130 °C for 93 h and poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was washed 4 times with ether. The combined organic layers were washed once with saturated aqueous sodium bicarbonate, once with 0.5 N hydrochloric acid, and once with water and dried with anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator and the residue purified by flash chromatography (5% ethyl acetate/hexanes) to yield 2.05 g (73%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 0.13 (s, 9), 0.83 (s, 3), 0.86, (s, 6), 0.92 (s, 3), 1.15–2.30 (m, 19); ^{13}C NMR ($CDCl_3$) δ 0.70, 18.4, 18.8, 20.3, 22.6, 22.8, 23.6, 23.8, 27.6, 28.0, 29.4, 34.9, 36.0, 37.4, 39.5, 43.7, 57.2, 128.0, 140.5.

9α-Fluoro-8-oxodes-*A*,*B*-cholestane (4). Under an argon atmosphere 1.87 g (7.10 mmol) of *N*-fluoropyridinium triflate (a gift from Onoda Cement Co., Japan) was added to 2.39 g (7.10 mmol) of kinetic silyl ether **2** in 36 mL of dry methylene chloride. The solution was refluxed for 2 h and subjected to a standard aqueous workup. The solvent was removed on a rotary evaporator and the residue was purified by flash chromatography (5% ethyl acetate/hexanes) to yield 139 mg (7%) of the α,β-unsaturated ketone 8,[14] 139 mg (7%) of *cis*-Grundmann's ketone (7),[14,15] 292 mg (14%) of 14β-fluoro ketone **6**, and 732 mg (36%) of a 3:1 mixture of 9α-fluoro ketone **4** and 14α-fluoro ketone **5**, all as colorless oils. Spectra for the 14-fluoro ketones will be given below. The 9α-fluoro ketone **4** was purified by HPLC (5% ethyl acetate/hexanes): IR (thin film) 2970, 1740, 1393, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (s, 3), 0.82 (d, 3, J = 1.1 Hz), 0.85 (d, 3, J = 1.1 Hz), 0.91 (d, 3, J = 6.4 Hz), 1.00–2.30 (m, 17), 3.03 (dt, 1, J_{HF} = 11.6 Hz, J_{AB} = 6.8 Hz), 4.56 (dt, 1, J_{HF} = 50.6 Hz, J_{AB} = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 11.9, 18.3, 18.7, 22.5, 22.8, 23.7, 27.5, 28.0, 30.3, 30.8, 33.9, 35.5, 35.9, 39.4, 51.3, 56.7, 57.8, 57.9, 91.3, 94.8, 206.4, 206.7; ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −184.8 (t, J_{HF} = 47.5 Hz); MS m/z (relative intensity) 282 (11, M^+), 221 (100). Anal. Calcd for $C_{18}H_{31}FO$: C, 76.53; H, 11.08. Found: C, 76.28; H, 10.90.

14α- and 14β-Fluoro-8-oxodes-*A*,*B*-cholestane (5 and 6). Under an argon atmosphere 1.56 g (6.09 mmol) of *N*-fluoropyridinium triflate was added to 2.05 g (6.09 mmol) of the thermodynamic silyl ether **3** in 30 mL of dry methylene chloride. The mixture was stirred for 24 h at room temperature and then subjected to a standard aqueous workup. The solvent was removed on a rotary evaporator and the residue was purified by flash chromatography (5% ethyl acetate/hexanes) to yield 283 mg (16%) of the 14α-fluoro ketone **5** [IR (thin film) 2970, 1738, 1476, 1394, 918 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65 (s, 3), 0.83 (d, 3, J = 1.1 Hz), 0.85 (d, 3, J = 1.1 Hz), 0.88 (d, 3, J = 6.0 Hz), 1.05–2.26 (m, 17), 2.83 (m, 2); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.8, 18.6, 22.5, 22.8, 23.2, 23.8, 24.7, 25.2, 26.0, 27.9, 31.5, 31.7, 31.8, 34.7, 36.1, 37.6, 39.5, 51.6, 52.1, 52.5, 107.9, 111.3, 207.3, 207.9; ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −151.6 (q, J = 20 Hz); MS m/z (relative intensity) 282 (20, M^+), 55 (100). Anal. Calcd for $C_{18}H_{31}FO$: C, 76.53; H, 11.08. Found: C, 76.70; H, 10.95] and 475 mg (27%) of the 14β-fluoro ketone **6**: IR (thin film) 2970, 1738, 1478, 1393, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3), 0.83 (s, 3), 0.87 (d, 3, J = 6.0 Hz), 1.01 (d, 3, J = 2.7 Hz), 1.04–1.90 (m, 16), 2.15–2.45 (m, 2), 2.56 (m, 1); ^{13}C NMR ($CDCl_3$) δ 16.0, 16.2, 19.4, 21.8, 22.5, 22.7, 24.5, 25.5, 25.6, 27.9, 28.7, 29.1, 34.2, 34.3, 36.9, 38.2, 39.3, 49.3, 51.7, 52.1, 103.6, 107.5, 207.2, 207.7; ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −166.4 (s); MS m/z (relative intensity) 282 (6, M^+), 95 (100).

(7*E*)-9-Hydroxyvitamin D_3 (10). Under an argon atmosphere, at −78 °C, were added 0.84 g (1.85 mmol) of the A-ring phosphine oxide **9**,[7] 18.5 mL of dry THF, and 1.26 mL (1.94 mmol, 1.05 equiv) of *n*-butyllithium (1.54 M solution in hexanes). An orange solution was obtained and stirred at −78 °C for 0.5 h. Compound **4** (0.54 g, 1.91 mmol) in 9.2 mL of dry THF was added. The solution was stirred at −78 °C for 1 h and warmed to room temperature, slowly. The solvent was removed on a rotary evaporator. The residue was dissolved in ether and subjected to a standard aqueous workup. The solvent was removed on a rotary evaporator and the residue purified by flash chromatography (10% ethyl acetate/hexanes) to yield 0.23 g (24%) of the C-3 silylated product as a colorless oil: IR (thin film) 3350, 2965, 1470, 1257, 1090, 871, 835, 772 cm^{-1}; UV (hex) λ_{max} 261 nm (ϵ = 12000); ^1H NMR ($CDCl_3$) δ 0.05 (s, 3), 0.06 (s, 3), 0.60 (s, 3), 0.83 (s, 3), 0.87 (s, 12), 0.92 (d, 3, J = 6.0 Hz), 1.10–2.64 (m, 24), 3.74 (septet, 1, J = 4.1 Hz), 4.08 (s, 1), 4.75 (s, 1), 5.02 (s, 1), 6.25 (d, 1, J = 11.3 Hz), 6.39 (d, 1, J = 11.4); ^{13}C NMR (C_6D_6) δ −4.4, 12.1, 18.3, 19.4, 22.8, 23.1, 24.4, 26.1, 26.5, 28.4, 28.9, 30.7, 32.9, 35.1, 36.4, 36.6, 36.7, 39.9, 46.7, 47.6, 50.4, 55.1, 70.8, 76.0, 113.2, 122.8, 124.8, 139.8, 142.2, 145.3; MS m/z (relative intensity) 515 (5, M^+), 75 (100). Anal. Calcd for $C_{33}H_{58}O_2Si$: C, 76.95; H. 11.37. Found: C, 76.79; H, 11.36.

Under an argon atmosphere 176 mg (0.34 mmol) of the above silylated material was added to 1.7 mL of dry THF and 0.85 mL (0.85 mmol) of tetrabutylammonium fluoride (1 M solution in THF). The solution was stirred for 3 h. The solvent was removed on a rotary evaporator and the residue purified by flash chromatography (1:1 ethyl acetate/hexanes) and by HPLC (1:1 ethyl acetate/hexanes) to yield 73 mg (53%) of a white crystalline solid: mp 105 °C dec; $[\alpha]_D$ = 133° (CH_2Cl_2, c 0.27); UV (MeOH) λ_{max} 260 nm (ϵ = 17500); IR ($CHCl_3$) 3620, 2965, 1255, 896 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.63 (s, 3), 0.86 (d, 3, J = 0.6 Hz), 0.88 (d, 3, J = 0.6 Hz), 0.95 (d, 3, J = 6.0 Hz), 1.05–2.67 (m, 26), 3.68 (septet, 1, J = 4.0 Hz), 4.05 (s, 1), 4.79 (s, 1), 5.07 (s, 1), 6.32 (d, 1, J = 11.0 Hz), 6.38 (d, 1, J = 11.0 Hz); ^{13}C NMR (CD_2Cl_2) δ 11.9, 19.2, 22.7, 23.0, 24.2, 26.5, 28.4, 28.7, 30.5, 33.0, 35.1, 36.2, 36.5, 36.6, 39.8, 46.7, 50.4, 54.3, 55.2, 70.1, 76.1, 113.6, 122.7, 124.9, 139.5, 141.9, 144.7; MS m/z (relative intensity) 401 (8, M^+), 382 (100). Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.09. Found: C, 80.62; H, 11.01.

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Registry No. **1**, 66251-18-1; **2**, 133447-45-7; **3**, 93895-18-2; **4**, 138313-13-0; **5**, 138313-14-1; **6**, 138313-15-2; **7**, 75197-02-3; **8**, 93922-90-8; **9**, 100858-27-3; **10**, 133447-44-6; **10** C-3 silylated derivative, 133447-43-5; **11**, 138313-16-3; **12**, 138313-17-4; [5*S*-(1*Z*)]-2-(5-(*tert*-butyldimethylsiloxy)-2-methylenecyclohexylidene)ethanol, 96685-53-9; [5*S*-(1*Z*)]-2-(5-(*tert*-butyldimethylsiloxy)-2-methylenecyclohexylidene)-1-chloroethane–triphenylphosphine, 138313-18-5; [5*S*-(1*Z*)]-[2-(5-(*tert*-butyldimethylsiloxy)-2-methylenecyclohexylidene)ethyl]triphenylphosphonium iodide, 138313-19-6; triethyl phosphonoacetate, 867-13-0; diethyl [5*S*-(1*Z*)]-2-(5-(*tert*-butyldimethylsiloxy)-2-methylenecyclohexylidene)ethylphosphonate, 138313-20-9; methyltriphenylphosphonium bromide, 1779-49-3; vitamin D_3, 67-97-0; *N*-fluoropyridinium triflate, 107263-95-6.

Supplementary Material Available: The graphical results of the NOESY experiment and experimental procedures for compounds **9**, **11**, and **12** and some materials used in related studies and complete spectroscopic characterization of **7** and **8** (5 pages). Ordering information is given on any current masthead page.

(14) For spectral properties of this compound see the supplementary material.

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A New Positive Halogen Reagent. Oxidation of Secondary Alcohols to Ketones by Bis(quinuclidine)bromine(I) Bromide in the Presence of Pyridinium Catalyst

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The search for new and improved methods to oxidize alcohols to corresponding carbonyl compounds endures as a major pursuit in chemical synthesis.[1] Currently popular

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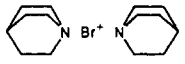
Table I. Oxidation of Secondary Alcohols to Ketones

alcohol, mmol	Br^+ complex, mmol	pyH^+,[a] mmol	reaction time, h	ketone	% yield[e]
cyclopentanol 2.12	1.01	2.05	2.5	cyclopentanone	92
2.07	1.03	2.06[b]	4.0		96
2.07	1.02	2.01[c]	3.0		97
2.02	1.01	2.04[d]	3.0		87
1.05	1.05	2.10	3.0		90
cyclohexanol 2.03	1.00	2.00	1.6	cyclohexanone	97
1.96	1.03	2.03[b]	3.5		93
2.01	0.99	2.04[c]	3.0		95
1.99	1.02	2.01[d]	3.0		90
1.02	1.08	2.06	1.5		96
2-pentanol 2.03	1.01	2.04	2.7	2-pentanone	97
0.97	1.05	2.05	4.5		97
4-methyl-2-pentanol 1.06	1.05	2.05	6.0	4-methyl-2-pentanone	92
2-octanol 0.97	1.05	2.03	5.0	2-octanone	87
3-pentanol 1.00	1.05	2.01	4.0	3-pentanone	96
2,4-dimethyl-3-pentanol 1.01	1.03	2.30	8.5	2,4-dimethyl-3-pentanone	92
2-*tert*-butylcyclohexanol 0.97	1.06	1.98	6.0	2-*tert*-butylcyclohexanone	92
4-*tert*-butylcyclohexanol 1.00	1.06	2.04	4.0	4-*tert*-butylcyclohexanone	99
menthol 1.03	1.11	2.05	7.0	menthone	92
borneol 1.02	1.06	2.10	4.0	camphor	94
cyclododecanol 1.00	1.05	2.01	4.0	cyclododecanone	95
sec-phenethyl alcohol 0.98	1.06	2.03	6.0	acetophenone	98
9-fluorenol 1.00	1.05	2.00	5.0	9-fluorenone	96

[a] Pyridinium trifluoroacetate except as indicated. [b] 3-Nitrobenzenesulfonate. [c] *p*-Toluenesulfonate. [d] Hydrochloride. [e] Yields were determined by gas chromatography and/or isolation of product.

are the Moffatt, Swern, and related methods of oxidation.[2] For some time, *N*-bromosuccinimide and related positive halogen reagents have been widely employed as well,[3] and these and other N-halogeno compounds continue to receive attention in the literature.[4]

Our interest in this area has been directed toward the preparation, characterization, and application of stable and isolable complexes of positive halogens of the type illustrated by 1, bis(quinuclidine)bromine(I).[5] These com-



1

plexes can be classified as 2-coordinate halogen(I) species and can be described as containing a central halogen that is hypervalent.[6] They are analogous to trihalides, xenon dihalides, and hydrogen-bonded complexes, all of which have received a great deal of attention at the fundamental level of chemical bonding.

Scheme I

Following our report on the preparation and structure of the tetrafluoroborate of 1,[7] we showed that 1 effectively oxidizes secondary alcohols to ketones when $AgBF_4$ is used as a coreactant.[8] We report herein refinements in the application of 1 for the oxidation of secondary alcohols to ketones which increase the effectiveness of this new positive halogen reagent. The refinements include: (1) the preparation and application of 1 under silver-free conditions; (2) the employment of 1 as the Br^- salt instead of the BF_4^- salt; (3) a two-phase dichloromethane–water solvent system for the oxidation; and most importantly, (4) a pyridinium catalyst that enhances the reactivity of 1 to the extent that Ag^+ is no longer required.

Results for the oxidation of several alcohols to ketones under the new conditions are included in Table I. Yields of ketone are high even when stoichiometric amounts of Br^+ complex are employed. These results compare favorably to other widely-used methods for the oxidation of alcohols.[1,2,9]

A practical advantage of 1 over other reagents is that added base is not required for the alcohol oxidation. The base is incorporated into the bis(amine) complex itself, in proper stoichiometric amount, to take up the H^+ produced in the reaction. The stoichiometry for the overall oxidation, confirmed by material-balance studies, is given in Scheme I.

The improvements for the oxidation of alcohols to ketones by 1 came from the desire to study the reactivity of

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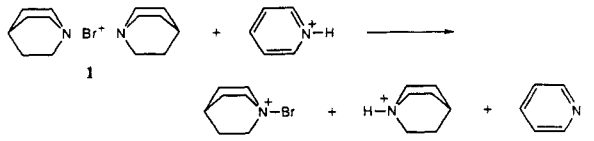
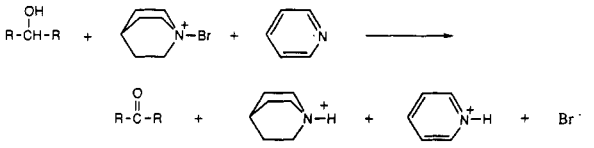
Scheme II



Scheme III



1 in the absence of Ag^+ and to find silver-free conditions to reduce cost. In place of the tetrafluoroborate of 1, we now use the bromide, the most readily accessible source of 1 prepared directly from the combination of Br_2 and quinuclidine.[7] Consequently, expensive $AgBF_4$ is no longer required to prepare the tetrafluoroborate.

Attempts to use 1 as the Br^- or BF_4^- salt to oxidize secondary alcohols to ketones in the absence of Ag^+ in dichloromethane alone resulted in low yields of ketone (~50%). We speculated that active bromine was being trapped in the solid phase by the quinuclidinium bromide produced during the course of the reaction. This reasoning led us to employ the two-phase system, dichloromethane and water, to extract in situ the quinuclidinium bromide from the dichloromethane where we believe the oxidation takes place.

The dichloromethane–water solvent system provides a clean reaction medium free of solids and affords higher yields of ketone than when dichloromethane is used alone. However, in the absence of Ag^+, rates of oxidation are low. For example, when 1.03 mmol of 2-octanol (100% excess) ad 0.524 mmol of bis(quinuclidine)bromine(I) tetrafluoroborate were stirred vigorously in 2 mL of dichloromethane and 2 mL of water at room temperature for 2.5 h the yield of 2-octanone was only 31%. Three days were required for the yields to reach 70–80%. Oxidation of several secondary alcohols under similar conditions by either the Br^- or BF_4^- salt of 1 were carried out. In general, to obtain 60–90% yields of ketone required reaction times of 3 days at room temperature, or 24 h at 50 °C in a closed reaction vial. From here, we proceeded to find a means to increase the reactivity of 1.

The strategy employed was to find a catalyst to promote the loss of quinuclidine in 1 which would free up active bromine for subsequent oxidation. We speculated that in oxidations where $AgBF_4$ is present Ag^+ plays this catalytic role through complexation with quinuclidine in the early stage of the reaction which ultimately is driven to completion by the formation of AgBr. Since quinuclidine is generally a stronger base toward H^+ than pyridine, we decided to try the pyridinium ion (pyH^+) as a catalyst to promote the removal of quinuclidine in 1 through protonation. As the results in Table I show, pyH^+ functions as an effective catalyst to reduced reaction times from days to a few hours at room temperature.

We speculate that in the presence of pyH^+ the oxidation of the alcohol takes place in two stages according to Schemes II and III. The combination of these schemes gives the overall oxidation of Scheme I and shows that pyH^+ is regenerated (confirmed by proton NMR studies of reaction mixtures involving CD_2Cl_2–D_2O).

If our postulate for the role of the pyH^+ catalyst is correct, one might expect that the reactivity of halogen–amine complexes in general would be enhanced by acids strong enough to protonate the complexing amine.

Experimental Section

General. GC analyses were performed on a Varian 3400 instrument equipped with a 3% Carbowax 20M/7% SE-30 column, 6 ft × 0.25 in., copper. Alcohols and ketones were used as supplied by commercial vendors. Quinuclidine was used as supplied by Aldrich. All other reagents and solvents were ACS or spectrophotometric grade and were used without further purification. Chloro- or bromobenzene were used as internal standards for GC analyses. ^{13}C and ^1H NMR spectra were obtained on Varian XL-200 and EM-360A instruments, respectively; δ values are parts per million relative to tetramethylsilane as the internal standard. IR spectra were obtained on a Perkin Elmer 710B spectrophotometer. Melting points were obtained on a Mel-Temp apparatus and are uncorrected.

Preparation and Characterization of Bis(quinuclidine)bromine(I) Bromide. The reagents, solvents, solutions, and reaction mixture were chilled at 0 °C throughout the procedure (a modification to our initial report[7]). A solution of Br_2 (2.284 g, 14.29 mmol) in 5 mL of CH_2Cl_2 was added immediately and dropwise with stirring to a freshly prepared solution of quinuclidine (4.079 g, 36.68 mmol) in 15 mL of CH_2Cl_2. A white solid appeared as the Br_2 was taken up. After 10 min, 25 mL of ethyl ether was added with continued stirring to precipitate more solid. After the mixture was stirred for an additional 30 min, the solid was collected by vacuum filtration in a glass adapter with a fritted disc of porosity C. Air was drawn through the adapter for 1 h to dry the solid. The yield of solid was 5.442 g (99.7%). This material is nonhygroscopic, homogeneous in texture and color, and adequate for direct application in synthesis. Samples stored on the shelf and used over a period of months show little or no decomposition as evidenced by NMR and thiosulfate titrations for active bromine. ^{13}C NMR (~1 mL of CD_3CN plus 4 drops of D_2O) δ 53.83 (C-2), 27.29 (C-3), 19.61 (C-4). The ^{13}C NMR spectrum for the bromide of 1 was identical within 0.5 ppm for each resonance to that for the tetrafluoroborate obtained in CD_3CN with no D_2O present. Similarly, the ^1H NMR spectra were identical within 0.1 ppm.

Oxidation of Cyclohexanol. GC Analysis. Bis(quinuclidine)bromine(I) bromide (0.412 g, 1.08 mmol), pyridinium trifluoroacetate (0.397 g, 2.06 mmol), and cyclohexanol (0.102 g, 1.02 mmol) were added to a 5-mL Wheaton V-vial equipped with a Teflon-coated spin vane and Teflon-lined screw-cap. Dichloromethane (2.654 g, 2.00 mL) and water (1.988 g, 1.99 mL) were added, and the reaction mixture was stirred for 1.5 h at room temperature. The yellow color of the dichloromethane layer diminished as the reaction went to completion. The organic layer was transferred by a Pasteur pipet to a 10-mL volumetric flask. The remaining aqueous layer was washed three times with 2-mL portions of dichloromethane, and the washings were added to the volumetric flask. Chlorobenzene (0.118 g, 1.05 mmol) was added as an internal standard to the volumetric flask, and dichloromethane was added to bring the total volume to the 10-mL mark. GC analysis on this solution showed the presence of 0.976 mmol of cyclohexanone (95.7% yield).

Oxidation of Cyclohexanol. Material Balance. Bis(quinuclidine)bromine(I) bromide (0.997 mmol), pyridinium trifluoroacetate (2.00 mmol), cyclohexanol (2.03 mmol), dichloromethane (2.02 mL), and water (1.98 mL) were employed in a reaction that was allowed to proceed according to the above procedure for 1.7 h. GC analysis showed the presence of cyclohexanone (0.966 mmol, 96.9% yield) and remaining cyclohexanol (1.038 mmol) for a material balance of 98.7%.

Oxidation of 4-*tert*-Butylclohexanol. Isolation and Confirmation of Products. Bis(quinuclidine)bromine(I) bromide (1.05 mmol), pyridinium trifluoroacetate (2.10 mmol), 4-*tert*-butylcyclohexanol (0.998 mmol), dichloromethane (2.08 mL), and water (2.00 mL) were employed in a reaction that was allowed to proceed according to the above procedure for 3.8 h. The aqueous layer was removed and the organic layer was washed successively with 2-mL portions of 0.1 M sodium thiosulfate, 0.5 M HCl (two times), aqueous $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4, and the dichloromethane was removed under reduced to pressure to leave a white solid (0.154 g, 100% yield, mp 43.5–46.6 °C). The IR and proton NMR spectra

of the product were identical to that of authentic 4-*tert*-butylcyclohexanone (mp 47–50 °C). Similarly, 9-fluorenone, cyclododecanone, and camphor were isolated and confirmed.

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Registry No. 1, 85282-84-4; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; 2-pentanol, 6032-29-7; 4-methyl-2-pentanol, 108-11-2; 2-octanol, 123-96-6; 3-pentanol, 584-02-1; 2,4-dimethyl-3-pentanol, 600-36-2; 2-*tert*-butylcyclohexanol, 13491-79-7; 4-*tert*-butylcyclohexanol, 98-52-2; menthol, 89-78-1; borneol, 507-70-0; cyclododecanol, 1724-39-6; *sec*-phenethyl alcohol, 98-85-1; 9-fluorenol, 1689-64-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 2-pentanone, 107-87-9; 4-methyl-2-pentanone, 108-10-1; 2-octanone, 111-13-7; 3-pentanone, 96-22-0; 2,4-dimethyl-3-pentanone, 565-80-0; 2-*tert*-butylcyclohexanone, 1728-46-7; 4-*tert*-butylcyclohexanone, 98-53-3; menthone, 89-80-5; camphor, 76-22-2; cyclododecanone, 830-13-7; acetophenone, 98-86-2; 9-fluorenone, 486-25-9; pyridinium trifluoroacetate, 464-05-1; pyridinium 3-nitrobenzenesulfonate, 84752-61-4; pyridinium *p*-toluenesulfonate, 24057-28-1; pyridinium chloride, 628-13-7.

Synthesis of 2-Amino Acids via Selective Mono-N-alkylation of Trichloroacetamide by 2-Bromo Carboxylic Esters under Solid–Liquid Phase-Transfer Catalysis Conditions

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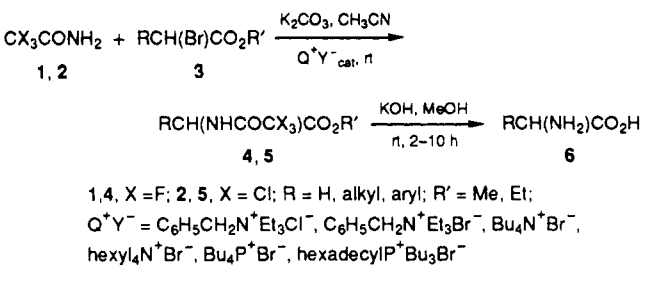
In a previous paper[1] we described a new procedure for the synthesis of 2-amino acids **6** via N-alkylation of trifluoroacetamide (**1**) with 2-bromo carboxylic esters **3** under solid–liquid phase-transfer catalysis (SL-PTC) conditions, followed by hydrolysis of the intermediate *N*-(trifluoroacetyl)-2-amino esters **4** (Scheme I). The use of an excess of trifluoroacetamide (**1**), which cannot be recovered at the end of the reaction, and its relatively high cost are severe limitations to the scale up of this process. Here we report that these drawbacks can be overcome by using the cheaper trichloroacetamide (**2**) instead of **1**. In fact **2** is selectively mono-N-alkylated by alkyl 2-bromo carboxylic esters **3** under SL-PTC conditions in the presence of anhydrous K_2CO_3, giving the corresponding *N*-(trichloroacetyl)-2-amino carboxylic esters **5**. Like trifluoro derivatives **4**, trichloroacetamides **5** are easily and quantitatively converted to 2-amino acids **6**.[2] Moreover the excess of **2** used in the process can be recovered from the reaction mixture and reused.

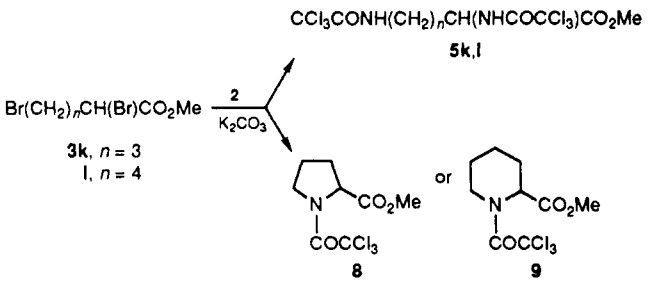
Results and Discussion

The alkylation reaction (Scheme I) was easily accomplished by stirring, at room temperature, an acetonitrile solution of trichloroacetamide (**2**) (3–4 mol), 2-bromo carboxylic ester **3** (1 mol), and a PTC catalyst (0.1 mol) over solid anhydrous potassium carbonate (4 mol). *N*-(trichloroacetyl)-2-amino carboxylic esters **5** were isolated in 51–95% yield and hydrolyzed in nearly quantitative yield to amino acids **6** with methanolic–aqueous potassium hydroxide at room temperature (see Table I).[2]

Scheme I



Scheme II



The best yields of **5** were obtained using 3–4 mol of **2** per mole of **3** and by working at room temperature under anhydrous conditions. Attempts to reduce reaction times for the less reactive bromo esters **3b–f,j–m** by working at higher temperature failed, because of the side decomposition of trichloroacetamide (**2**) (e.g. in the case of ester **3b**, at 80 °C 100% conversion was reached after 5 h, but **5b** was isolated in 54% yield, only). Benzyltriethylammonium chloride (TEBA) was again[1] the most efficient PTC agent. In the absence of the catalyst the reaction was much slower and the yields of **5** were poorer.

As shown in the table, the process works quite well using ethyl 2-bromoacetate (**3a**) and its higher homologues (**3b–e**) as alkylating agents; using 2-chloro derivatives resulted in unsatisfactory yields of **5**. Ethyl 2-bromo-2-phenylacetate (**3i**) afforded only traces of the corresponding trichloroacetamido ester **5i** together with a mixture of byproducts.

As found for **1**,[1] elimination reactions were observed only in the case of ethyl 2-bromo-3-phenylpropanoate (**3j**), the ethyl *trans*-cinnamate (**7**) (31%) being obtained together with comparable amounts (24%) of ethyl *N*-(trichloroacetyl)-2-amino-3-phenylpropanoate (**5j**). Steric requirements probably account for the very long reaction time (18 days) and poor yield (51%) found in the reaction of methyl 2-bromo-4-methylpentanoate (**3f**). Accordingly, ethyl 2-bromo-2-methylpropanoate (**3h**) and ethyl 2-bromo-3-methylbutanoate (**3g**) were recovered unchanged after the same reaction time. The methyl esters of 2,5-dibromopentanoic acid (**3k**) and 2,6-dibromohexanoic acid (**3l**) reacted with **2**, affording after 24 h 75% of methyl *N*-(trichloroacetyl)-2-pyrrolidinecarboxylate (**8**) and 60% of methyl *N*-(trichloroacetyl)-2-piperidinecarboxylate (**9**), respectively, together with small amounts of the *N,N'*-bis(trichloroacetyl)-α,ω-diamino carboxylic esters **5k** and **5l** (Scheme II).[3] In the case of methyl 5-bromopentanoate (**3m**), the same conditions led to 75% conversion after 20

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(2) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; pp 254–255 and references therein.
(3) The same results were previously found for the reaction of **3l** with **1**[1] or 2,6-dihalohexanoic acids with ammonia.[4]
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