronium salts, although it is limited to aliphatic halides.[3] The utility of these transformations as well as the hydride-abstracting ability of nitrosonium ion[4] prompted us to extend our studies to the Ritter-type reaction of hydrocarbons themselves with nitrosonium salts in the presence of nitriles.

We report that adamantane (1) reacts readily with a variety of nitriles (3) in the presence of nitrosonium hexafluorophosphate to afford the corresponding *N*-(1-adamantyl)amides (2) in high yield (eq 1). *N*-(1-



(1)

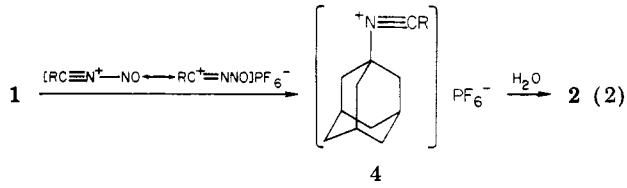
1 2

R = CH_3, C_2H_5, C_3H_7, C_6H_5, or $C_6H_5CH_2$

Adamantyl)amides (2) have previously been prepared by starting either from 1-adamantanol[5] or 1-haloadamantanes[6] in Ritter reactions, but no direct synthesis from adamantane was known. The compounds 2 are known to possess a wide range of pharmacological activities.[7] Further, several substituted 1-aminoadamantanes are known antiviral agents.[8] Thus, the present synthesis of 2 allows their economical and simple preparation directly from adamantane (1).

When a solution of $NO^+PF_6^-$ in acetonitrile was treated with a slurry of adamantane in dichloromethane at ambient temperature, the reaction was completed in about 5 h. Quenching of the reaction mixture with water afforded *N*-(1-adamantyl)acetamide in practically quantitative yield (see Table I). Similarly, propionitrile, butyronitrile, benzonitrile, and phenylacetonitrile reacted smoothly with 1 to give the corresponding amides in high yield (eq 1). In these latter cases, the reaction could be carried out in a mixture of solvents such as nitromethane and dichloromethane in order to solubilize both 1 and $NO^+PF_6^-$. It is interesting to note that, in all the cases studied, the reaction gave only the monosubstitution products with no traces of other products formed under the mild reaction conditions. Prolonged reaction intervals, however, yielded tarry mixtures of products.

The reaction is not considered to proceed via hydride abstraction from adamantane by $NO^+PF_6^-$ in the quite basic nitrile media to give 1-adamantyl cation and its subsequent alkylation of the nitrile but more probably via electrophilic attack by the nitrile-NO^+ complex to form Ritter intermediate 4 as shown in eq 2.



4

In summary, the present method of preparation of 2 is a highly efficient and inexpensive method and should find wide application in medicinal chemistry and pharmacology.

Experimental Section

Typical Procedure for the Conversion of Adamantane to *N*-(1-Adamantyl)acetamide. To a solution of nitrosonium hexafluorophosphate (3.5 g, 20 mmol) in dry acetonitrile (15 mL) under a stream of dry nitrogen was slowly added with continuous stirring a slurry of adamantane (1.36 g, 10 mmol) in dichloromethane (15 mL). Soon, the reaction started to take place with dissolution of adamantane, and the solution turned pale red. After 5 h of being stirred at ambient temperature,[9] the reaction mixture was quenched with water (10 mL) and taken up in ether (2 × 50 mL). The ethereal extract was washed successively with a 10% solution of aqueous sodium bicarbonate (2 × 25 mL), water, and brine and dried over Na_2SO_4. Removal of ether gave nearly pure crystalline *N*-(1-adamantyl)acetamide (1.89 g, 93%). It was further purified by recrystallizing in a hexane–chloroform (2:8) solvent mixture; mp 147 °C (lit. mp 148–149 °C).

Similar conditions were also used in the case of the reaction with propionitrile (Table I).

Typical Procedure for the Conversion of Adamantane to *N*-(1-Adamantyl)benzamide. To a solution of nitrosonium hexafluorophosphate (3.5 g, 20 mmol) in dry nitromethane (10 mL) in a 50-mL flask purged with dry nitrogen was added with continuous stirring benzonitrile (1.23 g, 12 mmol). To this mixture, a slurry of adamantane (1.36 g, 10 mmol) in dichloromethane (15 mL) was then slowly introduced. Soon, adamantane reacted to give a clear red solution. The reaction mixture was then stirred at ambient temperature for 5 h, quenched with water, and worked up as described above.[9] The crude product contained some unreacted benzonitrile. Purification was achieved by recrystallization of the product with hexane–chloroform (2:8) as the solvent mixture, which afforded 1.75 g (70%) of pure *N*-(1-adamantyl)benzamide identical with an authentic sample (Table I).

A similar procedure was employed in the case of the reactions with butyronitrile and phenylacetonitrile (Table I).

Acknowledgment. Support of our work by the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

Registry No. 1, 281-23-2; 2 (R = CH_3), 880-52-4; 2 (R = C_2H_5), 3717-46-2; 2 (R = C_3H_7), 3717-49-5; 2 (R = C_6H_5), 19026-84-7; 2 (R = $C_6H_5CH_2$), 16790-82-2; 3 (R = CH_3), 75-05-8; 3 (R = C_2H_5), 107-12-0; 3 (R = C_3H_7), 109-74-0; 3 (R = C_6H_5), 100-47-0; 3 (R = $C_6H_5CH_2$), 140-29-4.

(3) (a) R. D. Bach, J. W. Holubka, and T. A. Taaffee, *J. Org. Chem.*, 44, 1739 (1979); (b) R. D. Bach, J. W. Holubka, R. C. Badger, and S. J. Rajan, *J. Am. Chem. Soc.*, 101, 4416 (1979).

(4) G. A. Olah, G. Salem, J. S. Staral, and T. L. Ho, *J. Org. Chem.*, 43, 173 (1978).

(5) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 70, 4045 (1948).

(6) S. Tadashi, E. Shoji, and T. Takeshi, *Bull. Chem. Soc. Jpn.*, 41, 236 (1968).

(7) R. C. Fort, Jr., "Adamantane: the Chemistry of Diamond Moleucles", Marcel Dekker, New York, 1976.

(8) (a) P. E. Aldrich, E. C. Herman, W. E. Meier, M. Paulshock, W. W. Prichard, J. A. Snyder, and J. C. Watts, *J. Med. Chem.*, 14, 535 (1971); (b) E. I. duPont de Nemours and Co., Netherlands Appl. 6 403 294; *Chem. Abstr.*, 63, 9838b (1965); (c) E. I. duPont de Nemours and Co., Belgian Patent 646 581; *Chem. Abstr.*, 63, 1472b (1965); (d) M. Paulshock and J. C. Wats (to E. I. duPont de Nemours and Co.), US Patent 3 310 469; *Chem. Abstr.*, 67, 11275 (1967).

(9) The reaction time can be shortened by warming the reaction mixture to 50–60 °C (~0.5–2 h).