The Reactions of Secondary Amides with a Diaryldialkoxysulfurane. A Selective Method for the Rapid Cleavage of Secondary Amides[1]

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Abstract: Sulfurane **1** [$Ph_2S(OR_F)_2$, where $R_F = PhC(CF_3)_2$] reacts with secondary amides RCONHR′ to form sulfilimines ($R'N{=}SPh_2$) and esters (RCO_2R_F) or, in the case of amides with bulky R′ substituents, to form imidates [$R'N{=}C(OR_F)R$]. The amide cleavage reaction occurs within seconds at room temperature for a favorable case and is selective for secondary amides. Tertiary amides do not react. Primary amides give *N*-acylsulfilimines. Evidence is presented for the intermediacy in the reaction of diaryl(amido)sulfonium ions ($Ph_2S^+N(COR)R'$) which react with alkoxide (R_FO^-) at the carbonyl carbon to yield amide cleavage products in a step following the rate-determining step of the reaction. Mechanistic evidence is reviewed which points to the probability that the rate-determining step of the reaction is the ligand exchange reaction in which an alkoxy ligand to sulfurane sulfur is replaced by an amido ligand. It is suggested that ligation of the bidentate amide at the carbonyl oxygen rather than at the nitrogen leads to the formation of imidates. Procedures are described for the facile recovery of amines from the sulfilimine or imidate products of this reaction, providing a remarkably selective and mild procedure for the removal of the acyl group from a secondary amide function. This suggests the utility of this reaction in removing masking amide functions used in protecting primary amine functions during synthetic operations.

The versatility of sulfurane reagents in synthetic organic chemistry has been demonstrated by showing that sulfurane **1** [$Ph_2S(OR_F)_2$, where $R_F = PhC(CF_3)_2$] reacts with secondary or tertiary alcohols to form olefins in excellent yield under uniquely mild conditions,[2] with glycols to form epoxides and other cyclic ethers in a single step reaction,[3] and with primary amines or amides[1,4] to form sulfilimines, including some unavailable by any other route. We here report a study of the cleavage of secondary amides by reaction with sulfurane **1**, a reaction of significant synthetic and degradative potential, which serves to delineate the scope of the reaction and provides evidence for a mechanistic scheme of considerable predictive value.

Experimental Section

Sulfurane **1** was prepared according to a published[2] procedure or according to a simplified standard procedure developed by us.[5] All reactions were carried out in vessels allowing rigorous exclusion of water or under dry nitrogen in an inert atmosphere box.

Elemental analyses for the new compounds reported in this paper are, unless otherwise indicated, within 0.3% of the calculated values for C, H, N, and S.

Where NMR peak integrals are used for product analyses, any ambiguity in assignment of the peak was removed by addition of a small amount of authentic material to the reaction mixture, and the increase in area of all peaks assigned to the substance was monitored. This was particularly important for the assignment of ^{19}F NMR peaks which, in these compounds, show appreciable solvent dependence of chemical shift.

Alternative Preparation of Esters and Imidates. The esters and imidates of Table II were alternatively prepared by stirring a solution of the respective acid chloride or imidoyl chloride (prepared by refluxing the corresponding amide in $SOCl_2$ and distillation of the imidoyl chloride under reduced pressure)[6] with 1 equiv of KOR_F for 1–2 hr, filtration of KCl, and distillation under reduced pressure and/or passage through a short silica column (pentane) to provide an oil, which crystallized from pentane (at ca. −25°). Two of the esters (p-$ClC_6H_4CO_2R_F$ and p-$O_2NC_6H_4CO_2R_F$) crystallized directly by adding pentane to the crude reaction mixture (after filtration of KCl) and cooling. All of the esters and imidates gave substantial molecular ions in their 70-eV mass spectra.

Reactions of Amides with Sulfurane 1. (a) *N*-Methylbenzamide. Samples of sulfurane **1** (212.3 mg, 0.316 mmol) and *N*-methylbenzamide (27.4 mg, 0.203 mmol) were combined in ca. 2 ml of $CDCl_3$. The ^1H NMR spectrum revealed the disappearance of the doublet of *N*-methylbenzamide at δ 3.0 and the appearance of the singlet of *S,S*-diphenyl-*N*-methylsulfilimine at δ 2.6, formed in 98% yield by NMR integration using the integral of the total aromatics as an internal standard. The ^{19}F spectrum displayed two singlets at 70.4 and 75.2 ppm upfield from $CFCl_3$ ($PhCO_2C(CF_3)_2Ph$, 98% by NMR integration, and $HOC(CF_3)_2Ph$). To monitor the rate of reaction, a sample of **1** (142.3 mg, 0.212 mmol) and *N*-methylbenzamide (23.9 mg, 0.177 mmol) were combined at ca. −50° in 2 ml of $CDCl_3$ in an NMR tube. The ^1H NMR methyl peaks of *N*-methylbenzamide and *S,S*-diphenyl-*N*-methylsulfilimine were monitored after warming the NMR tube to 0°; 50% of the starting amide was consumed within 10 min.

To confirm the identity of *S,S*-diphenyl-*N*-methylsulfilimine, a preparative scale reaction was carried out. Samples of 2.44 g (3.63 mmol) of **1** and 0.47 g (3.48 mmol) of *N*-methylbenzamide were combined in ca. 10 ml of ether. After all of the amide dissolved, addition of pentane and crystallization gave 1.3 g (2.83 mmol, 82%) of $CH_3N{=}SPh_2{\cdot}HOR_F$ which, after two crystallizations from ether–pentane, gave a mp (89–90°) and an NMR spectrum identical with those of an authentic sample prepared from **1** and methylamine.[1]

(b) Benzanilide. A solution of benzanilide (42.9 mg, 0.217 mmol) and **1** (211.8 mg, 0.316 mmol) in 2 ml of dimethylformamide was made up at 0° and warmed to 41° while the ^{19}F spectrum was monitored in an NMR probe. The amide underwent 50% reaction in less than 3 min, as reflected in the appearance of the ^{19}F singlet of $PhCO_2R_F$ and the disappearance of the ^{19}F absorption of **1**. The integral of the ^{19}F spectrum indicated 98% yield of the ester $PhCO_2R_F$.

Treatment of 1.15 g (5.86 mmol) of benzanilide in 40 ml of ether with 4.32 g (6.41 mmol) of **1** with stirring for 3 hr, followed by direct crystallization (ether–pentane), gave 1.16 g (4.18 mmol, 72%) of fine yellow needles of triphenylsulfilimine, mp 109.5–110.5°, identical by NMR, infrared spectroscopy, and elemental analysis with an authentic sample prepared by the direct reaction of **1** with aniline.[1]

(c) Acetanilide. Sulfurane **1** (274.2 mg, 0.41 mmol), acetanilide (27.8 mg, 0.21 mmol), and benzotrifluoride $PhCF_3$ (74.6 mg, 0.51 mmol) were combined in 0.76 ml of $CDCl_3$ at ca. −50°. Warming to 41° led to complete consumption of the acetanilide within 3 min to form the ester $CH_3CO_2R_F$ (60% yield by integration of the ^{19}F NMR singlet at 70.5 ppm upfield from $CFCl_3$ using the singlet of $PhCF_3$ as an internal standard, or 62% yield by integration of the methyl peak of $CH_3CO_2R_F$ in the ^1H spectrum, using the total aromatic integral as an internal standard) and ylide **19**, $Ph_2S{=}CHCO_2R_F$ (24% yield by integration of the ^{19}F singlet at 70.2 ppm upfield from $CFCl_3$). To 0.98 g (7.25 mmol) of acetanilide in ether was added 5.43 g (8.1 mmol) of **1**. Concentration of the solution

and addition of pentane led to separation of an oil and white crystals (169 mg, 0.36 mmol, 5%) of **19** which, after recrystallization from ether–pentane, gave the analytical sample, mp 159–161°: 220-MHz ^{1}H NMR ($CDCl_3$) δ 7.6–7.1 (complex unresolved aromatic spectrum); ^{19}F NMR 70.2 ppm upfield from $CFCl_3$ (s, $-CF_3$ of OR_F); ir (KBr) 1680 cm^{-1} (C=O); mass spectrum (70 eV) m/e 470 ($M^{\cdot+}$), 186 ($M^{\cdot+} - CHCO_2R_F$). Further reduction in volume caused deposition of 0.381 g (2.46 mmol, 34%) of $PhN{=}SPh_2$, identical (mp, NMR, ir, and mass spectrum) with a sample prepared from **1** and benzanilide. Treatment of 1.5 g (11.1 mmol) of acetanilide with 8 g (11.9 mmol) of sulfurane in a second preparative reaction in ether (50 ml) and work-up as above increased the isolated yield of $PhN{=}SPh_2$ to 50%.

(d) *N*-*n*-Butylacetamide. Samples of 33.5 mg (0.29 mmol) of *N*-*n*-butylacetamide and **1** (392.7 mg, 0.59 mmol) were combined in 1.09 ml of $CDCl_3$. After 10 min at 25°, the ^{1}H NMR spectrum of the reaction mixture revealed 50% consumption of the starting amide. After 3 hr, no detectable starting amide remained. The 220-MHz ^{1}H NMR spectrum of the reaction mixture showed absorptions of the ester $CH_3CO_2R_F$ (47%), the imidate n-$C_4H_9N{=}C(OR_F)CH_3$ (49%), and the sulfilimine n-$C_4H_9N{=}SPh_2$ (47%). Yields were determined by integration of the fully resolved aliphatic peaks of each product using the total aromatic integral as an internal standard. The ^{19}F NMR spectrum revealed three peaks, at 69.3, 70.3, and 75.3 ppm upfield from $CFCl_3$ ($-CF_3$'s of n-$C_4H_9N{=}C(OR_F)CH_3$, $CH_3CO_2R_F$, and R_FOH). The infrared spectrum of the reaction mixture displayed strong absorptions at 1790 (C=O of $CH_3CO_2R_F$) and 1720 cm^{-1} (C=N of n-$C_4H_9N{=}C(OR_F)CH_3$). Treatment of 1.11 g (9.6 mmol) of *N*-*n*-butylbenzamide with 8.815 g (13.1 mmol) of **1** in 25 ml of CH_2Cl_2 gave, after standing overnight and after three extractions with 15% aqueous NaOH, removal of CH_2Cl_2 and chromatography of the resulting oil on a short silica gel column (pentane), 1.77 g of a clear oil which contained $CH_3CO_2R_F$ (0.19 g, 0.66 mmol, 7%), n-$C_4H_9N{=}C(OR_F)CH_3$ (0.91 g, 2.7 mmol, 29%), and R_FOH (0.67 g), determined by ^{1}H NMR. Preparative GLC of this mixture on a 5 ft × 0.25 in. 20% SE-30 on Chromosorb W column at 175° provided an analytical sample of liquid n-$C_4H_9N{=}C(OR_F)CH_3$: 220-MHz NMR ($CDCl_3$) δ 7.3 (s, 5 H, $C_6H_5C(CF_3)_2-$), 3.0 (t, 2 H, NCH_2), 2.0 (s, 3 H, n-$C_4H_9N{=}C(OR_F)CH_3$), 1.16 (m, 2 H, NCH_2CH_2), 0.91 (m, 2 H, $NCH_2CH_2CH_2$), 0.71 (t, 3 H, $NCH_2CH_2CH_2CH_3$); ir (salt plate) 1720 cm^{-1} (C=N); mass spectrum (70 eV) m/e 341 ($M^{\cdot+}$).

(e) *N*-2-Propylacetamide. Treatment of 26 mg (0.27 mmol) of *N*-2-propylacetamide with 360 mg (0.54 mmol) of **1** in 1.0 ml of $CDCl_3$ resulted in 50% consumption of the amide in 20 min at 25°, determined by monitoring the aliphatic ^{1}H NMR spectrum. After 12 hr, 94% conversion to the product ($(CH_3)_2CHN{=}C(OR_F)CH_3$) was evidenced by NMR integration using the integral of the total aromatics as an internal standard. The ^{19}F NMR spectrum displayed peaks at 69.1 and 75.0 ppm upfield from $CFCl_3$ ($-CF_3$'s of $CH_3C(OR_F){=}NCH(CH_3)_2$ and R_FOH). The infrared spectrum ($CDCl_3$) of the reaction mixture displayed a strong absorption at 1720 cm^{-1} (C=N). Treatment of 1.8 g (17.8 mmol) of *N*-2-propylacetamide with 18.08 g (27 mmol) of **1** in ca. 30 ml of CH_2Cl_2 for 10 hr, followed by three extractions with 15% aqueous NaOH, removal of solvent, and passage of the resulting oil through a short silica column (pentane), gave 3.2 g (9.8 mmol, 55%) of $CH_3C(OR_F){=}NCH(CH_3)_2$, pure by NMR, which was further purified for microanalysis by preparative GLC on a 5 ft × 0.25 in. 20% SE-30 on Chromosorb W column: NMR ($CDCl_3$) δ 7.20 (s, 5 H, $OC(CF_3)_2C_6H_5$), 3.27 (septet, 1 H, $NCH(CH_3)_2$), 1.95 (s, 3 H, $CH_3C(OR_F)(=NCH(CH_3)_2)$), 0.7 (d, 6 H, $NCH(CH_3)_2$); ir (salt plate) 1720 cm^{-1} (C=N); mass spectrum (70 eV) m/e 327 ($M^{\cdot+}$).

(f) *N*-*n*-Butylbenzamide. Samples of *N*-*n*-butylbenzamide (35.6 mg, 0.20 mmol) and **1** (28.08 mg, 0.42 mmol) were combined in 0.77 ml of $CDCl_3$. After 2 hr, 50% of the starting amide had been consumed, as evidenced by integration of the NCH_2 ^{1}H NMR peaks of the starting amide and products using the total integral of the aromatics as an internal standard. The ^{19}F and 220-MHz ^{1}H NMR spectra of the final reaction mixture revealed formation of $PhCO_2R_F$ (61%), n-$C_4H_9N{=}C(OR_F)Ph$ (36%) and the sulfilimine n-$C_4H_9N{=}SPh_2$ (61%). The aliphatic n-butyl absorptions of the sulfilimine and the imidate were fully resolved at 220 MHz.

(g) *N*-Phenyl-2,2-dimethylpropionamide. Treatment of 201 mg (0.30 mmol) of **1** with 26.6 mg (0.15 mmol) of *N*-phenyl-2,2-dimethylpropionamide in 0.56 ml of $CDCl_3$ resulted in 50% consumption of the amide after 2.5 hr at 25° as determined by integration of the ^{1}H aliphatic NMR peaks using the total aromatic integral as an internal standard. A solution of **1** (8.31 g, 12.4 mmol) and *N*-phenyl-2,2-dimethylpropionamide (1.41 g, 8.06 mmol) in ca. 20 ml of CH_2Cl_2 was allowed to stand 24 hr, the solvent was removed, and the resulting oil was passed through a short silica column (pentane). The resulting pentane solution was extracted three times with 15% aqueous NaOH, concentrated, and passed through a second short silica column (pentane) to give 3.11 g (7.78 mmol, 96%) of the imidate $PhN{=}C(OR_F)C(CH_3)_3$, which, after two recrystallizations from pentane (−50°), gave the analytical sample, mp 75.0–75.5°: NMR ($CDCl_3$) 7.38 (broad s, 5 H, $C_6H_5C(CF_3)_2-$), 7.3–6.2 (m, 5 H, NC_6H_5), 1.2 (s, 9 H, $(CH_3)_3C-$); ^{19}F NMR 68.9 ppm upfield from $CFCl_3$ (s, $-CF_3$ of $-OR_F$); infrared ($CHCl_3$) 1720 cm^{-1} (C=N); mass spectrum (70 eV) m/e 403 ($M^{\cdot+}$).

(h) *N*-Benzylbenzamide. Samples of 7.47 g (11.1 mmol) of **1** and 1.28 g (6.07 mmol) of *N*-benzylbenzamide were mixed in 20 ml of $CDCl_3$. After 3 hr at 25°, the ^{1}H NMR spectrum indicated 50% consumption of starting amide, by integration of the benzyl aliphatic peaks using the total aromatic integral as an internal standard. After 10 hr, the ^{19}F NMR spectrum of the reaction mixture revealed the presence of a singlet at 70.4 ppm upfield from $CFCl_3$ ($-CF_3$ of $PhCO_2R_F$) and 75 ppm ($-CF_3$ of R_FOH). The infrared spectrum of the reaction mixture ($CDCl_3$) displayed absorptions at 2240 cm^{-1} (C≡N of PhCN) and at 1760 cm^{-1} (C=O of $PhCO_2R_F$). The reaction mixture was washed twice with 20% aqueous NaOH to remove R_FOH, dried over Na_2SO_4, filtered, and, after evaporation of the solvent, chromatographed on a short silica gel column (pentane) to give diphenyl sulfide (1.47 g, 7.9 mmol, 71%) and the ester $PhCO_2R_F$ (0.88 g, 2.43 mmol, 42%), both giving NMR and infrared spectra identical with those of authentic materials. Elution with ether gave an oil containing benzonitrile and benzaldehyde. This mixture was analyzed by quantitative GLC on a 5 ft × 0.25 in. 20% SE-30 on Chromosorb W column at 100° using authentic standards and was found to contain 147 mg (1.39 mmol, 23%) of benzaldehyde and 125 mg (1.21 mmol, 20%) of benzonitrile. Continued elution with ether gave benzamide (207 mg, 1.71 mmol, 28%).

(i) *N*-2-Propylbenzamide (36.1 mg, 0.22 mmol) and **1** (300 mg, 0.45 mmol) were combined in 0.81 ml of $CDCl_3$. After 6 hr, the isopropyl doublet of the amide at δ 1.2 in the ^{1}H NMR spectrum had decreased to 50% of its initial peak area and displayed a peak area equal to that of a new doublet appearing at δ 0.71. At the same time, a singlet appeared at 69.0 ppm upfield from $CFCl_3$ in the ^{19}F NMR spectrum. After 4 days at room temperature, the reaction was complete, giving 96% yield of the imidate $(CH_3)_2CH{-}N{=}C(OR_F)Ph$, determined by NMR integration using the total aromatic integral as an internal standard or using the ^{19}F peak at 69.0 ppm. The infrared spectrum of the reaction mixture ($CDCl_3$) displayed a strong absorption at 1700 cm^{-1} (C=N).

(j) *N*-*n*-Butyl-2,2-dimethylpropionamide. Samples of **1** (313.4 mg, 0.467 mmol) and *N*-*n*-butyl-2,2-dimethylpropionamide (38.4 mg, 0.244 mmol) were combined in 0.87 ml of $CDCl_3$. The methyl singlets of the starting amide and product ($(CH_3)_3CCONH$-n-C_4H_9 and n-C_4H_9-$N{=}C(OR_F)C(CH_3)_3$) were monitored to determine the rate of reaction. After 49 hr at 25°, 50% consumption of starting amide was achieved. After 2 weeks, no detectable amide remained. The yield of product was 99%, determined by NMR integration of the fully resolved aliphatic peaks of the product using the aromatic integral as an internal standard. The infrared spectrum of the reaction mixture displayed a strong absorption at 1710 cm^{-1} (C=N).

(k) *N*-*tert*-Butyl-2,2-dimethylpropionamide. A solution of 36.3 mg (0.184 mmol) of *N*-*tert*-butyl-2,2-dimethylpropionamide and 332.5 mg (0.495 mmol) of **1** in 0.92 ml of $CDCl_3$ underwent no reaction after 1 month at room temperature, as determined by monitoring the mixture NMR spectrum.

(l) Succinimide. A sample of finely ground succinimide (290 mg, 2.93 mmol) and **1** (1.99 g, 2.96 mmol) were stirred in ca. 15 ml of ether for 3 hr, filtered to remove unreacted succinimide, and reduced to an oil. The NMR spectrum of the oil indicated ca. 79%

yield of **22**, from the integral of the aliphatic product peaks, using the total aromatic integral as an internal standard. The oil was washed with pentane to remove R_FOH, leaving crude **22** (1.05 g, 1.95 mmol, 68%), which crystallized after 3 weeks at −25° from ether–pentane to give the analytical sample (310 mg, 0.59 mmol, 20%): mp 58–60°; 220-MHz NMR ($CDCl_3$) δ 7.68 (m, 4 H, *S*-phenyl ortho protons), 7.5–7.1 (m, 11 H, meta and para *S*-phenyl protons and protons of OR_F), 2.90 (AA′BB′ m, 4 H, $CH_2CH_2CO_2R_F$); ^{19}F NMR ($CDCl_3$) 70.1 ppm upfield from $CFCl_3$ (s, $-CF_3$ of CO_2R_F); mass spectrum (70 eV) *m/e* 527 ($M\cdot^+$); ir (KBr) 1792 (C=O).

(m) Reaction of Sulfurane 1 and *N*-Methylformamide. Solutions of sulfurane **1** (2.05 g, 3.05 mmol) and *N*-methylformamide (178 mg, 3.02 mmol) in $CHCl_3$ were degassed on a vacuum line with two freeze–thaw cycles and mixed at room temperature. The gas above the reaction mixture at −78° was trapped in a gas infrared cell and shown by infrared spectroscopy to be carbon monoxide.[7] The ^{19}F NMR spectrum of the reaction mixture showed the singlet of R_FOH. Removal of the solvent from the crude reaction mixture and crystallization from ether–pentane gave 720 mg (1.57 mmol, 50%) of the R_FOH complex of *S,S*-diphenyl-*N*-methylsulfilimine, identical by mp and NMR with an authentic sample.

(n) Reaction of Sulfurane 1 with Diamide 23. To a sample of 58.8 mg (0.15 mmol) of spirobicyclic sulfurane **23**[8] in ca. 1 ml of $CDCl_3$ was added 0.796 g (1.18 mmol) of sulfurane **1** in ca. 3 ml of $CDCl_3$. After 12 hr, the solution was filtered, and the ^1H NMR spectrum revealed a complex aromatic spectrum and the singlet at δ 2.30 of ester **6**, R = CH_3, ca. 80% yield, with no detectable starting material. Addition of ether to the reaction mixture caused precipitation of 63.8 mg (0.095 mmol, 64%) of crystalline bissulfilimine **24**, mp 197–200° dec. The 220-MHz NMR spectrum revealed a complex aromatic pattern (δ 7.7–7.1) and no aliphatic absorptions. Infrared (KBr) 1720 cm^{-1} (C=O). Mass spectrum (70 eV) *m/e* 186 ($Ph_2S\cdot^+$), no $M\cdot^+$ observed. Field desorption mass spectrometry gave a molecular ion (*m/e* 670) and base peak (*m/e* 186) ($Ph_2S\cdot^+$), a mode of cleavage characteristic of *S,S*-diarylsulfilimines.[1]

Competitive Reaction of *N*-Methylbenzamide and *p*-Chloro-*N*-methylbenzamide with Sulfurane 1. To a solution of 159 mg (0.94 mmol) of *p*-chloro-*N*-methylbenzamide and 132 mg (0.98 mmol) of *N*-methylbenzamide in $CHCl_3$ was added a solution of 772 mg (1.15 mmol) of **1** in $CHCl_3$ with rapid stirring. The ^{19}F NMR indicated 87% (0.995 mmol) conversion of amides to esters (based on **1**). Integration of the partially resolved peaks of $PhCO_2R_F$ and *p*-$ClC_6H_4CO_2R_F$ with a Du Pont Model 310 curve resolver gave 0.427 mmol of $PhCO_2R_F$ and 0.567 mmol of *p*-$ClC_6H_4CO_2R_F$. Using the integrated rate equation $k_{rel} = [\log((A - X)/A)]/[\log((B - Y)/B)]$, where *A* and *B* are starting concentrations of *p*-chloro-*N*-methyl- and *N*-methylbenzamide, and *X* and *Y* are concentrations of the product esters *p*-$ClC_6H_4CO_2R_F$ and $PhCO_2R_F$; k_{rel} is calculated to be 1.69 (*p*-Cl > H).

Competitive Reaction of *p*-Nitro-*N*-methylbenzamide and *N*-Methylbenzamide with 1. To a solution of 39.7 mg (0.294 mmol) of *N*-methylbenzamide in 2.0 ml of $CHCl_3$ was added 14.8 ml of a solution of 53.8 mg (0.299 mmol) of *p*-nitro-*N*-methylbenzamide. To this rapidly stirring solution was added 247 mg (0.442 mmol) of sulfurane **1** in 2.0 ml of $CHCl_3$. The total yield of esters was 59.8% (0.264 mmol), based on **1** determined by ^{19}F NMR. Integration of the ester singlets in the ^{19}F NMR spectrum with a Du Pont Model 310 curve resolver showed 37% (0.0978 mmol) formation of $PhCO_2R_F$ and 63% (0.166 mmol) formation of *p*-$O_2NC_6H_4CO_2R_F$. Using the integrated rate equation as above, k_{rel} = 2.00 (*p*-NO_2 > H). Some local depletion of reagents may have occurred as the result of inefficient mixing of the rapidly reacting reagents, resulting in a compressed k_{rel} value in this experiment.

Reaction of 3 with KOR_F, HOR_F, and *p*-Chloro-*N*-methylbenzamide. Compound **3** was generated in situ by combining a solution of *S,S*-diphenyl-*N*-methylsulfilimine (71 mg, 3.3 mmol) of benzoyl chloride (458 mg, 3.27 mmol) in 5 ml of $CHCl_3$. (A control reaction was run to demonstrate the formation of **12**; consumption of *S,S*-diphenyl-*N*-methylsulfilimine by an equimolar quantity of the acid chloride is seen to occur within seconds at −30° in $CDCl_3$, monitoring the disappearance of the sulfilimine NCH_3 peak at δ 2.6 and the appearance of the methyl peak of **12a** at δ 3.3.) The solution containing **12** was added with rapid stirring to a solution in $CHCl_3$ (4 ml) and ether (3 ml) of KOR_F (998 mg, 3.54 mmol), HOR_F (899 mg, 3.68 mmol), and *p*-chloro-*N*-methylbenzamide (608 mg, 3.6 mmol). The ^{19}F NMR spectrum displayed the sharp singlet of $PhCO_2R_F$ (91% yield, based on PhCOCl) and no detectable *p*-$ClC_6H_4CO_2R_F$.

Reaction of 12b with KOR_F, HOR_F, and *N*-Methylbenzamide. To a slurry of *p*-nitrobenzoyl chloride (0.262 g, 1.41 mmol) in 5 ml of $CHCl_3$ was added 0.319 g (1.48 mmol) of *S,S*-diphenyl-*N*-methylsulfilimine in 3 ml of $CHCl_3$. The solution immediately became homogeneous. A solution of KOR_F (501 mg, 1.78 mmol), HOR_F (320 mg, 1.31 mmol), and *N*-methylbenzamide (276 mg, 2.04 mmol) in 5 ml of ether was added with rapid stirring to the chloroform solution. The reaction mixture was concentrated to an oil, dissolved in ca. 1.5 ml of $CDCl_3$, and excess unreacted amide and KCl were removed by filtration. The ^1H NMR spectrum displayed a singlet at δ 8.25 (*p*-$O_2NC_6H_4CO_2R_F$) and no detectable absorptions at δ 8.25–8.0 (ortho protons of $C_6H_5CO_2R_F$). The ^{19}F NMR spectrum displayed only a singlet of *p*-$O_2NC_6H_4CO_2R_F$ and no detectable $PhCO_2R_F$.

Preparation and Reaction of 15 with KOR_F and HOR_F. A sample of *S,S*-diphenyl(*N*-*n*-butylbenzamido)sulfonium chloride (**15**) was prepared by treating 910 mg (3.54 mmol) of *S,S*-diphenyl-*N*-*n*-butylsulfilimine (*n*-$C_4H_9N{=}SPh_2$) in a dry box with excess benzoyl chloride in dry ether at ca. −30°. The resulting precipitate was filtered and washed thoroughly with dry ether to remove traces of excess benzoyl chloride and dried under vacuum to give 1.2 g (3.02 mmol, 85%) of **15**: NMR ($CDCl_3$) δ 8.25–7.1 (m, 15 H, $(C_6H_5)_2SNCOC_6H_5$), 4.25 (t, 2 H, NCH_2), 1.8–0.8 (m, 7 H, $NCH_2CH_2CH_2CH_3$). Addition of water to the NMR sample resulted in hydrolysis within 3 min to a 1:1 mixture of diphenyl sulfoxide and *N*-*n*-butylbenzamide.

Treatment of 0.5 g (1.20 mmol) of **15** in $CHCl_3$ with a solution of 1.2 g (4.3 mmol) of KOR_F and 1.0 g (4.1 mmol) of HOR_F in ether–chloroform (3:4) (7 ml) gave, after filtration of KCl, peaks in the ^{19}F NMR spectrum of $PhCO_2R_F$ (70.4 ppm upfield fro $CFCl_3$) and R_FOH (75.3 ppm) and no detectable imidate.

Attempted Reactions of Alkoxysulfonium Triflate 14 with *N*-Methylbenzamide and *N*-*n*-Butylbenzamide. Equimolar quantities of **14**[9] and *N*-methylbenzamide or *N*-*n*-butylbenzamide were combined in $CDCl_3$. In neither case did the ^1H and ^{19}F NMR spectra show a change from those of starting materials after 24 hr.

Hydrolysis of Imidate 9 (R = Ph, R′ = $CH(CH_3)_2$). A sample of 474 mg (1.45 mmol) of the imidate was stirred in 5 ml of absolute methanol with 10 drops of concentrated H_2SO_4. The ^{19}F NMR spectrum, taken after 10 mm of stirring, revealed the complete disappearance of the imidate and the formation of R_FOH. The mixture was stirred for 3 hr after adding 10 drops of water and reduced to an oil under vacuum. The oil was treated with 10 ml of $CHCl_3$ containing excess benzoyl chloride and shaken with 15% aqueous KOH. The chloroform phase was reduced to an oil and stirred with 15% aqueous KOH for 2 hr to remove excess benzoyl chloride. The oil was redissolved in chloroform, dried over Na_2SO_4, and filtered. Removal of the solvent left crystalline *N*-isopropylbenzamide, 192 mg (1.18 mmol, 81%), identical by NMR and ir with an authentic sample.

Hydrolysis of Imidate 9 (R = Ph, R′ = *n*-C_4H_9). A solution of 2.09 g (5.18 mmol) of the imidate in 8 ml of absolute methanol was treated with 7 drops of concentrated H_2SO_4 and stirred for several minutes. The ^{19}F NMR spectrum of the mixture showed complete disappearance of the singlet of **9** at 69 ppm upfield from $CFCl_3$ and the appearance of R_FOH at 75 ppm. The solution was treated with 20 drops of water and stirred for 2 hr, diluted to 20 ml with dilute aqueous HCl, and extracted with 15 ml of CCl_4. The NMR spectrum of the CCl_4 solution, after extraction with aqueous NaOH to remove R_FOH, showed no detectable *N*-*n*-butylbenzamide and was identical with the NMR spectrum of an authentic sample of methyl benzoate. Chromatography of the solution on a 5 ft × 0.25 in. 20% SE-30 on Chromosorb W GLC column at 100° gave a peak with retention time identical with that of authentic methyl benzoate.

Results

Table I lists the reactions of sulfurane **1** with secondary amides. Some of the reactions of Table I were run under uniform conditions of solvent and concentration. In those cases, the time required for 50% reaction is tabulated. Table

Table I. Reactions of Sulfurane **1** with Secondary Amides

Amide	Solvent	Products	Yield, %	Reaction time[a]
$PhCONHCH_3$	$CDCl_3$, (or ether)[b]	$PhCO_2R_F$	98[c]	Fast[g]
		$CH_3N{=}SPh_2{\cdot}HOR_F$	98[c] (82[d])	
PhCONHPh	DMF (or ether)[b]	$PhCO_2R_F$	98[c]	<3 min (in DMF)
		$Ph_2S{=}NPh$	(72[d])	
$CH_3CONHPh$	$CDCl_3$ (or ether)[b]	$CH_3CO_2R_F$	60[c]	<3 min
		$Ph_2S{=}CHCO_2R_F$	24,[c] 5[d]	
		$Ph_2S{=}NPh$	34[c] (50[d])	
CH_3CONH-n-C_4H_9	$CDCl_3$ (or CH_2Cl_2)[b]	$CH_3CO_2R_F$	47[c]	10 min
		n-$C_4H_9N{=}SPh_2$	47[c]	
		n-$C_4H_9N{=}C(OR_F)CH_3$	49[c] (29[d])	
$CH_3CONHCH(CH_3)_2$	$CDCl_3$ (or CH_2Cl_2)[b]	$(CH_3)_2CHN{=}C(OR_F)CH_3$	94[c] (55[d])	20 min
$PhCONH$-n-C_4H_9	$CDCl_3$	$PhCO_2R_F$	61[c]	2 hr
		n-$C_4H_9N{=}C(OR_F)C_6H_5$	36[c]	
		n-$C_4H_9N{=}S(C_6H_5)_2$	61[c]	
$(CH_3)_3CCONHPh$	$CDCl_3$ (or CH_2Cl_2)[b]	$PhN{=}C(OR_F)C(CH_3)_3$	(96[d])	2.5 hr
$PhCONHCH_2Ph$	$CDCl_3$	$PhCO_2R_F$	42[d]	3 hr
		Ph_2S	71[d]	
		$PhCONH_2$	28[d]	
		PhCN	20[e]	
		PhCHO	23[e]	
$PhCONHCH(CH_3)_2$	$CDCl_3$	$(CH_3)_2CHN{=}C(OR_F)C_6H_5$	96[c]	6 hr
$(CH_3)_3CCONH$-n-C_4H_9	$CDCl_3$	n-$C_4H_9N{=}C(OR_F)C(CH_3)_3$	96[c]	49 hr
$(CH_3)_3CCONHC(CH_3)_3$	$CDCl_3$			No reaction
Succinimide	Ether	**22**	79,[c] 20[d]	*f*
$HCONHCH_3$	$CHCl_3$	CO	*f*	
		$CH_3N{=}SPh_2{\cdot}HOR_F$	52[d]	
23	$CDCl_3$	**24**	62[d]	*f*
		$CH_3CO_2R_F$	80[c]	

[a] Time for 50% consumption of amide at ca. 25°, using ca. 0.54 *M* **1** and 0.27 *M* amide. [b] Solvent used for preparative runs for which yields are listed in parentheses. [c] Yield determined by ^{19}F or ^1H NMR. [d] Yields based on weights of isolated products. [e] Yield determined by quantitative GLC. [f] Not determined. [g] <10 min at 0°.

Table II. Esters and Imidates

Compd[a]	Mp, °C	^{19}F chemical shift[b]	^1H NMR[c]
$CH_3CO_2R_F$	45–47	70.5	δ 7.43 (s, 5 H, $CH_3CO_2C(CF_3)_2C_6H_5$), 2.30 (s, 3 H, CH_3)
$(CH_3)_3CCO_2R_F$	37–38	70.1	δ 7.4 (s, 5 H, $(CH_3)_3CCO_2C(CF_3)_2C_6H_5$), 1.4 (s, 9 H, $C(CH_3)_3$)
$C_6H_5CO_2R_F$	47.5–49	70.4	δ 8.25–8.0 (m, 2 H, ortho benzoyl protons), 7.7–7.3 (m, 3 H, meta and para benzoyl protons), 7.45 (s, 5 H, $C_6H_5CO_2C(CF_3)_2C_6H_5$)
p-$O_2NC_6H_4CO_2R_F$	138–139	70.65	δ 8.25 (s, 4 H, p-$O_2NC_6H_4$), 7.38 (s, 5 H, $C(CF_3)_2C_6H_5$)
p-$ClC_6H_4CO_2R_F$	90–91	70.64	δ 8.0 and 7.42 (pair of AA'BB' doublets, 4 H, p-ClC_6H_4), 7.40 (s, 5 H, $OC(CF_3)_2C_6H_5$)
n-$C_4H_9N{=}C(OR_F)C(CH_3)_3$	*d*	68.94	(220 MHz) δ 7.4 (s, 5 H, $OC(CF_3)_2C_6H_5$), 3.34 (t, 2 H, NCH_2), 1.37 (s, 9 H, $(CH_3)_3C$), 1.02 (m, 2 H, NCH_2CH_2), 0.71 (m, 2 H, NCH_2CH_2), 0.71 (m, 2 H, $NOH_2CH_2CH_2$), 0.59 (t, 3 H, $NCH_2CH_2CH_2CH_3$)
n-$C_4H_9N{=}C(OR_F)C_6H_5$	46.5–48.5	68.99	(220 MHz)(NMR-4) δ 7.7–7.3 (m, 10 H, $N{=}C(OC(CF_3)_2C_6H_5)C_6H_5$), 3.2 (t, 2 H, NCH_2), 1.1 (m, 2 H, NCH_2CH_2), 0.89 (m, 2 H, $NCH_2CH_2CH_2$), 0.64 (t, 3 H, $NCH_2CH_2CH_2CH_3$)
i-$C_3H_7N{=}C(OR_F)C_6H_5$	58.5–59.5	68.97	(220 MHz) δ 7.63–7.35 (m, 10 H, $N{=}C(OC(CF_3)_2C_6H_5)C_6H_5$), 3.51 (septet, 1 H, $NCH(CH_3)_2$), 0.71 (d, 6 H, $NCH(CH_3)_2$)

[a] $R_F = (C(CF_3)_2C_6H_5)$. [b] All compounds gave singlets; chemical shifts are in parts per million upfield from $CFCl_3$ of 10% solutions in $CDCl_3$. [c] In $CDCl_3$. [d] Bp 100° (ca. 1 Torr).

II lists esters and imidates prepared by independent routes for comparison with products of the reactions of **1** with secondary amides and lists their ^1H and ^{19}F NMR spectra. The ^{19}F NMR chemical shifts of Table II and throughout the experimental section vary with concentration and temperature, typically over a range of 0.2 ppm. Thus the chemical shift for the same ^{19}F-containing ester may vary slightly between experiments.

Discussion

The "Typical" Reaction. The reactions of secondary amides with **1** follow two principal routes which can be illustrated by the reaction of *N*-methylbenzanilide (which gives almost exclusively cleavage products) and *N*-isopropylbenzanilide (which gives almost exclusively the imidate) as illustrated below.

$$PhCONHCH_3 + \mathbf{1} \longrightarrow \underset{98\%}{PhCO_2R_F} + \underset{98\%}{CH_3N{=}SPh_2{\cdot}HOR_F}$$

$$PhCONHCH(CH_3)_2 + \mathbf{1} \longrightarrow \underset{96\%}{(CH_3)_2CHN{=}C(OR_F)C_6H_5}$$

For certain other amides, such as *N*-*n*-butylbenzanilide, both modes of reaction are seen.

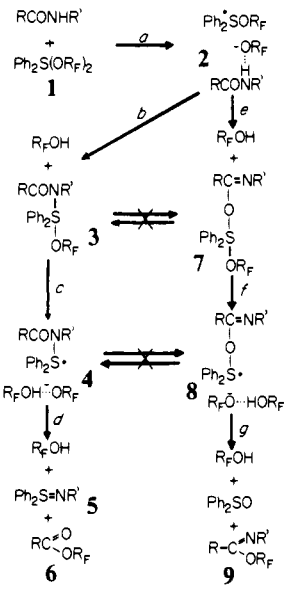
$$PhCONH\text{-}n\text{-}C_4H_9 + 1 \longrightarrow$$

$$\underset{47\%}{PhCO_2R_F} + \underset{47\%}{n\text{-}C_4H_9N{=}SPh_2} + \underset{49\%}{n\text{-}C_4H_9N{=}C(OR_F)CH_3}$$

Certain other secondary amides with specific structural features such as *N*-methylformamide (which gives CO instead of ester in the amide cleavage reaction) and *N*-alkylacetamides (which under certain circumstances yield sulfur ylides) are found to react with **1** to give products which are not those expected from these two typical reactions. We discuss below those structural features of secondary amides likely to favor "atypical" reactions as well as those which mediate the choice between the two typical pathways.

Mechanism of the Amide Cleavage Reaction. Analogy with previously reported mechanistic studies of the reactions of sulfurane **1** with alcohols,[2,9] hydroquinones,[9] glycols,[3] and amines[1] has led us to suggest[4] that the reactions of **1** with secondary amides occur via a dissociative displacement reaction introducing an ambident amido ligand to sulfur in exchange for an alkoxy ligand of **1**. Scheme I

Scheme I



suggests that this can lead either to sulfurane containing a nitrogen-centered ligand (**3**), which is the precursor to the observed esters (**6**) and sulfilimines (**5**), or to sulfurane **7**, with the oxygen-centered amido ligand providing the locus for reaction leading to imidate **9**.

Several experiments provide evidence for the mechanism of Scheme I. The proposed role of ion pair **4** in Scheme I was established by generating **4** by an alternative route. Treatment of sulfilimine **10** with benzoyl chloride provides amidosulfonium chloride **12a.** Solvated sulfonium alkoxide ion pair **4,** a precursor to amidoalkoxysulfurane **3,** was generated from sulfonium chloride **12a** by treatment with KOR_F and HOR_F. When this was done in the presence of *N*-methyl-*p*-chlorobenzamide, the reaction regenerated sulfilimine **10** and formed benzoate **13a** with no detectable amount of *p*-chlorobenzoate ester **13c.** This provides good evidence that attack of alkoxide at the carbonyl of **4** (Scheme I) is faster than reversal of step c, b, and a to regenerate amide (and sulfurane **1,** whose further reaction with the added amide to produce the crossover ester **13c** was not observed) and that step d is therefore not rate determining. In an experiment which was the inverse of this one with respect to the substituents on the amide and the amido ligand, the reaction of the *p*-nitrobenzamidosulfonium salt **12b** with KOR_F–HOR_F led only to *p*-nitrobenzoate ester **13b,** with no detectable amount of benzoate ester **13a** when carried out in the presence of the unsubstituted *N*-methylbenzamide (see Scheme II).

Scheme II

$$\underset{10}{Ph_2S{=}NCH_3} + \underset{\mathbf{11a},\ X=H;\ \mathbf{b},\ X=NO_2;\ \mathbf{c},\ X=Cl}{p\text{-}XC_6H_4COCl} \longrightarrow \underset{\mathbf{12a},\ X=H;\ \mathbf{b},\ X=NO_2;\ \mathbf{c},\ X=Cl}{Ph_2\overset{+}{S}N(CH_3)COC_6H_3X\text{-}p}\ Cl^-$$

$$\mathbf{12a} + p\text{-}ClC_6H_4CONHCH_3 + KOR_F + HOR_F \longrightarrow \underset{\mathbf{13a},\ X=H}{10 + p\text{-}XC_6H_4COOR_F}\ (\text{no } \mathbf{13c},\ X=Cl)$$

$$\mathbf{12b} + C_6H_5CONHCH_3 + KOR_F + HOR_F \longrightarrow \underset{\mathbf{13b},\ X=NO_2}{10 + p\text{-}XC_6H_4COOR_F}\ (\text{no } \mathbf{13a},\ X=H)$$

Competitive reactions of limited quantities of **1** with mixtures of *N*-methylbenzamide and its *p*-chloro- and *p*-nitro-substituted analogs gave relative rates of amide cleavage in the order H(1.0) < *p*-Cl(1.7) < *p*-NO_2(2.0). The increase in rate seen with electron-withdrawing substituents[10] suggests that the approach to the transition state involves the partial transfer of the amide proton[11] to R_FO^-. Such would be expected for steps a and b (or e) in Scheme I but not for step c (or f).

Ligand exchange of alkoxysulfonium triflate **14** with R_FOH (eq 1) is slow on the NMR time scale. Secondary amides do not react with **14** (eq 2) at room temperature. These observations can be understood to reflect the importance of the base catalysis in step b (or e) in Scheme I, with the substitution of the less basic triflate anion for the alkoxide anion of **2** in Scheme I making the collapse to covalent sulfuranes **3** or **7** less probable. Related observations of exchange rates for alkoxysulfonium salts with alkoxides (fast) and alcohols (slow) have been reported by Johnson and Phillips.[13]

$$\underset{\mathbf{14}}{CF_3SO_3^-\ Ph_2SOR_F'} + HOR_F' \overset{\text{slow}}{\rightleftharpoons} CF_3SO_3^-\ Ph_2SOR_F' + HOR_F \quad (1)$$

$$\mathbf{14} + RCONHR' \longrightarrow \text{no reaction} \quad (2)$$

$$Ph_2S(OR_F)_2 + KOR_F' \overset{\text{slow}}{\rightleftharpoons} Ph_2S(OR_F')(OR_F) + KOR_F \quad (3)$$

$$Ph_2S(OR_F)_2 + HOR_F' \overset{\text{fast}}{\rightleftharpoons} Ph_2S(OR_F')(OR_F) + HOR_F \quad (4)$$

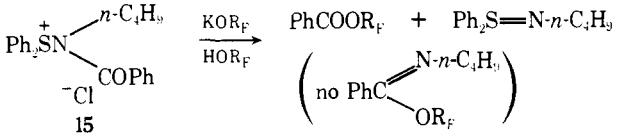
The ionization of sulfurane **1** in step a of Scheme I parallels the rapid ionization which has been established[2,9] to be the first step in the rapid ligand exchange reactions between sulfurane **1** and alcohols. The rates of degenerate ligand exchange reactions of **1** are rapid enough to be accessible to study by NMR lineshape analysis.[2,9] Since exchange of **1** is slower with KOR_F (eq 3) than with HOR_F (eq 4) it has been suggested[2,9] that the ionization is acid catalyzed. In

the analogous step a in Scheme I, the amide serves as general acid catalyst for this ionization.

The rates of reaction of amides with **1** (Table I) generally decrease with the increasing bulk of substituents about the amide bond, consistent with increasing steric hindrance to ligand attachment at the crowded sulfur. For example, in the series of benzamides, PhCONHR, rates of reaction with sulfurane **1** in $CDCl_3$ decrease in the order R = CH_3 > *n*-C_4H_9 > CH_2Ph > $CH(CH_3)_2$. (Although benzanilide (R = Ph) is about as fast as acetanilide, the reaction was run in a different solvent (DMF) and involves a considerably more acidic amide.[11]) The reactivity order *N*-*n*-butylacetamide > *N*-*n*-butylbenzanilide > *N*-*n*-butylpivalamide reflects the order of steric bulk in the acyl portion of the amide with the more sterically hindered amides reacting more slowly. Unambiguous analysis of this point must await more extensive studies of the reactions of **1** with amides. For synthetic applications, all but the most hindered secondary amides react within range of times from a few minutes to several hours at room temperature.

The formation of imidates is favored in the reactions of **1** with the more sterically hindered amides, such as the pivalamides and *N*-isopropylamides. Ligation of the amide at oxygen, to give unsymmetrical sulfurane **7** and eventually imidate **9**, removes the steric bulk of an N-substituent two bond lengths further from the sulfur than is the case for ligation at nitrogen and allows conformations to be adopted which minimize repulsive interactions involving a bulky acyl substituent.

The partitioning between sulfilimine (**5**) and imidate (**9**) products may in principal occur via the direct interconversion of azasulfonium ion **4** and oxasulfonium ion **8** (or of the sulfurane analogs, **3** and **7**) by a sigmatropic 1,3-shift of diphenyl sulfide.[14] Though the reaction of *N*-*n*-butylbenzamide with **1** results in the formation of both imidate (**9**, R = phenyl) and ester (**6**, R = phenyl) plus sulfilimine (**5**, R′ = *n*-C_4H_9), treatment of amidosulfonium salt **15** with KOR_F and HOR_F gives only the ester.



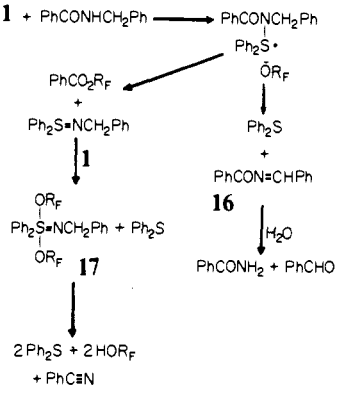
This observation argues against a direct interconversion of **4** and **8** (or **3** and **7**) which is rapid relative to alkoxide attack and, in conjunction with the evidence outlined earlier, points to steps b and e as the product-determining (and rate-determining) steps in the mechanism of Scheme I.

In this scheme, step g can be viewed as proceeding by alkoxide attack on the C=N bond of **8**, with loss of diphenyl sulfoxide from the resulting tetrahedral intermediate, or by loss of Ph_2SO from **8** to form the nitrilium alkoxide which collapses to form **9**. The solvolysis of imidoyl chlorides in aqueous acetone is known[6] to proceed via a nitrilium chloride ion pair in a process closely analogous to the latter pathway.

Oxidations

We have reported[1] oxidations of secondary amines to imines by reaction with **1**. A similar reaction is seen for certain secondary amides. For example, *N*-benzylbenzamide is oxidized to Schiff base **16** which is hydrolyzed to give 23% of benzaldehyde product. The oxidation to benzonitrile (20%) by **1** probably follows the normal amide cleavage pathway shown in Scheme III with subsequent oxidation of the sulfilimine to the nitrile, possibly via sulfurane imine **17** as discussed in the preceding paper of this series.[1]

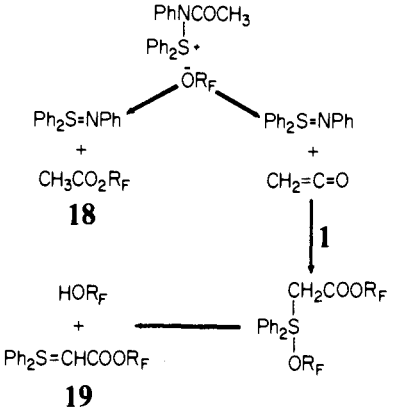
Scheme III



Oxidations such as that leading to **16** are probably to be expected when the substituent on nitrogen contains an α-proton with a somewhat enhanced acidity, as the benzylic protons might be expected to show in the reactions of Scheme III.

The reaction of acetanilide with sulfurane **1** gives ylide **19**, in addition to ester **18** and triphenylsulfilimine. Compound **19** may arise via the generation of ketene and its reaction with sulfurane **1**. Mechanisms by which ester **18**

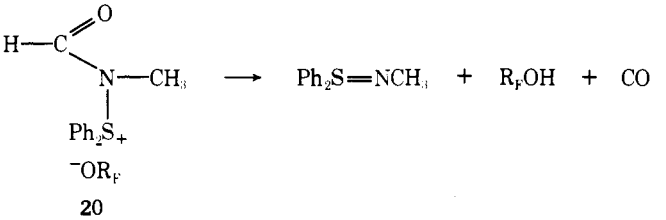
Scheme IV



reacts directly with **1** or with triphenylsulfilimine are ruled out since **18** is stable in the presence of **1** and triphenylsulfilimine under the conditions of the reaction.

Related Reactions

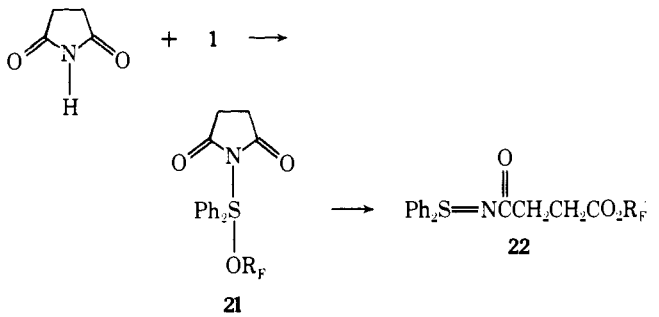
Sulfurane **1** reacts rapidly with *N*-methylformamide, forming sulfilimine **10** and carbon monoxide. The reaction presumably proceeds via amidosulfonium alkoxide **20**. Such



a reaction would, of course, be possible only for formamides.

The reaction of succinimide with **1** to give **22** is postulated to proceed by an analogous route involving the intermediacy of **21**. A closely related set of intermediates has been postulated[15] in a study of the reaction of *N*-chlorosuccinimide with dimethyl sulfide.

Kapovits' spirobicyclic sulfurane[8] **23** reacts with **1** to lose its acetyl groups to yield **24**, in a reaction which selectively cleaves the secondary amide functions while leaving the hydrolytically sensitive sulfuranyl function intact. This



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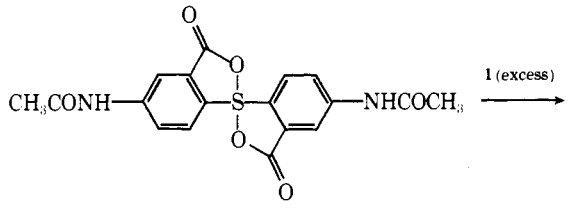
suggests a potential synthetic application of this reaction in the removal of protective groups from primary amines. This reaction proceeds in high yield with **23,** as well as with other



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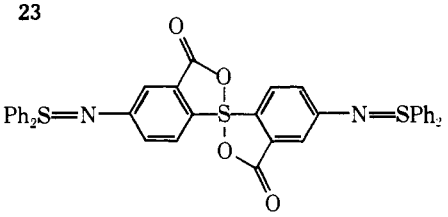

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secondary acetamides of Table I, without detectable incursion of the ylide-forming reaction observed in the reaction with acetanilide. Although further work will be required to determine the conditions under which ylides will be formed, the greater acidity of the N-H protons in **23** relative to those of acetanilide[9] is one factor favoring the amide cleavage in this case.

The efficient recovery of amines from sulfilimines has been achieved by treatment with hydrogen chloride, which leads to the rapid deamination of *N*-alkylsulfilimines[1,16]

$$Ph_2S{=}NR' + HCl \longrightarrow Cl^- H_3\overset{+}{N}R' + Ph_2S + \text{chlorinated products}$$

$$R = (CH_3)_3C, CH_2Ph, CH_3$$

or by catalytic hydrogenolysis, which liberates the parent sulfide and the free amine from *N*-aryl- and *N*-alkylsulfilimines.[1,17]

$$Ph_2S{=}NR' \xrightarrow[C_2H_5OH]{\text{1 atm } H_2,\ 5\%\ Pd/C} Ph_2S + H_2NR'$$

Recovery of the amine from imidate product is readily achieved by acid catalyzed methanolysis of the imidate followed by acidic hydrolysis of the resulting methyl imidates. In this two-step process, imidates **9a** and **9b** produced the

$$R'N{=}C(OR_F)R \xrightarrow[2.\ H_2O]{1.\ CH_3OH,\ H_2SO_4}$$

9a, $R = C_6H_5$; $R' = CH(CH_3)_2$
b, $R = C_6H_5$; $R' = n\text{-}C_4H_9$

$$R'NH_2 + RCO_2CH_3 + R_FOH$$

corresponding free amines with no detectable formation of the parent amides. Direct heterogeneous acid hydrolysis of the *O*-fluoroalkyl imidates leads primarily to regeneration of the amide.[18]

Conclusions

The reactions of **1** with secondary amides are, for some purposes, superior to alternative methods of cleaving the amide bond. Secondary amides require relatively extreme conditions of temperature and medium to achieve useful rates of hydrolyses.[19] Other comparable procedures involve other methods for conversion of the amide to a more readily hydrolyzable species, for example, by treatment with trimethyloxonium tetrafluoroborate followed by acidic hydrolysis of the resulting imidate.[20]

$$RCONHR' \xrightarrow{(CH_3)_3\overset{+}{O}BF_4^-} RC(OCH_3){=}\overset{+}{N}HR'\ BF_4^- \xrightarrow{H_2O} RCO_2CH_3 + R'NH_2$$

Treatment of an amide with thionyl chloride[21] or phosphorus pentachloride[22] forms the corresponding imidoyl chloride (R'N=C(Cl)R), which, after alcoholysis to the corresponding imidate (R'N=C(OR)R), undergoes facile hydrolysis to the free amine. The reactions of NaH—CS_2[23] and SF_4[24] with secondary amides also result in cleavage of the amide bond.

The high overall yields and mild conditions of the reactions of **1** with secondary amides, when combined with efficient methods of recovery of amines from amide cleavage products, make further synthetic applications of this reaction highly attractive. In particular this reaction makes it possible to view the secondary amide function as a viable, selectively removeable blocking group of potential utility in synthetic organic chemistry.

Acknowledgments. Support for this research was provided by Grant No. CA 13963 from the National Cancer Institute of the National Institutes of Health.

References and Notes

(1) Paper XVII in a series of papers on sulfuranes. For paper XVI in this series, see J. A. Franz and J. C. Martin, *J. Am. Chem. Soc.*, **97**, 583 (1975). This paper was abstracted in part from the Ph.D. thesis of J.A.F., University of Illinois, 1974.
(2) R. J. Arhart and J. C. Martin, *J. Am. Chem. Soc.*, **94**, 4997, 5003 (1972).
(3) J. C. Martin, J. A. Franz, and R. J. Arhart, *J. Am. Chem. Soc.*, **96**, 4604 (1974).
(4) For a preliminary account of part of this work, see J. A. Franz and J. C. Martin, *J. Am. Chem. Soc.*, **95**, 2017 (1973).
(5) J. C. Martin, R. J. Arhart, J. A. Franz, E. F. Perozzi, and L. J. Kaplan, *Org. Synth.*, submitted.
(6) I. Ugi, F. Beck, and U. Fetzer, *Chem. Ber.*, **95**, 126 (1962).
(7) R. H. Pierson, A. N. Fletcher, and E. Gantz, *Anal. Chem.*, **28**, 1218 (1956).
(8) A sample of **23** was kindly donated by Professor Istvan Kapovits.
(9) L. J. Kaplan and J. C. Martin, *J. Am. Chem. Soc.*, **95**, 793 (1973).
(10) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structures", McGraw-Hill, New York, N.Y., 1968, p 241, and leading references therein.
(11) For a discussion of the acidities of amides and leading references, see R. B. Homer and C. D. Johnson, "The Chemistry of Amides", J. Zabicky, Ed., Interscience, New York, N.Y., 1970, p 187.
(12) When a sample of R_FOH is added to **14** in $CDCl_3$, no detectable broadening of the ^{19}F singlets for the two species is seen at 41° at concentrations similar to those at which the degenerate exchange of R_FOH with alkoxy ligand of **1** is rapid at −10°.[2]
(13) C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 1926 (1967).
(14) For a discussion of related rearrangements of silicon analogs, see J. Slutsky and H. Kwart, *J. Am. Chem. Soc.*, **95**, 8678 (1973).
(15) E. Vilsmaier and W. Sprügel, *Tetrahedron Lett.*, 625 (1972), and references therein.
(16) See H. J. Shine and K. Kim, *Tetrahedron Lett.*, 99 (1974), for a similar report of the formation of sulfides from sulfilimines upon treatment with HCl, and T. Numata and S. Oae, *Kagaku Kogyo*, 277 (1972), for a related observation of a reaction of diphenyl sulfoxide.
(17) M. A. McCall, D. S. Tarbell, and M. A. Havill, *J. Am. Chem. Soc.*, **73**, 4476 (1951), describe the hydrogenolyses of *N*-sulfonylsulfilimines.
(18) This is in contrast with the observation that ordinary *O*-alkyl imidates are hydrolyzed in acid to give esters and free amines: R. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, **90**, 4413 (1968). It is possible that the difference in products may be attributed to the fact that Chaturvedi and Schmir used homogeneous reaction media.

(19) B. C. Challis and J. A. Challis, "The Chemistry of Amides", J. Zabicky, Ed., Interscience, New York, N.Y., 1970, p 731 ff.
(20) See, for example, S. Hanessian, *Tetrahedron Lett.*, 1549 (1967).
(21) (a) J. v. Braun and W. Pinkernelle, *Chem. Ber.*, **67**, 1218 (1934); (b) G. D. Lander, *J. Chem. Soc.*, **81**, 591 (1902).
(22) See, for example, H. W. O. Weissenburger and M. G. van der Hoeven, *Recl. Trav. Chim. Pays-Bas*, **89**, 1081 (1970).
(23) I. Shahak and Y. Sasson, *J. Am. Chem. Soc.*, **95**, 3440 (1973).
(24) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

Electroorganic Chemistry. XXI.[1] Selective Formation of α-Acetoxy Ketones and General Synthesis of 2,3-Disubstituted 2-Cyclopentenones through the Anodic Oxidation of Enol Acetates

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Abstract: The anodic oxidation of enol acetates in acetic acid gave two types of products, namely α-acetoxy ketones (type A) and α,β-unsaturated enones (type B), and their distribution was remarkably influenced by the character of the supporting electrolyte. In the anodic oxidation of α-alkylated alicyclic enol acetates, the exclusive formation of α,β-unsaturated enones in an excellent yield was achieved by the use of tetraethylammonium tosylate (T salt). On the contrary, the employment of potassium acetate (or triethylamine) instead of T salt brought about the selective formation of α-acetoxy ketones from acyclic and α-nonalkylated alicyclic enol acetates in a sufficient yield. Furthermore, applying this anodic technique, a number of 2,3-disubstituted 2-cyclopentenones were synthesized in the satisfactory overall yield.

In our previous study,[2] it was demonstrated that the anodic oxidation of enol acetates in acetic acid using tetraethylammonium *p*-toluenesulfonate (T salt) as a supporting electrolyte gave α-acetoxy ketones (type A) and/or α,β-unsaturated carbonyl compounds (type B) (see Scheme I). The initiation process of this anodic oxidation has been established to be the electron transfer from enol ester to anode yielding a cationic species. The electrophilic attack of the cationic intermediate to the solvent gave the product of type A, whereas the proton elimination from the intermediate in concert with the second electron transfer yielded α,β-unsaturated enones (type B). The existence of the α-alkyl substituent R on the starting enol acetates was one of the main factors to control the relative rates of these two competitive pathways A and B. For instance, acyclic and α-nonsubstituted alicyclic enol acetates gave preferentially α-acetoxy ketones (type A), whereas α-alkylated alicyclic enol acetates yielded α,β-unsaturated enones (type B) exclusively.

In the present study, we report our new findings that the nature of the supporting electrolyte also possesses a significant influence on the relative rates of these competitive pathways A and B, and the selective formation of α-acetoxy ketones or α,β-unsaturated enones in a good or excellent yield is successfully attainable. Furthermore, a novel and general synthetic method of α-acetoxy ketones[3] or 2,3-disubstituted 2-cyclopentenones[4] including dihydrojasmone was established.

Results and Discussion

As shown in Table I, the use of potassium acetate (or triethylamine) instead of T salt as a supporting electrolyte generally brought about a remarkable improvement in the yield of α-acetoxy ketones (the type A product) in the anodic oxidation of enol acetates in acetic acid. Namely, the selective formation of α-acetoxy ketones **1a–4a** in a good yield was observed in the reaction of acyclic and α-nonalkylated alicyclic enol acetates **1–4**. Moreover, the introduction of an acetoxy group even to a hindered tertiary position could be achieved in the oxidation of α-alkylated alicyclic enol acetates **5** and **6** which, on the contrary, gave α,β-unsaturated enones **5b** and **6b** exclusively when T salt was used as a supporting electrolyte. When the alkyl substituent of cyclopentenyl acetates is allyl- (**7**), *trans*-2-butenyl- (**8**), or propargyl- (**9**), the anodic oxidation of them using potassium acetate (or triethylamine) gave α-acetoxy ketones **7a**, **8a**, or **9a** in a moderate yield, whereas the substitution of T salt for potassium acetate resulted in the formation of a large

Scheme I