and 1.6 g of NaH_2PO_4 in 20 mL of water and 5.0 mL (5.2 × 10^{-2} mol) of 35% H_2O_2, keeping the temperature at 10 °C with water cooling. Oxygen evolved from the solution was monitored until the end of the reaction (about 1 h) with a bubbler connected to the apparatus. A small amount (~0.5 g) of Na_2SO_3 was added to destroy the unreacted HOCl and H_2O_2. Acidification with 10% aqueous HCl afforded 7.0 g (95%) of cinnamic acid, as crystalline solid, mp 131–133 °C (lit.[13] mp 133 °C). TLC and GLC analyses revealed not valuable impurities. ^1H NMR ($CDCl_3$) δ 6.41 (d, 1 H), 7.17–7.69 (m, 5 H), 7.73 (d, 1 H), 11.85 (s, 1 H).

Procedure B. It differs from procedure A since a 5:1 molar ratio H_2O_2–aldehyde is used, and the pH of the medium is lowered to about 2.0 by cautious addition of 37% HCl to the NaH_2PO_4 buffer. The reactions are faster than those of procedure A.

General Oxidation Procedure with $NaClO_2$–Me_2SO. A solution of 8.0 g (7.0 × 10^{-2} mol) of 79% $NaClO_2$ (iodometric titration) in 70 mL of H_2O was added dropwise in 2 h at room temperature to a stirred mixture of 6.6 g (5.0 × 10^{-2} mol) of cinnamaldehyde in 50 mL of Me_2SO and of 1.6 g of NaH_2PO_4 in 20 mL of water. The mixture was left overnight at room temperature, then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted 3 times with CH_2Cl_2 and acidified with 10 M aqueous HCl, and the precipitated cinnamic acid was collected: 7.0 g (95% yield), mp 130–132 °C. TLC and GLC analyses revealed no appreciable impurity nor contamination from Me_2SO or dimethyl sulphone.

General Oxidation Procedure with $NaClO_2$–H_2NSO_3H. The general procedure A was followed, but 6.3 g (6.5 × 10^{-2} mol) of sulfamic acid as scavenger dissolved in 60 mL of water and 6.6 g (5 × 10^{-2} mol) of cinnamaldehyde in 50 mL of *tert*-butyl alcohol was used. After 2 h at room temperature, a crude product was isolated and purified by column chromatography (silica gel; 8:2 ethyl ether–*n*-hexane): 4.4 g (60%) of cinnamic acid, mp 131–133 °C, 1.64 g (25%) of cinnamonitrile, mp 20 °C (lit.[13] mp 20–21 °C), and 0.1 g (1.2%) of *tert*-butyl cinnamate, bp 70 °C (0.1 torr) (lit.[13] bp 140 °C (9 torr)).

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Registry No. (*E*)-C_6H_5CH=CHCHO, 14371-10-9; (*E*)-C_6H_5CH=C(CH_3)CHO, 15174-47-7; (*E*)-C_6H_5CH=C(Cl)CHO, 99414-74-1; (*E*)-C_6H_5CH=C(Br)CHO, 99686-39-2; (*E*)-*o*-$O_2NC_6H_4CH$=CHCHO, 66894-06-2; p-$CH_3CONHC_6H_4CHO$, 122-85-0; p-HOC_6H_4CHO, 123-08-0; (*E*)-CH_3CH=CHCHO, 123-73-9; (*E*)-C_2H_5OCH=C(CH_3)CHO, 62055-46-3; (*Z*)-$(CH_3)_2C$=$CH(CH_2)_2C(CH_3)$=CHCHO, 106-26-3; (*E*)-$(CH_3)_2C$=$CH(CH_2)_2C(CH_3)$=CHCHO, 141-27-5; $CH_3(CH_2)_4CHO$, 66-25-1; (*E*)-C_6H_5CH=$CHCO_2H$, 140-10-3; (*E*)-C_6H_5CH=$C(CH_3)CO_2H$, 1895-97-2; (*E*)-C_6H_5CH=C(Cl)CO_2H, 705-55-5; (*E*)-C_6H_5CH=C(Br)CO_2H, 15894-30-1; (*E*)-*o*-$O_2NC_6H_4CH$=$CHCO_2H$, 882-06-4; $C_6H_5C{\equiv}CCO_2H$, 637-44-5; p-$CH_3CONHC_6H_4CO_2H$, 556-08-1; p-$CH_3SOC_6H_4CO_2H$, 33963-58-5; p-$CH_3SO_2C_6H_4CO_2H$, 4052-30-6; (*E*)-$CH_3(CH_2)_2CH$=$CHCO_2H$, 13419-69-7; (*E*)-CH_3CH=$CHCO_2H$, 107-93-7; 2-HO-3-$CH_3OC_6H_3CO_2H$, 877-22-5; (*E*)-$(CH_3)_2C$=$CH(CH_2)_2C(CH_3)$=$CHCO_2H$, 4698-08-2; (*Z*)-$(CH_3)_2C$=$CH(CH_2)_2C(CH_3)$=$CHCO_2H$, 4613-38-1; C_6H_5C<<-tbdCCHO, 2579-22-8; C_6H_5CHO, 100-52-7; p-$CH_3OC_6H_4CHO$, 123-11-5; 2-OH-3-$(OCH_3)C_6H_3CHO$, 148-53-8; p-$H_2NC_6H_4CHO$, 556-18-3; p-$CH_3SC_6H_4CHO$, 3446-89-7; 2-$CH_3C_6H_4CHO$, 529-20-4; $C_6H_5CO_2H$, 65-85-0; p-$CH_3COC_6H_4CO_2H$, 100-09-4; $CH_3(CH_2)_4CO_2H$, 142-62-1; 2-$CH_3C_6H_4CO_2H$, 118-90-1; $NaClO_2$, 7758-19-2; H_2O_2, 7722-84-1; Me_2SO, 67-68-5; H_2NSO_3H, 5329-14-6; pyridine-4-carboxaldehyde, 872-85-5; thiophene-2-carboxaldehyde, 98-03-3; 5-nitro-2-furancarboxaldehyde, 698-63-5; furan-2-carboxaldehyde, 98-01-1; pyrole-2-carboxaldehyde, 1003-29-8; hydroquinone, 123-31-9; methyl pyridine-4-carboxylate, 2459-09-8; 5-nitro-2-furancarboxylic acid, 645-12-5; 2-furancarboxylic acid, 88-14-2; maleic acid, 110-16-7; cyclohexene-3-carboxaldehyde, 100-50-5; cyclohexene-3-carboxylic acid, 4771-80-6; thiophene-2-carboxylic acid, 527-72-0.

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Synthesis of Novel 6*H*-1,3-Oxazine Derivatives with Perfluoroalkyl Substituents

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Recently, the reactions of perfluoro-2-methylpent-2-ene (**1**),[1,2] a dimer of hexafluoropropene, with various nucleophiles such as alcohols, carboxylic acids, amines and thiols (or their conjugate bases) have been investigated,[3,4] and it has been reported that the reaction proceeded via an apparent nucleophilic substitution reaction.

The reaction of **1** as a 1,3-bidentate electrophile has been studied in recent years and various heterocycles with five-, six-, seven-, and eight-membered rings resulted from the reactions with bidentate nucleophiles such as *N,N*-dimethylhydrazine,[5] acylhydrazones,[6] benzoylacetonitrile, benzoyltrifluoroacetone, acetoacetanilide, catechol, *o*-phenylenediamine, *o*-aminophenol, and salicylaldehyde.[7-9]

In the present work, new 6*H*-1,3-oxazines with perfluoroalkyl substituents (**3a–d**) were obtained in moderate yields from **2** and **1** in the presence of base.

Results and Discussion

When a tetrahydrofuran (THF) solution of **1** was treated with a THF suspension of the sodium salt of **2a**, a single oxazine was cleanly formed as demonstrated by ^{19}F NMR. The spectrum of the product showed the presence of only one pentafluoroethyl, one trifluoromethyl, and one difluoromethylene group. However, spectral data did not rule out one of the two possible structures (**3a** and **4a**). To distinguish between these two possibilities, the product was treated with 1,1-dimethylhydrazine.[10] The ^{19}F NMR spectrum of the resulting compound showed the disappearance of two fluorine atoms from the original product (**3a** or **4a**); a band assigned to carbonyl absorption (1720 cm^{-1}) appeared in the IR spectrum. Furthermore, the mass spectrum of the dimethylhydrazine-treated product displayed a very strong fragment of relative abundance of 69

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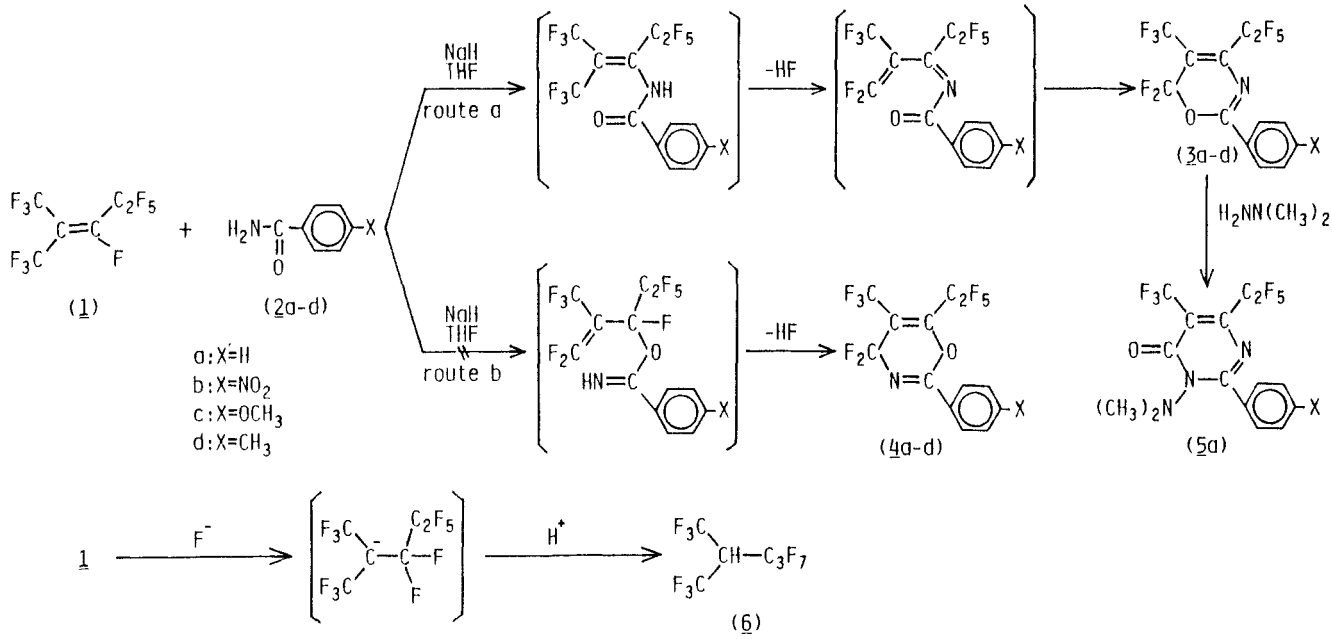
0022-3263/86/1951-0569$01.50/0

Scheme I



at m/z 103, assigned to PhC≡N$^+$, and a negligible fragment at m/z 105, assigned to PhC≡O$^+$. While in the original product (**3a** or **4a**), the relative abundance of the PhC≡O$^+$ fragment was 100 and that of the PhC≡N$^+$ fragment was 15, sharply representing the transformation of —OC(C_6H_5)=N— moiety to =NC(C_6H_5)=N—. Thus, the structure of the dimethylhydrazine-treated product was assigned as **5a** and the structure of the original product as **3a**, since it may be reasonable to consider that **3a** gives **5a** via the intermediacy of acid fluoride which may be formed by a nucleophilic attack of the hydrazine on the ring-carbon-bearing phenyl group, while **4a** may not give **5a**.

The yield of **3a** varied considerably depending on the reaction conditions. Thus, it was enhanced from 21% to 48% by increasing the sodium hydride from an equimolar amount (**1**:**2a**:NaH = 1.0:1.0:1.0) to a four-fold excess (1.0:1.0:4.0) and was further enhanced to 55% by doubling the amount of **2a** (1.0:2.0:3.0). One explanation for this enhancement is that hydrogen fluoride, released during the progress of reaction, would consume **1**. Increasing the amount of sodium hydride, would decrease the consumption of **1**.

Syntheses of the four benzyl derivatives **3a–d** was done without optimization, but an effect of the para substituent on the yield was not observed.

Experimental Section

Melting points and boiling points are uncorrected. ^{1}H NMR spectra were obtained with a JEOL JNM-PS-100 spectrometer operating at 100 MHz; chemical shifts are reported in parts per million from tetramethylsilane as internal standard with the downfield direction taken as positive. ^{19}F NMR spectra were obtained with a JEOL JNM-PS-100 spectrometer at 94 MHz; chemical shifts are calculated in parts per million upfield from benzotrifluoride (63.7 ppm) as internal standard. Mass spectra were recorded on a Hitachi RMU-6E spectrometer; m/z values are quoted for the lowest isotopic species. Infrared spectra were recorded on a Hitachi 260-10 spectrometer.

Perfluoro-2-methylpent-2-ene (**1**) was donated by NEOS Co. Ltd., Kobe, Japan, and purified by distillation under atmospheric pressure at 51 °C before use. Benzamides except for *p*-methylbenzamide were guaranteed grade reagents from commercial sources. *p*-Methylbenzamide was prepared from *p*-toluoyl chloride and ammonia gas and purified by recrystallization from water, mp 164–166 °C (lit.[11] mp 159.1–160.1, 166 °C).

2-Phenyl-4-(pentafluoroethyl)-5-(trifluoromethyl)-6,6-difluorooxazine (3a). (Typical procedure for the preparation of oxazines.) Compound **1** (2.48 g, 8.3 mol) in THF (10 mL) was added dropwise to a suspended mixture of **2a** (2.0 g, 16.5 mmol) and sodium hydride (0.59 g, 24.6 mmol) in THF (30 mL), in a closed system cooled with an ice–water bath. Then, the solution was stirred at 60 °C over a period of 1 h. Unreacted sodium hydride and other THF-insolubles were removed from the solution by filtration. The solvent of the filtrate was evaporated to give a viscous residue. The crude product was extracted several times with hexane from the residue. The orange hexane extracts were evaporated and Kugelrohr distillation of the residual viscous liquid gave 1.75 g (55%) of a colorless waxy material: bp 70 °C (1 mmHg); mp 36.0–36.5 °C; IR (cm^{-1}) 1140–1280 (br, ν_{CF}), 1580 ($\nu_{C=O}$), 1600 (Ph), 1660 ($\nu_{C=N}$); MS, m/z (relative intensity) 381 (M$^+$), 105 (PhC≡O$^+$, 100), 103 (PhC≡N$^+$, 15), 77 (Ph$^+$); ^{1}H NMR ($CDCl_3$, δ) 7.4–7.7 (m, 5 H); ^{19}F NMR ($CDCl_3$, δ) −21.6 (qt, J = 10.9 Hz, J = 1.9 Hz, 2 F), −8.0 (ttq, J = 18.8 Hz, J = 10.9 Hz, 3 F), 17.8 (m, 3 F), 49.6 (qm, J = 18.8 Hz, J = 1.9 Hz, 2 F).

Anal. Calcd for $C_{13}H_5NOF_{10}$: C, 40.96; H, 1.32; N, 3.67. Found: C, 40.55; H, 1.41; N, 4.10.

2-(*p*-Nitrophenyl)-4-(pentafluoroethyl)-5-(trifluoromethyl)-6,6-difluorooxazine (3b). The procedure was the same as for **3a**. The solution of the reaction mixture was evaporated to leave a reddish yellow solid, which was recrystallized from hexane to give yellow leaves, in 37% yield: mp 69.5–71.0 °C; MS, m/z (relative intensity) 426 (M$^+$), 150 (100); ^{1}H NMR ($CDCl_3$, δ) 7.3 (m, 2 H), 8.4 (m, 3 H); ^{19}F NMR ($CDCl_3$, δ) −20.0 (qt, J = 11.3 Hz, J = 1.9 Hz, 2 F), −7.6 (ttq, J = 18.8 Hz, J = 11.3 Hz, 3 F), 18.0 (m, 3 F).

Anal. Calcd for $C_{13}H_4N_2O_3F_{10}$: C, 36.64; H, 0.95; N, 6.57. Found: C, 36.82; H, 1.06; N, 6.63.

2-(*p*-Methoxyphenyl)-4-(pentafluoroethyl)-5-(trifluoromethyl)-6,6-difluorooxazine (3c): colorless needles; yield 30%; bp 40 °C (3 mmHg); mp 52.0–53.0 °C; MS, m/z 411 (M$^+$); ^{1}H NMR ($CDCl_3$, δ) 3.9 (s, 3 H), 7.0 (m, 2 H), 8.1 (m, 2 H); ^{19}F NMR ($CDCl_3$, δ) −21.0 (qt, J = 11.3 Hz, J = 1.9 Hz, 2 F), −8.9 (ttq, J = 18.8 Hz, J = 11.3 Hz, 3 F), 18.0 (m, 3 F), 49.4 (qt, J = 18.8 Hz, J = 1.9 Hz, 2 F).

Anal. Calcd for $C_{14}H_7NO_2F_{10}$: C, 40.89; H, 1.72; N, 3.41. Found: C, 40.87; H, 1.77; N, 3.51.

2-(*p*-Methylphenyl)-4-(pentafluoroethyl)-5-(trifluoromethyl)-6,6-difluorooxazine (3d): white waxy material; yield

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21%; mp 44.0–46.0 °C; IR (cm^{-1}) 1640, 1590, 1560, 1140–1270; MS, m/z 395 (M^+); ^1H NMR ($CDCl_3$, δ) 2.4 (s, 3 H), 7.3 (m, 2 H), 8.0–8.1 (m, 2 H); ^{19}F NMR ($CDCl_3$, δ) −21.4 (qt, J = 11.3 Hz, J = 1.9 Hz, 2 F), −7.8 (ttq, J = 18.8 Hz, J = 11.3 Hz, 3 F), 18.0 (m, 3 F), 47.3 (qt, J = 18.8 Hz, J = 1.9 Hz, 2 F).

Anal. Calcd for $C_{14}H_7NOF_{10}$: C, 42.55; H, 1.79; N, 3.54. Found: C, 42.39; H, 1.89; N, 3.66.

6-(Pentafluoroethyl)-5-(trifluoromethyl)-2-phenyl-3-(dimethylamino)pyrimidin-4-one (5a). Excess 1,1-dimethylhydrazine was directly added to **3a** (0.5 g, 1.3 mmol) dissolved in ether at room temperature and heated to reflux over a period of 2 h. The ether insolubles were removed by filtration and the ether was evaporated from the filtrate to leave a yellow solid. The residue was extracted with hexane to give 0.2 g (25%) of a pale yellow solid: mp 140–142 °C; IR (cm^{-1}) 1140, 1160, 1210, 1240, 1530, 1580, 1720 ($\nu_{C=O}$); MS, m/z (relative intensity) 401 (M^+), 358 ($M^+ + 1 - N(CH_3)_2$, 100), 357 ($M^+ - N(CH_3)_2$, 67), 103 ($PhC{\equiv}N^+$, 69); ^1H NMR ($CDCl_3$, δ) 3.0 (s, 6 H), 7.59 (m, 5 H); ^{19}F NMR ($CDCl_3$, δ) −3.8 (t, J = 19.3 Hz, 3F), 17.0 (m, 3 F), 47.3 (q, J = 19.3 Hz, 2 F).

Anal. Calcd for $C_{15}H_{11}N_3OF_8$: C, 44.90; H, 2.76; N, 10.47. Found: C, 44.51; H, 2.87; N, 10.85.

2-(Trifluoromethyl)-1,1,1,3,3,4,4,5,5,5-decafluoropentane (6). Compound **6** was isolated as a THF solution by distillation of the reaction mixture of **1** and **2a**, at 66 °C under atmospheric pressure, and was characterized from ^{19}F NMR analysis which corresponded to that reported in literature.[12]

Registry No. **1**, 1584-03-8; **2a**, 55-21-0; **2b**, 619-80-7; **2c**, 3424-93-9; **2d**, 619-55-6; **3a**, 99838-04-7; **3b**, 99838-05-8; **3c**, 99883-78-0; **3d**, 99838-06-9; **5a**, 99838-07-0; **6**, 30320-28-6; H_2N-$N(CH_3)_2$, 57-14-7; *p*-toluoyl chloride, 874-60-2.

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Nuclear Magnetic Resonance Determination of the Site of Acylation of the Tautomeric Nucleophile 4-Thioxopyridine

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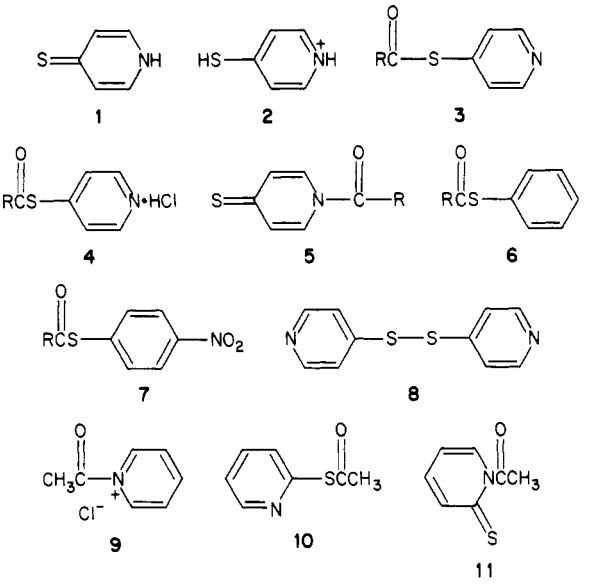
The tautomeric nucleophile 4-thioxopyridine (1) and the corresponding disulfide are useful mechanistic tools as electrophile and nucleophile traps, respectively.[1] We recently employed the title compound to elucidate the details of an enzymatic reaction mechanism, and it became imperative to unequivocally assign the site of acylation of this ambident nucleophile. While the ambiguity in the structure assignment was recognized before,[2,3] those assignments were based solely on UV–vis evidence and excellent chemical intuition. We have synthesized a number of derivatives and are now in a position to make unequivocal assignments based on ^{13}C and ^1H NMR spectroscopy. Conditions were found under which the *N*-acyl (amide) and *S*-acyl (thiol ester) derivatives could be interconverted reversibly. While most straight chain acyl derivatives can exist either as an *S*- or an *N*-acyl isomer, the pivaloyl and benzoyl derivatives exist exclusively as the thiol ester.

Chart I[a]



[a] R = Me (**a**), Et (**b**), *t*-Bu (**c**), Ph (**d**), PhCH=CH (**e**), *p*-ClPhCH=CH (**f**), MeO (**g**), PhO (**h**).

Results and Discussion

The model compounds employed in our studies are listed in Chart I. Syntheses are discussed in the Experimental Section. Most relevant to our analysis are the ^{13}C and ^1H NMR data summarized in Table I. There are three types of structures evident in all these data: the *S*-acyl thiol ester hydrochloride **4**, the *S*-acyl thiol ester **3**, and the *N*-acyl (amide) compounds **5**. All the observed reactions and rearrangements are shown in Scheme I.

Salient features of the structure assignments follow. Reaction of pivaloic anhydride with **1** yielded a colorless liquid **3** [bp 95–100 °C (0.1 torr)] that according to ^{13}C NMR comparisons (the *tert*-butyl methyl and quaternary as well as the carbonyl chemical shifts) with **6c** and **7c**, exists as the thiol ester. While compound **3c** is a liquid (λ_{max} = 250 nm), reaction of **1** with acetic anhydride for 6 h at room temperature produces orange crystals of **5a**[2] (λ_{max} = 375 nm). By contrast reaction of **1** with acetyl chloride in acetone at room temperature produces **4a**[3] (λ_{max} = 276 nm). When a CD_3CN solution of **5a** was saturated with HCl gas, it yielded a product that was spectroscopically indistinguishable from **4a**. When a 0.5 M solution of **5a** dissolved in CD_3CN was incubated in the NMR probe at 22 °C, **5a** was converted to **3a** with a half-life of about 2 h. In water and in methanol at room temperature, **5a** was hydrolyzed (within hours) to **1** according to UV–vis spectroscopic measurements. When compounds **4a**,[2] **4b**, **4e**, **4f**, or **4g**[2] were neutralized with aqueous $NaHCO_3$ and extracted into ethyl ether, UV spectral features of **3** and **5** as well as of **1** could be observed. Therefore, the interconversion of **3** and **5** for certain R groups can be effected from either direction under certain conditions.

The thiol ester structure for **3a** is assigned by comparison of the acetyl methyl and carbonyl ^{13}C chemical shifts

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