NMR ($CDCl_3$) δ 6.1 (t, J = 54 Hz) and 9.7 (br NH, OH); ^{19}F NMR ($CDCl_3$) δ −126.3 (d, J = 54 Hz).

2,2-Difluoro-*N*,*N*′-dihydroxy-1,3-propanediamide (7). A solution of 1.19 mol of sodium methoxide in 500 mL of methanol was added dropwise to a stirred suspension of 82.71 g (1.19 mol) of hydroxylamine hydrochloride in 150 mL of methanol. The precipitated NaCl was filtered off, and 100 g (0.595 mol) of dimethyl difluoromalonate[4] was added dropwise. The reaction mixture was stirred overnight and then evaporated to dryness to give 100 g (99% yield) of 2,2-difluoro-*N*,*N*′-dihydroxy-1,3-propanediamide as colorless crystals. A sample was recrystallized from acetonitrile: mp 143–145 °C; IR (KBr) 1715 cm^{-1} (C=O); ^{19}F NMR (acetone-d_6) δ −114.6 (s). Anal. Calcd for $C_3H_4F_2N_2O_4$: C, 21.19; H, 2.37; F, 23.34; N, 16.47. Found: C, 20.89; H, 2.44; F, 22.28; N, 16.47.

2,2,3,3,4,4-Hexafluoro-*N*,*N*′-dihydroxy-1,5-pentanediamide. A solution of 0.168 mol of sodium methoxide in 100 mL of methanol was added dropwise to a stirred suspension of 11.8 g (0.168 mol) of hydroxylamine hydrochloride in 50 mL of methanol. The precipitate, NaCl, was filtered off, and 24.87 g (0.084 mol) of diethyl perfluoroglutarate was added to the filtrate. The reaction mixture was stirred overnight and then evaporated to dryness to give 22.0 g (97% yield) of 2,2,3,3,4,4-hexafluoro-*N*,*N*′-dihydroxy-1,5-pentanediamine as colorless crystals. A sample was recrystallized from ethyl acetate for analysis: mp 156–160 °C; IR (neat) 1680 cm^{-1} (C=O); ^{19}F NMR (Me_2SO-d_6) δ −118.6 (4 F), −122.9 (2 F). Anal. Calcd for $C_5H_4F_6N_2O_4$: C, 22.24; H, 1.49; N, 10.37. Found: C, 22.21; H, 1.68; N, 9.70.

Registry No. 1 (R_f = CH_2F), 760-29-2; 1 (R_f = CHF_2), 92144-81-5; 1 (R_f = CF_3), 1514-45-0; 1 (R_f = CF_3CF_2), 87051-00-1; 1 (R_f = $CF_3(CF_2)_2$), 87050-96-2; 1 (R_f = $CF_3(CF_2)_6$), 15435-88-8; (*Z*)-2 (R_f = CH_2F), 92144-84-8; (*E*)-2 (R_f = CH_2F), 92144-92-8; 2 (R_f = CHF_2), 92144-85-9; 2 (R_f = CF_3), 60556-44-7; 2 (R_f = CF_3CF_2), 92144-86-0; 2 (R_f = $CF_3(CF_2)_2$), 92144-87-1; 2 (R_f = $CF_3(CF_2)_6$), 92144-88-2; 4 (R_f = CH_2F), 462-48-6; 4 (R_f = CHF_2), 372-10-1; 4 (R_f = CF_3), 460-49-1; 4 (R_f = CF_3CF_2), 356-74-1; 4 (R_f = $CF_3(CF_2)_2$), 424-62-4; 4 (R_f = $CF_3(CF_2)_6$), 335-91-1; 6, 92144-91-7; 7, 92144-83-7; $Me_3SiNHSiMe_3$, 999-97-3; $HONHC(O)(CF_2)_3C(O)NHOH$, 92144-82-6; $Me_3SiOH{=}C(OSiMe_3)(CF_2)_3C(OSiMe_3){=}NOSiMe_3$, 92144-89-3; $Me_3SiON{=}C(OSiMe_3)CF_2C(OSiMe_3){=}NOSiMe_3$, 92144-90-6; $CF_2(CF_2NCO)_2$, 13044-43-4; $FCH_2C(O)OEt$, 459-72-3; $F_2CHC(O)OEt$, 454-31-9; $F_2C(C(O)OMe)_2$, 379-95-3; $EtOC(O)(CF_2)_3C(O)OEt$, 424-40-8.

(4) England, D. C.; Kraft, R. L.; Krespan, C. G. U.S. Patent 4 316 986, 1982.

Synthesis under High Pressure. Michael Additions to a Sterically Hindered Steroidal 4-En-3-one System[1,2]

Shiro Hashimoto, Kiyoshi Matsumoto,* and Shinichi Otani

Department of Chemistry, College of Liberal Arts and Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Received April 3, 1984

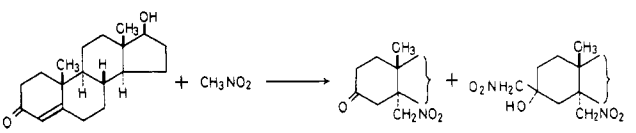
Michael additions to the C-1 and C-5 in steroidal 1-en-3-one and 4-en-3-one systems are generally difficult to achieve, probably due to steric hindrance; they are limited to attack of cyanide and/or phenyl thiolate ion.[3] Indeed, Michael additions of nitromethane[4] to these steroidal enones have been reported to be unsuccessful.[3c] The steroidal 4-en-3-one system is apparently more hindered than the 1-en-3-one system since sulfur nucleophiles are reported to give 1α adducts with 1,4-dien-3-one.[3c,5] Thus, in view of recent work on high pressure Michael reactions,[6,7] we chose to investigate the problem using testosterone (1) as a first example of 4-en-3-one systems.

Table I. Michael Addition of Testosterone (1) with Nitromethane (2) at 9 kbar and 30 °C for 6 Days

				isolated yield, %		
entry	1, mmol	2, mmol	catalyst/solvent	3	4	1
1[a]	5	50	0.5 M TBF/THF	8	5	81
2	5	50	0.5 M TBF/THF	5	79	5
3	5	10	0.5 M TBF/THF	22	36	18
4	5	5	0.5 M TBF/THF	25	15	41
5	3	30	DBU(3 mmol)/CH_3CN	4	57	8
6	3.5	7	DBU(3.5 mmol)/CH_3CN	38	7	31

[a] At 1 bar and room temperature for 1 week.

At atmospheric pressure, 1 is inert to nitromethane (2) in the presence of such bases as 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and triethylamine. The reaction of 1 with excess of 2 catalyzed by tetra-*n*-butylammonium fluoride (TBF)[8] proceeds poorly (ca. 10% after 1 week). At high pressure, the reaction of 1 with 2 was carried out either in 0.5 M TBF/THF or DBU/CH_3CN in a 8-mL Teflon capsule stored for 6 days at 900 MPa (1 MPa ≈ 10 atm) and ca. 30 °C. The usual workup and chromatographic separation (see Experimental Section) gave the 1:1 adduct 3, mp 209–211 °C and the 1:2 adduct 4, mp 172–174 °C.



1 2 3 4

The results are summarized in Table I. Both 3 and 4 appeared to be a single substance as revealed by ^{13}C NMR and TLC (Experimental Section). The configuration of these adducts is presumed to be 5α-nitromethyl and 3β,5α-bis(nitromethyl), respectively, based upon steric consideration. The use of a large excess of 2 led to the predominant formation of 4 arising from initial Michael addition followed by nitro-aldol reaction (entries 2 and 5). The formation of 4 could be considerably suppressed by employing 1 or 2 equiv of 2 (entries 3, 4, and 6), although this also led to lower conversion. For this purpose, DBU in acetonitrile proved to be a superior base.

Thus, the high pressure Michael addition may be useful for functionalization of the sterically hindered steroidal 4-en-3-one systems. Our studies on the high pressure Michael additions of other steroidal enones to a variety of nucleophiles are continuing.

(1) Dedicated to Professor N. H. Cromwell on the occasion of his retirement and of his 70th birthday.

(2) Presented at the 49th National Meeting of the Chemical Society of Japan, April, 1984, Tokyo.

(3) (a) Nagata, W.; Hirai, S.; Itazaki, H.; Takeda, K. *J. Org. Chem.* **1961**, *26*, 2413. (b) Nagata, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4654. (c) Campbell, M. M.; Jigajinni, V. R.; Wightman, R. H. *Tetrahedron Lett.* **1979**, 2455; *J. Chem. Res., Synop.* **1981**, 184; *J. Chem. Res., Miniprint* **1981**, 2537 and references cited.

(4) For review of the utility of the nitroaliphatic compounds in organic synthesis, see: Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1.

(5) Granwell, J. F.; Benson, H. D.; Johnston, J. O.; Petrov, V. *Steroids* **1976**, *27*, 759.

(6) (a) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642. (b) Dauben, W. G.; Gerdes, J. M. *Tetrahedron Lett.* **1983**, *24*, 3841. (c) Matsumoto, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 770; **1980**, *19*, 1013.

(7) For most recent examples of the concise reviews of high pressure reactions, see: le Noble, W. J. *Chem. Unserer Zeit* **1983**, *17*, 152. Welzel, P. *Nachr. Chem. Techn. Lab.* **1983**, *31*, 148.

(8) For an example of Michael reaction catalyzed by tetra-*n*-butylammonium fluoride, see: Hashimoto, S.; Matsumoto, K.; Otani, S.; Hayami, J.; Yoshida, H. *Synthesis* **1984**, 164.

0022-3263/84/1949-4543$01.50/0

Experimental Section

Melting points were taken on a Yanagimoto micro hotstage and are uncorrected. Infrared spectra on KBr pellets of solids were measured on a JASCO IR-G spectrophotometer. ^1H NMR spectra of $CDCl_3$ solutions with Me_4Si as internal standard (δ = 0 ppm) were recorded on a Hitachi R-40 (90 MHz) spectrometer. The ^{13}C NMR spectra of $CDCl_3$ solutions with Me_4Si as internal standard were taken on a JEOL FX-90Q spectrometer.

General Procedure for High Pressure Reactions. A mixture of testosterone and nitromethane (see Table I) in 0.5 M tetra-*n*-butylammonium fluoride/tetrahydrofuran[9] or in 1,8-diazabicyclo[5.4.0]undec-7-ene/acetonitrile (see Table I) in a 8-mL Teflon tube was pressurized at 900-MPa hydrostatic pressure for 6 days at ca. 30 °C.[10] After release of the pressure, the sample was removed from the high pressure vessel, diluted with ethyl acetate (100 mL), and washed either with water (50 mL × 6 in the case of TBF) or with 1 N HCl, 1 N $NaHCO_3$, and water (in the case of DBU), and then dried over $MgSO_4$. The mixture was concentrated and chromatographed on silica gel with benzene–ethyl acetate (7/3, v/v) as eluent, giving the 1:1 adduct **3** and the 1:2 adduct **4**.

5α-(Nitromethyl)-17β-hydroxyandrostan-3-one (3): mp 209–211 °C; IR (KBr) 1375, 1545 (NO_2), 1715 (CO) cm^{-1}; ^1H NMR (90 MHz) δ 0.77 (s, 3), 1.03 (s, 3), 1.0–4.0 (complex, 22), 2.95 (d, J = 15 Hz, 1), 4.46 (s, 2); ^{13}C NMR (90 MHz) δ 10.9, 17.1, 20.6, 23.2, 26.4, 29.7, 30.3, 31.5, 34.4, 36.5, 36.8, 38.3, 42.0, 45.2, 51.0, 81.3 (d, C-17), 82.5 (t, 5α-CH_2NO_2), 209.5 (s, C=O). Anal. Calcd for $C_{20}H_{31}O_4N$: C, 68.72; H, 8.76; N, 4.01. Found: C, 68.69; H, 9.09; N, 4.09.

3β,5α-Bis(nitromethyl)-17β-hydroxyandrostan-3α-ol (4): 172–174 °C; IR (KBr) 1380, 1545 (NO_2), 3375, 3500 sh (OH) cm^{-1}; ^1H NMR (90 MHz) δ 0.74 (s, 3), 0.94 (s, 3), 1.0–4.0 (complex, 22), 3.80 (s, 1) 4.43 (br s, 4), 5.49 (d, J = 10 Hz, 1); ^{13}C NMR (90 MHz) δ 10.9, 17.6, 20.3, 23.3, 26.7, 27.2, 29.0, 30.6, 31.2, 32.7, 34.7, 36.6, 38.4, 40.5, 41.8, 42.6, 51.2, 71.2 (s, C-3), 81.6 (d, C-17), 83.7 (t, 5α-CH_2NO_2), 86.2 (t, 3β-CH_2NO_2). Anal. Calcd for $C_{21}H_{34}O_6N_2$: C, 61.44; H, 8.35; N, 6.82. Found: C, 61.39; H, 8.35; N, 6.82.

Registry No. 1, 58-22-0; 2, 75-52-5; 3, 92078-58-5; 4, 92078-59-6.

(9) TBF (1 M) in THF is purchased from Aldrich Chemical Co. and is used upon dilution to 0.5 M in THF.

(10) For a description of the high pressure apparatus employed in this study, see: Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis*, in press.

Methanesulfonic Acid.[1] A Useful Cyclizing Acidic Reagent

Alberto A. Leon,*† Guido Daub,‡ and I. Robert Silverman

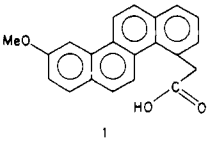
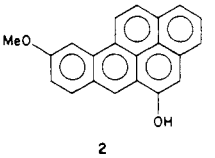
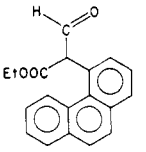
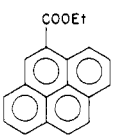
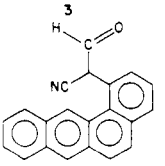
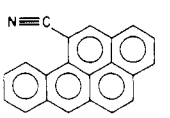
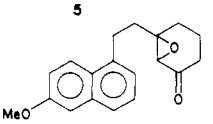
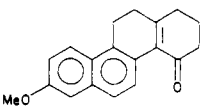
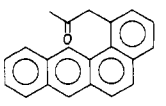
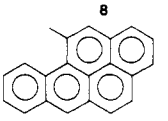
Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

Received October 3, 1983

The development of novel synthetic approaches to polycyclic aromatic hydrocarbons (PAH) often requires cyclization reactions of carbonyls (aldehydes, ketones, carboxylic acids, and esters) into aromatic rings. In the past, different conditions have been used to carry out the above-mentioned transformations. Among them, HF, phosphoric acid, and sulfuric acid are the most widely used.

This note intends to introduce methanesulfonic acid (neat and as a CH_2Cl_2 solution) as a milder and versatile reagent for the cyclization of a wide variety of substrates.

Table I

substrate	product[a]	isolated yield,[b] %	method
 1	 2	85	A
 3	 4	84 94	A B
 5	 6	86	B
 7	 8	70	B
 9	 10	74	A[7]

[a] All products were properly characterized. [b] Reported yields correspond to analytical pure material.

Results and Discussion

Methanesulfonic acid (MSA) first came to our attention when we considered Eaton's reagent[2] (MSA/P_2O_5) as a suitable alternative to phosphoric acid for the cyclization of a group of aromatic carboxylic acids. When attempting to test the solubility of our starting materials (benz[*a*]-anthracene and chryseneacetic acids)[3] in MSA we discovered that excellent yields of cyclization product could be obtained by excluding the P_2O_5 from the mixture.

Further investigations have shown that MSA is capable of cyclizing aldehydes and ketones[4] as well as carboxylic acids.[5] Yields are generally excellent and the appearance of often found polymeric material is virtually eliminated.

In some cases, we found that an even milder cyclizing agent was required due to the high sensitivity of the starting material toward polymerization. Solutions of MSA in different organic solvents were tested as an alternative. A 5–10% (v/v) solution of MSA in methylene chloride was found to be a more efficient reagent than neat MSA for the cyclization of very reactive systems such as β-formyl esters[6] and α-epoxy ketones.[5] Some representative examples are given in Table I.

Experimental Section

MSA was obtained as reagent grade from Aldrich and was distilled under reduced pressure (3.0 torr, 70 °C) before using.

(1) MSA is a slightly viscous liquid (d = 1.48) which can be easily purified by distillation at reduced pressure. Most cyclizable substrates are soluble in this reagent. MSA is also soluble in a variety or organic solvents (ethyl, ether, THF, CH_2Cl_2, etc.).

(2) Eaton, P. E.; Carlson, C. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

(3) Bodine, R. S.; Hylarides, M. D.; Daub, G. H.; VanderJagt, D. L. *J. Org. Chem.* **1978**, *43*, 4025.

(4) Lyle, T. E.; Daub, G. H. *J. Org. Chem.* **1979**, *44*, 4933.

(5) Silverman, I. R.; Daub, Tg. H., unpublished results.

(6) Leon, A. A.; Daub, G. H.; VanderJagt, D. L. *J. Org. Chem.*, in press.

(7) Bodine, R. S.; Daub, G. H. *J. Org. Chem.* **1979**, *44*, 4461.

† Graduate Fellow FONINVES, Caracas, Venezuela (1979–1983). Present address: Radiology Department, UNM School of Medicine, Albuquerque, NM 87131.

‡ Deceased June 4, 1984.

0022-3263/84/1949-4544$01.50/0