protons acid moiety), 7.26–7.40 (m, 5 H, aromatic protons of alcohol moiety). The NMR spectrum was identical to an authentic sample prepared from (*R*)-**5** and (*S*)-**5**. HRFABMS (M + Cs^+) for $C_{18}H_{16}O_3NF_3$: expected, 484.0137; observed, 484.0137. Anal. Calcd: C, 61.71; H, 4.57; N, 3.71. Found: C, 61.75; H, 4.50; N, 3.70. The ester showed no racemization in ATE or BICINE buffer.

Antibody-Catalyzed Transesterification with 1-(2-Pyridyl)ethanol. To 180 μL of a 100 mM solution of enol ester **3** in DMSO was added a solution containing 7.5 mL of BICINE, 0.5 mL of the antibody solution, and 0.36 mL of the alcohol solution in DMSO (100 mM) and 0.4 mL of DMSO. The reaction progress was monitored by TLC (EtOAc/MeOH = 10/1). After 6 h the reaction mixture was extracted with ethyl acetate. The aqueous layer was saturated with NaCl and again extracted with ethyl acetate. The combined organic layer was dried with $MgSO_4$ and after evaporation of the solvent the product was isolated by preparative TLC (EtOAc/MeOH = 10/1) to yield 1.5 mg (30% yield) of the desired product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3 H, J = 6.6 Hz, CH_3 of alcohol moiety); 2.18 (s, 3 H, Ac); 3.66 (s, 2 H, benzylic protons of acid moiety); 5.92 (q, 1 H, C-H alcohol); 7.12 (s, 1 H, NH); 7.17–7.23 (m, 6 H, H-3, H-5 phenyl, H-3, H-4 pyridyl); 7.45 (d, 2 H, J = 9.5 Hz, H-2, H-6 phenyl); 7.63 (dd, 1 H, J = 8.8 Hz, J = 6.3, H-5 pyridyl); 8.57 (d, 1 H, J = 5.7 Hz, H-6 pyridyl). HRFABMS (M + Cs^+) for $C_{17}H_{18}N_2O_3$: expected, 431.0372; observed, 431.0372. Anal. Calcd: C, 68.92; H, 6.08; N, 8.78. Found: C, 68.89; H, 6.04; N, 8.77. The enantiomeric excess was determined to be 92% by HPLC as described above.

Preparation and Test of Enol Esters 17 and 18. Enol ester **17** was prepared in 74% yield, using the same procedure described for **3**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3 H, Ac); 4.69 (dd, 1 H, H-2 of vinyl: J(H-2, H-2′) = 1.6 Hz, J(H-2, H-1) = 6.3 Hz); 5.06 (dd, 1 H, H′-2 of vinyl: J(H-2′, H-2) = 1.6 Hz, J(H-2′, H-1) = 14 Hz); 7.27 (s, 1 H, NH); 7.50 (dd, 1 H, H-1 vinyl, J(H-1, H-2) = 6.3 Hz, J(H-1, H′-2) = 13.8 Hz); 7.63 (d, 2 H, J = 8.7 Hz, H-2 and H-6 of aromatic moiety), 8.07 (d, 2 H, H-3 and H-5 of aromatic moiety, J = 8.8 Hz). To test **17** as a substrate for antibody 21H3, 846 μL of ATE buffer, 54 μL of 21H3 solution in PBS (11.9 mg/mL), 20 μL of 100 mM solution of (*S*)-1-phenylethanol in DMSO, and 70 μL of DMSO were mixed and equilibrated over 10 min. The reaction was then started by adding 10 μL of 100 mM enol ester **17** in DMSO and followed by TLC and HPLC. No formation of the ester was observed. The enol ester **17** is about twice as stable as enol ester **3** ($t_{1/2}$ = 20 h at pH 8.5 and 16 h at pH 9, 25 °C). The same conditions were used to test **18** (10 μL of a 100 mM solution of vinyl acetate in DMSO were added). No transesterification or hydrolysis was observed.

Hydrolysis of Enol Ester 3 with Lipase SAM II and with 21H3. A mixture containing 850 μL of ATE, 50 μL of a solution containing 3.2 mg of SAM II in 600 μL of ATE, 90 μL of DMSO, and 10 μL of a 100 mM solution of enol ester **3** in DMSO was stirred gently at room temperature. Samples of 50 μL of the reaction solution were taken and mixed with 50 μL of a 0.15 mM solution of benzophenone in CH_3CN and analyzed by HPLC. No enzymatic hydrolysis was found. The same result was obtained with 21H3.

Attempted Lipase-Catalyzed Transesterification of Racemic 1-Phenylethanol with Enol Ester 3. A mixture containing 1.33 M of enol ester **3**, 0.33 M of 1-phenylethanol, and 3.33 mg/mL of lipase in CH_2Cl_2 was stirred for 3 days, and the reaction was monitored by TLC and/or HPLC. Nine lipases were tested for this reaction in CH_2Cl_2 (lipase SAM II, lipase PS-800, *Candida cylindracea* lipase, lipase MAP 10 from *Mucor* species, lipase N, *porcine pancreatic* lipase, lipase P, lipase AP 12 (*Aspergillus niger*), lipase FAP (*Rhizopus japonics*). None of them showed transesterification.

Attempted Transesterification Using Antibody 21H3 in CH_2Cl_2. A mixture containing 920 μL of CH_2Cl_2, 20 μL of 100 mM (*S*)-1-phenylethanol in CH_2Cl_2, and 10 μL of 100 mM enol ester **3** in CH_2Cl_2 (enol ester and alcohol can be mixed together) was added 54 μL of 21H3 (11.9 mg/mL in PBS). The reaction was followed by TLC and HPLC. No transesterification took place after 5 days.

Kinetics. For the antibody-catalyzed transesterifications, the initial rates were determined by following the formation of acetaldehyde or the ester product according to the reported procedures.[3] For lipase-catalyzed reactions, K_m and V_{max} were determined from Lineweaver–Burke plots and K_i was determined from a Dixon plot.

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Solvolytic Kinetic Studies by ^{19}F NMR

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Over the years we and others have employed the trifluoroacetate leaving group in a number of solvolytic kinetic studies. In terms of reactivity, the trifluoroacetate leaving group lies between the commonly used *p*-nitrobenzoate and tosylate leaving groups.[1] It is comparable to chloride in leaving-group ability. One of the main advantages of this leaving group lies in the ease of preparation of trifluoroacetates by reaction of alcohols with trifluoroacetic anhydride in the presence of amine bases. We have used gas chromatographic methods[2] for measuring rates, as well as spectrophotometric kinetic methods.[3] Conductometric methods have also been used to measure rates,[4,5] as well as titrimetric methods.[1,6] During the course of solvolytic studies, we have encountered systems where rates could not be easily determined by these kinetic methods. We now report a simple method for determination of solvolytic rates of trifluoroacetates ($ROCOCF_3$), as well as triflates ($ROSO_2CF_3$) and triflones (RSO_2CF_3), by ^{19}F NMR spectroscopy.

Since titrimetric methods for determination of rate constants are not useful in the commonly used solvent acetic acid, and gas chromatographic methods are unsuccessful for thermally unstable trifluoroacetates, we have turned our attention to ^{19}F NMR spectroscopy as a simple kinetic method. We have found that solvolytic rates for a variety of substrates (**1**–**8**) can be determined in a variety of solvents using this method. The ionic trifluoroacetate ion usually has a significantly different chemical shift than the covalent trifluoroacetate. Shift differences range from a relatively small value of 0.028 ppm (7.9 Hz) for **5** to 0.713 ppm for **1**. This allows facile determination of rate constants. Another advantage of this method lies in the sensitivity of modern Fourier transform spectrometers which allows rates to be determined using very small quantities (typically 5 mg or less) of substrate. Deuterated solvents are not necessary since spectra can be recorded in the unlocked mode. Figure 1 shows typical data for cumyl trifluoroacetate, **1**, in methanol and the corresponding first-order kinetic plot for this relatively reactive substrate. Such high correlations (r > 0.9997) are routine

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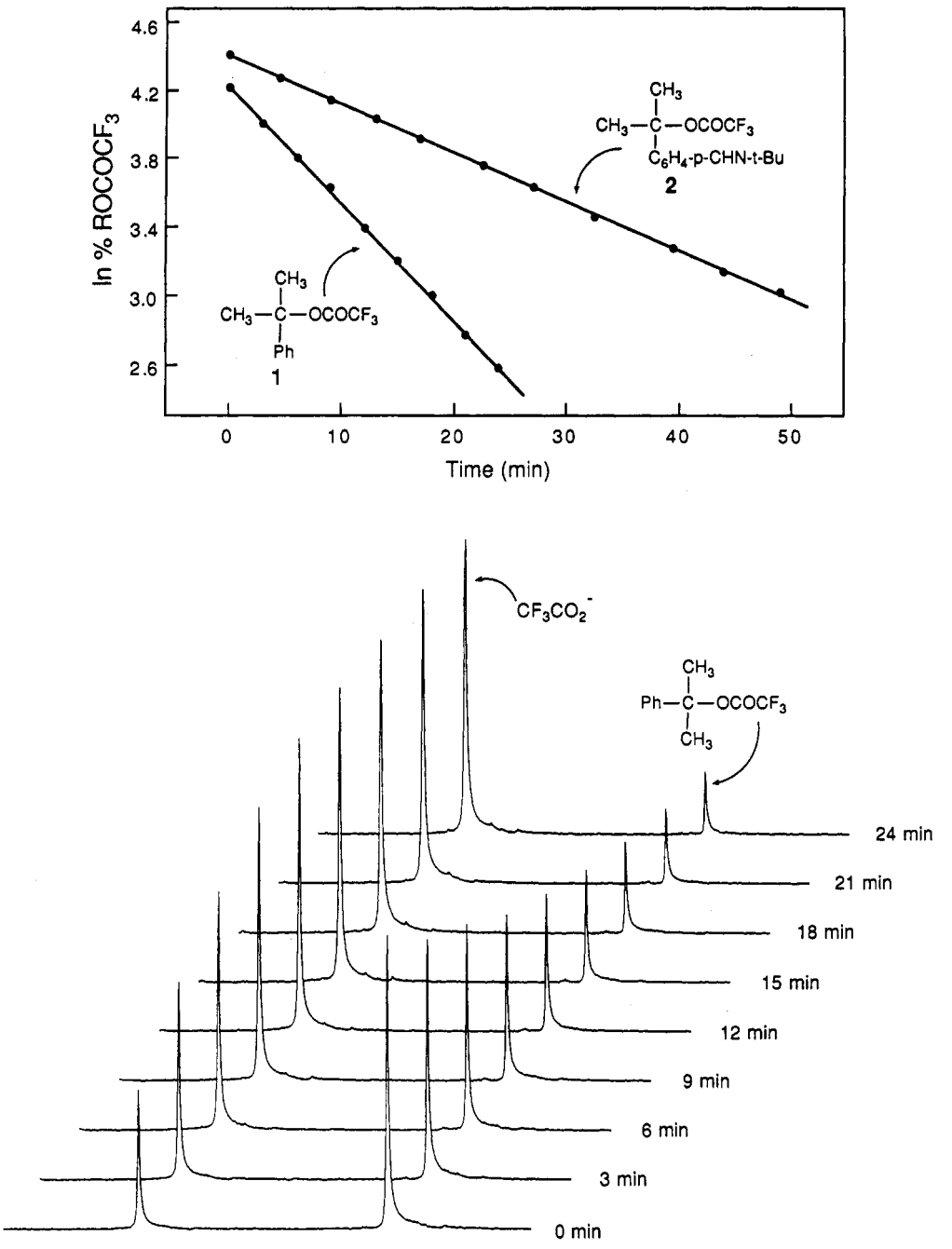


Figure 1. ^{19}F NMR spectra as a function of time for reaction of 1 in methanol at 25 °C. The first-order kinetic plot is shown along with a comparison with the *p*-CH=N-*t*-Bu analog 2.

Chart I

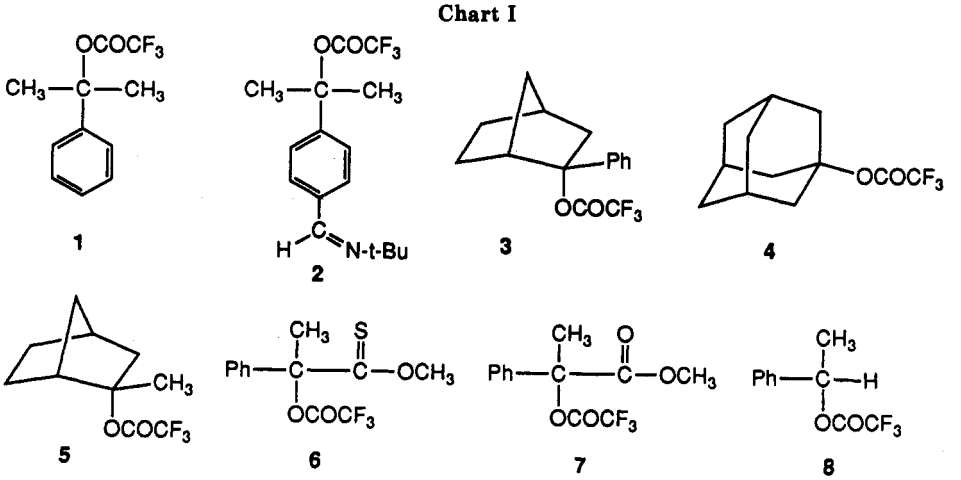


Table I. Solvolysis Rates of Various Substrates As Determined by ^{19}F NMR

compd	solvent	T, °C	k, s^{-1}
1	CH_3OH	25.0	1.13×10^{-3} [a]
	HOAc	25.0	3.71×10^{-4} [b]
2	CH_3OH	25.0	4.74×10^{-4}
3	HOAc	25.0	1.57×10^{-3} [c]
4	HOAc	100.0	5.05×10^{-5}
		80.0	5.07×10^{-6}
		25.0	1.91×10^{-9} [i]
	HCO_2H	25.0	4.45×10^{-5}
	CF_3CH_2OH	70.0	1.79×10^{-4} [d]
5	HOAc	80.0	2.04×10^{-4}
		60.0	1.98×10^{-5}
		25.0	1.57×10^{-7} [i]
6	HOAc	70.0	8.97×10^{-5}
		50.0	7.28×10^{-6}
		25.0	1.97×10^{-7} [i]
7	HOAc	120.0	8.59×10^{-5}
		100.0	9.48×10^{-6}
		25.0	1.81×10^{-10} [i]
8	HOAc	90.0	1.61×10^{-4}
		70.0	1.72×10^{-5}
		25.0	3.77×10^{-8} [i]
9	HOAc	100.0	4.26×10^{-5} [e]
10	HOAc	45.0	5.77×10^{-5} [f]
11	CH_3OH	25.0	3.00×10^{-5} [g]
12	HCO_2H	60.0	3.99×10^{-4} [h]

[a] Spectrophotometric rate = 1.08×10^{-3} s^{-1}. [b] Spectrophotometric rate = 3.98×10^{-4} s^{-1}. [c] Previously reported rate[3a] in HOAc = 1.26×10^{-3} s^{-1}. [d] Previously reported conductometric rate[5] in CF_3CH_2OH = 1.81×10^{-4} s^{-1}. [e] Previously reported titrimetric rate[10] in HOAc = 3.85×10^{-5} s^{-1}. [f] Previously reported titrimetric rate[3a] in HOAc = 5.79×10^{-5} s^{-1}. [g] Previously reported titrimetric rate[11] in CH_3OH = 2.87×10^{-5} s^{-1}. [h] Rate constant for approach to equilibrium. [i] Extrapolated from data at higher temperatures.

for kinetic studies by ^{19}F NMR. Table I summarizes data for substrates 1–8 as well as rates determined by alternative methods.

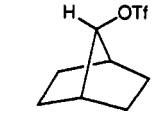
The methanolysis of **2** represents a reaction not easily monitored by other methods. In conjunction with other studies, we had need to determine the σ^+ value for the imino functional group. Because of the acid sensitivity of this group, rates must be measured in alcohol solution under buffered conditions. 2,6-Lutidine (a commonly used buffer) interfered with spectrophotometric rate determination and use of Et_3N as a buffer led to facile transesterification of the trifluoroacetate to give the corresponding cumyl alcohol. However, the ^{19}F NMR method using 2,6-lutidine as a buffer gave excellent first-order kinetic results. The rate of this substrate is 2.38 times slower than that of **1**. This corresponds to a σ^+ value of +0.078 in methanol; i.e., the *p*-CHN-*t*-Bu group is weakly cation destabilizing relative to *p*-H.

This ^{19}F NMR method has been used to redetermine the rate of **3** in acetic acid. Previously, the rate of this substrate was determined spectrophotometrically.[3a] This determination was complicated by the fact that one of the products of the reaction, *endo*-2-phenyl-*exo*-2-norbornyl acetate, is not stable under the reaction conditions and undergoes conversion to the other product, 2-phenylnorbornene, at a significant rate. This leads to an unstable "infinity" reading and a significant uncertainty in determination of the first-order rate constant for acetolysis of **3**. The ^{19}F NMR method eliminates these problems since only the disappearance of covalent trifluoroacetate and the appearance of ionic trifluoroacetate are used in the determination of the rate constant. Secondary processes do not interfere, and the rate reported in Table I is more accurate than our previously reported spectrophotometric rate.

1-Adamantyl[7] and 2-adamantyl[8] derivatives have been utilized as standard systems for determination of solvent effects in limiting (k_c) solvolysis reactions. 1-Adamantyl trifluoroacetate, **4**, has been previously prepared, and rates of solvolysis in alcohol and aqueous alcohol solvents have been measured by conductometric methods.[5] Data for this substrate have not been reported in acetic acid and formic acid, two commonly used solvents for solvolytic studies. The ^{19}F NMR method has now been used to determine rates in these solvents. Rates of solvolysis of **4** in trifluoroethanol can also be determined by ^{19}F NMR despite the large solvent signal since the ^{19}F signal of **4** (−1.62 ppm) and $CF_3CO_2^-$ (−2.17 ppm) are far enough removed from those of CF_3CH_2OH which appears at −3.32 ppm. The rate determined by ^{19}F NMR agrees well with the previously reported conductometric rate.

The trifluoroacetate **5** represents a system where the shift difference between the covalent trifluoroacetate and the trifluoroacetate ion is only 7.9 Hz. Despite this small difference, rates can easily be determined. Trifluoroacetates **6** and **7** represent two further systems that are of interest with respect to our studies on carbocations substituted with electronegative groups.[9] These substrates allow a comparison between thioester and ester groups on solvolytic reactivity. ^{19}F NMR is the most convenient method for monitoring acetolysis rates for these substrates as well as for the α-H analog **8**. Our data indicate that the rate of the thioester **6** is significantly enhanced relative to the ester analog **7**.

In view of the ease of solvolytic rate determinations for trifluoroacetates using ^{19}F NMR, attention was next turned to other fluorinated leaving groups. We have found that triflate solvolysis rates can also be determined by the ^{19}F NMR method. Shift differences between anionic triflate ($CF_3SO_3^-$) and covalent triflates **9**[10] and **10**[3a] are quite large



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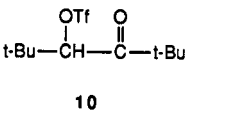

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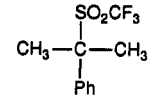

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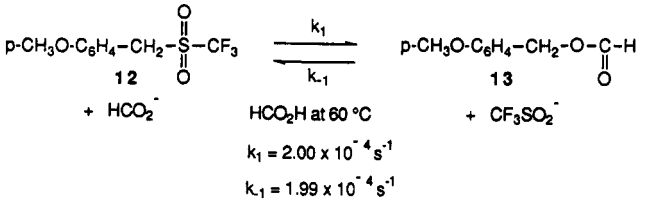

(2.90 and 3.68 ppm, respectively), with the anion appearing further upfield. This permits facile determination of acetolysis rates which agree well with titrimetrically determined rates. Solvolyses of the triflones **11** and **12** have also been monitored by ^{19}F NMR. These substrates lose the sulfinate ion $CF_3SO_2^-$ under solvolytic conditions and form substitution products.[11] The sulfinate ion appears 17–18 ppm upfield from the covalent sulfone **11** and 9.4 ppm upfield from the covalent substrate **12**. In the case of triflone **12**, solvolysis in formic acid (0.05 M in sodium formate and 0.012 M in **12**) does not go to completion but

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reaches an equilibrium position containing 50% covalent sulfone and 50% $CF_3SO_2^-$. From the rate of approach to equilibrium (3.99×10^{-4} s^{-1}), the values of k_1 and k_{-1} could be determined. The use of ^{19}F NMR greatly simplifies determination of these values as well as the equilibrium position.

In summary, ^{19}F NMR permits facile determination of solvolytic reaction rates of trifluoroacetates, triflates, and triflones. The major advantage of this method lies in the ease of accurate rate determination from NMR integrals. Also of importance is the fact that, because of the sensitivity of ^{19}F NMR, rates can be easily determined using very small amounts of sample.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a General Electric GN 300 spectrometer. ^{19}F NMR spectra were recorded on a Nicolet NT 300 spectrometer at 282.3 mHz, and shifts are relative to CF_3CO_2H in $CDCl_3$. Mass spectra were recorded on a Finnigan MAT 8430 high-resolution spectrometer. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were carried out using EM science 230–400 mesh silica gel 60. Trifluoroacetates **1**,[3c] **3**,[3a] **5**,[3c] and **8**[1,3c] have been previously prepared. Triflates **9**[10] and **10**[3a] as well as triflones **11**[11] and **12**[11] were available from our previous studies.

Preparation of 4-(2-Hydroxy-2-propyl)benzaldehyde. A solution of 3.68 g of *p*-bromobenzaldehyde dimethyl acetal[12] in 15 mL of tetrahydrofuran was cooled to −78 °C, and 11 mL of 1.6 M *n*-BuLi in hexanes was added dropwise to the stirred mixture. After 20 min at −78 °C, a solution of 970 mg of acetone in 5 mL of tetrahydrofuran was added dropwise. The mixture was slowly warmed to room temperature, and water was added. The mixture was transferred to a separatory funnel with ether, and the organic phase was washed with water and saturated NaCl solution and dried over $MgSO_4$. After solvent removal using a rotary evaporator, the crude residue was chromatographed on 35 g of silica gel and eluted with ether in hexanes. The product 4-(2-hydroxy-2-propyl)benzaldehyde dimethyl acetal (1.94 g; 58%) eluted with 30% ether in hexane.

A solution of 1.94 g of 4-(2-hydroxy-2-propyl)benzaldehyde dimethyl acetal in 15 mL of tetrahydrofuran was stirred at room temperature as 15 mL of 0.5% H_2SO_4 in water was added. The mixture was stirred at room temperature for 3 h and then taken up into ether. The ether extract was washed with $NaHCO_3$ solution and saturated NaCl solution and then dried over $MgSO_4$. The solvent was removed using a rotary evaporator, and the residue was distilled to give 1.42 g (94%) of 4-(2-hydroxy-2-propyl)benzaldehyde, bp 110 °C (0.1 mm): ^1H NMR ($CDCl_3$) δ 9.928 (s, 1 H), 7.81 and 7.66 (AA'BB' aromatic quartet, 4 H), 3.120 (br s, 1 H), 1.601 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 192.19, 156.34, 134.80, 129.78, 125.20, 72.47, 31.60. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.27. Found: C, 73.26; H, 7.17.

Preparation of the *tert*-Butylimine Derivative of 4-(2-Hydroxy-2-propyl)benzaldehyde. A solution of 350 mg of 4-(2-hydroxy-2-propyl)benzaldehyde and 468 mg of *tert*-butylamine in 8 mL of CCl_4 was stirred at room temperature, and 6.0 g of anhydrous $MgSO_4$ was added. Stirring was continued for 65 h, and the mixture was then filtered and the solvent was removed using a rotary evaporator. The solid residue was washed with cold hexanes and collected to give 428 mg (91%) of the *tert*-butylimine derivative of 4-(2-hydroxy-2-propyl)benzaldehyde, mp 63–65 °C: ^1H NMR ($CDCl_3$) δ 8.269 (s, 1 H), 7.73 and 7.24 (aromatic AA'BB' quartet), 1.76 (br, 1 H), 1.588 (s, 6 H), 1.297 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.76, 151.25, 135.71, 127.81, 124.56, 72.57, 57.22, 31.75, 29.73. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.75; H, 9.50.

Preparation of Trifluoroacetate 2. A solution of 73 mg of 4-(2-hydroxy-2-propyl)benzaldehyde *tert*-butylimine and 44 mg of 2,6-lutidine in 3 mL of ether was cooled to −15 °C, and 77 mg of trifluoroacetic anhydride was added dropwise. After 10 min at −15 °C and 5 min at 0 °C, ice–water was added to the stirred mixture. The water was decanted using a pipet, and $NaHCO_3$ solution was added. The usual HCl wash was omitted since, in a separate run, washing the solution with cold, dilute HCl led to complete hydrolysis of the imine function and formation of the trifluoroacetate derivative of 4-(2-hydroxy-2-propyl)benzaldehyde as the sole product. The mixture was then dried using saturated NaCl solution, and $MgSO_4$ was added. The solution was filtered, and the solvent was removed from a small portion using a rotary evaporator. ^1H NMR analysis showed the trifluoroacetate **2** along with 18% of the trifluoroacetate derivative of 4-(2-hydroxy-2-propyl)benzaldehyde. A trace of 2,6-lutidine was also present. This mixture was used for kinetic studies: ^1H NMR of **2** ($CDCl_3$) δ 8.263 (s, 1 H), 7.76 and 7.41 (aromatic AA'BB' quartet), 1.891 (s, 6 H), 1.287 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.65 (q, J_{CF} = 42 Hz), 154.28, 144.97, 136.90, 128.17, 124.48, 114.35 (q, J_{CF} = 287 Hz), 87.18, 57.38, 29.66, 27.99; exact mass calcd for $C_{16}H_{20}F_3NO_2$ 315.1446, found 315.1442.

Preparation of Trifluoroacetate 4.[5] A mixture of 326 mg of 1-adamantanol and 376 mg of 2,6-lutidine in 10 mL of ether was cooled to 0 °C, and 631 mg of trifluoroacetic anhydride was added dropwise. The alcohol dissolved during the addition of the anhydride. After 5 min at 0 °C, ice–water was added to the stirred mixture. The water was decanted using a pipet, and cold, dilute HCl was then added to the stirred mixture maintained at 0 °C. The aqueous extract was again decanted, and $NaHCO_3$ solution was added. The mixture was then dried using saturated NaCl solution, and $MgSO_4$ was added. The solution was filtered, and the solvent was removed using a rotary evaporator. The residue was distilled to give 484 mg (91%) of trifluoroacetate **4**, bp 60 °C (1 mm) (lit.[5] bp 216 °C): ^1H NMR ($CDCl_3$) δ 2.24 (m, 3 H), 2.183 (d, J = 3.0 Hz, 6 H), 1.694 (t, J = 3.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.89 (q, J_{CF} = 41 Hz), 114.41 (q, J_{CF} = 287 Hz), 86.92, 40.88, 35.85, 31.08.

Preparation of Trifluoroacetate 6. Acetophenone cyanohydrin[13] (4.40 g, 1.0 equiv) was dissolved in 40 mL of anhydrous diethyl ether under nitrogen. The mixture was cooled to 0 °C, and 7.04 g of methanol (7.3 equiv) was added. Hydrogen chloride gas was slowly bubbled into the solution for a total of 70 min. During this time the imino ester hydrochloride began to crystallize. The mixture was then kept at room temperature for 20 h. The solid was collected on a Buchner funnel, washed with anhydrous ether, and dried under vacuum to give 5.76 g (89%) of the imino ester hydrochloride, mp 121–123 °C.

The imino ester hydrochloride was immediately dissolved in 150 mL of anhydrous pyridine under nitrogen and cooled to 0 °C. Gaseous hydrogen sulfide was bubbled through the solution for 1.25 h. The reaction mixture was kept at room temperature for an additional 17 h. The mixture was then transferred to a separatory funnel with water and extracted twice with ether. The ether extracts were combined and washed with two portions of water, 10% hydrochloric acid, and saturated NaCl solution. The ether extract was dried over $MgSO_4$ and the solvent was removed using a rotary evaporator to give 1.25 g of crude methyl 2-hydroxy-2-phenylthiopropionate. The entire product was purified by chromatography on 12 g of silica gel and 1.23 g (24%) of methyl 2-hydroxy-2-phenylthiopropionate eluted with 3% ether in hexanes: ^1H NMR ($CDCl_3$) δ 7.58–7.25 (m, 5 H), 4.750 (s, 1 H), 4.136 (s, 3 H), 1.838 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 228.028, 143.779, 128.150, 127.601, 125.558, 80.400, 61.079, 27.265.

A solution of 0.25 g of methyl 2-hydroxy-2-phenylthiopropionate in 4 mL of anhydrous pyridine was cooled to 0 °C and 0.66 g of trifluoroacetic anhydride was added dropwise. After the addition, the reaction mixture was stirred at 0 °C for 5 min and transferred to a separatory funnel with ether, and 5 mL of hexane was added. The organic layer was washed with cold water, 10% hydrochloric acid, and saturated NaCl solution and then dried over $MgSO_4$. The solvent was removed using a rotary evaporator to give 0.37 g (99%) of trifluoroacetate **6** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.60–7.36 (m, 5 H), 4.06 (s, 3 H), 2.267 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.40, 155.53 (q, J_{C-F} = 42 Hz), 139.11, 128.77, 128.67, 124.91, 114.49 (q, J_{C-F} = 286 Hz), 91.83, 59.95, 25.64; exact mass

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calcd for $C_{12}H_{11}F_3O_3S$ 292.0381, found 292.0381.

Preparation of Trifluoroacetate 7. A solution of 302 mg of methyl 2-hydroxy-2-phenylpropionate (atrolactic acid methyl ester) and 265 mg of 2,6-lutidine in 6 mL of ether was cooled to 0 °C, and 493 mg of trifluoroacetic anhydride was added dropwise. After 10 min at 0 °C water was added to the stirred solution. A rapid aqueous workup followed using consecutive washings with cold HCl, $NaHCO_3$, and saturated NaCl solutions. The ether extract was dried over $MgSO_4$ and filtered, and the solvent was removed using a rotary evaporator. The residue was distilled to give 420 mg (91%) of the trifluoroacetate 7, bp 50 °C (0.05 mm): ^1H NMR ($CDCl_3$) δ 7.55–7.48 (m, 2 H), 7.45–7.33 (m, 3 H), 3.732 (s, 3 H), 2.076 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.32, 156.07 (q, J_{C-F} = 43 Hz), 137.71, 129.09, 128.91, 124.75, 114.49 (q, J_{C-F} = 286 Hz), 85.75, 53.27, 23.21. Anal. Calcd for $C_{12}H_{11}F_3O_4$: C, 52.18; H, 4.01. Found: C, 52.40; H, 4.26.

Kinetics Procedures. Before beginning a kinetic run, the spectrometer was shimmed using a $CDCl_3$ sample of the same volume as the kinetics sample. Approximately 5–10 mg of the appropriate trifluoroacetate was dissolved per 1 mL of the given solvent, and part of the solution was placed in an NMR tube. For runs at 25 °C, the tube was placed in the NMR probe held at 25.0 ● 0.2 °C. The sample was allowed to thermally equilibrate for 3 min, and ^{19}F spectra were recorded periodically. Spectra were recorded in the unlocked mode with a 4-s delay between pulses. For substrates that react at elevated temperatures, the NMR tube was sealed and the tube was placed in a constant temperature bath at the appropriate temperature for certain time periods. The tube was then withdrawn, quenched in cold water, and analyzed by ^{19}F NMR (unlocked) at room temperature (where the reaction proceeds at a negligible rate). The reactions were monitored over approximately 2 half lives. First-order rate constants were calculated by standard least-squares procedures. Correlation coefficients were all greater than 0.9996. Maximum standard deviations in duplicate runs were ±2%.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for 2 and 6 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

Regioselective Alkylation of Phenoxy-Substituted 3-(Methylthio)indolin-2(3*H*)-ones. Preparation of 3-, 1,3-, and 1,3,3-Substituted Indolin-2(3*H*)-ones

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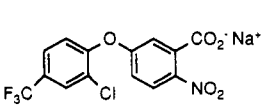
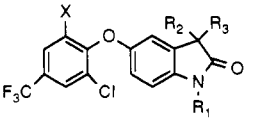
Diphenyl ethers are an important class of herbicides and thus have attracted considerable attention in the agricultural chemical community. They act as contact herbicides, causing chlorosis and tissue necrosis.[1] Recent mechanistic elucidation of acifluorfen, 1, a typical diphenyl ether herbicide, has determined the site of action to be the enzyme protoporphyrinogen oxidase.[2] Inhibition of this enzyme causes protoporphyrin IX buildup which leads to singlet oxygen formation and ultimate membrane damage.



1



2

X = H, halogen
R_1, R_2, R_3 = H, alkyl

In connection with a synthesis program directed toward diphenyl ethers containing the indolin-2(3*H*)-one (oxindole) moiety 2,[3,4] we required an efficient route to a variety of functionalized indolin-2-ones in an effort to fully explore their herbicidal activity. Two major structural variations were chosen for study: substitution patterns in the lactam ring (mono-, di-, and trisubstitution) and isomeric substitution of the phenoxy group in the benzenoid ring.

The literature is replete with methods for the preparation of indolin-2-ones.[5] Several classical approaches have been used including reduction of the corresponding isatins,[6] modification of the Fisher indole synthesis via oxidation of methyleneindoline intermediates,[7,8] reduction of *o*-nitrophenylacetic acid derivatives,[9] as well as others.[9d,10,11] Major drawbacks of many of these approaches include the harsh reaction conditions as well as the availability of the starting materials needed for the substitution patterns in the final products. More recent approaches include radical cyclizations[12,13] of substituted acetanilides, hypohalite degradation of homophthalimides,[14] Pummerer rearrangements,[15] and carbenoid insertions of β-diazoacetanilides.[16] Most of these approaches require N-substitu-

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