  Bull. Chem. Soc. Jpn., 61, 247—253 (1988)

Water-Soluble Acylating Agents: Preparation of 2-Acylthio-1-alkylpyridinium Salts and Acylation of Phenols, Acids, and/or Amines with These Salts in an Aqueous Phase

Tohru SAKAKIBARA,* Yukie WATABE,† Masahide YAMADA,† and (the late) Rokuro SUDOH†
Department of Chemistry, Yokohama City University, Seto, Kanazawa-ku, Yokohama 236
†Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152
(Received June 9, 1987)

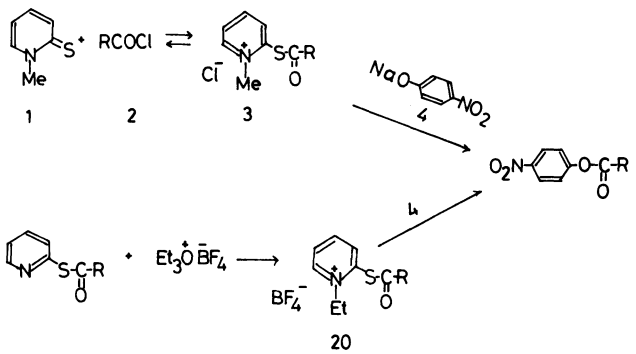
Reaction of phenols, amines, and acids with 2-benzoylthio-1-methylpyridinium chloride prepared in situ from benzoyl chloride and 1-methyl-2(1*H*)-pyridinethione, afforded the corresponding benzoyl derivatives in good yields. In the reaction of *p*-nitrophenol, even a catalytic amount of 1-methyl-2(1*H*)-pyridinethione proved to be effective. Similar reactions of *p*-nitrophenol with isobutyryl chloride and acetyl chloride in the presence of 1-methyl-2(1*H*)-pyridinethione afforded *p*-nitrophenyl isobutyrate and *p*-nitrophenyl acetate in 63 and 44% yields, respectively. 2-Benzoylthio-, 2-acetylthio-, and 2-isobutyrylthio-1-ethylpyridinium tetrafluoroborates were prepared by treatment of the corresponding 2-acylthiopyridines with triethyloxonium tetrafluoroborate. These pyridinium salts also acted as acylating agents in an aqueous phase. Some competitive reactions of 2-aminoethanol and phenols with 2-benzoylthio-1-methylpyridinium chloride were also investigated.

Conversion of the reaction medium from a nonaqueous phase into an aqueous phase can be useful, especially for treatment of enzymes or proteins, because they are generally more or less denatured in organic solvents. On the other hand, esters of carbothioic *S*-acids are much more reactive than the corresponding carboxylic acid esters and frequently serve as acylating agents in biological reactions, e.g., acetyl-CoA.[1] As one of the candidates for water-soluble acylating agents, we chose 2-acylthio-1-alkylpyridinium salts;[2] the pyridinium moiety should not only activate the *S*-thioester but also make the compounds water-soluble.[3]

Results and Discussion

Treatment of 1-methyl-2(1*H*)-pyridinethione (**1**) with benzoyl chloride (**2a**) in refluxing acetonitrile for 2 h afforded 2-benzoylthio-1-methylpyridinium chloride (**3a**) as a highly hygroscopic precipitate. Its ^{1}H NMR spectrum showed that the salt **3a** was stable in D_2O, at least for 1 h, suggesting that it might act as a benzoylating agent in an aqueous layer. In fact, addition of sodium *p*-nitrophenoxide (**4**) to an aqueous solution containing a crude **3a** gave *p*-nitrophenyl benzoate (**5a**) in 50% yield. The salt **3a**, however, was in equilibrium with the starting materials (**3a**:**1**=ca. 1:4) in chloroform-*d*.

When **1** and **2a** were mixed in $CDCl_3$–D_2O, it is shown later that the salt **3a** formed in the organic layer is selectively extracted into the aqueous layer. This led to a more convenient 'one-pot' procedure; without isolation of **3a**, direct addition of water-soluble sodium *p*-nitrophenoxide (**4**) to a chloroform–water solution of **1** and **2a** afforded the ester **5a** in 81% yield. Similar treatment of phenol, 2,4-dinitrophenol, and 2-aminoethanol in the presence of an equimolar amount of 1 M NaOH (1 M=1 mol dm^{-3}) gave phenyl benzoate (**6**), 2,4-dinitrophenyl benzoate (**7**), and *N*-(2-hydroxyethyl)benzamide (**8**) in 83, 73, and 67% yields, respectively.



a; R=Ph, b; R=CHMe$_2$, c; R=Me, d; R=OEt

Since 1-methyl-2(1*H*)-pyridinethione (**1**) regenerates after benzoylation, a catalytic amount of **1** might promote the reaction.[4] Benzoylation of **4** was performed, therefore, in changing the amounts of **1**. As shown in Table 1, benzoylation was accelerated with the increase of **1**, but even 0.01 equimolar amount of **1** was found to be effective, giving **5a** in 65% yield.

If a product formed in an aqueous phase is extracted smoothly into an organic phase, a heterogeneous system is applicable for the preparation of such a fairly water-sensitive compound as an acid anhydride. Sodium acetate, therefore, was added to a chloroform–water solution of **1** and **2a**, providing acetic benzoic anhydride **10** in 83% yield as estimated from ^{1}H NMR spectroscopy. Formation of acetanilide (59%) by addition of aniline to the crude product proved that acid anhydride **10** had been generated. Similar reactions of **3a** with several acids in the

Table 1. The Effect of the Amounts of **1** in Benzoylation of **4**

Relative amount of **1** to **2a** and **4**	Reaction time/min	Yield of **5a**[c]/%
0[a]	70	4
0[a]	480	24
0.01[a]	420	65
0.05[a]	70	26
0.1[a]	70	41
0.2[a]	70	69
1[a]	70	81
0[b]	70	7
0.1[b]	20	71
0.1[b]	40	77

a) Compound **2a** (1 mmol) and **4** (1 mmol) were treated in H_2O (5 ml)–$CHCl_3$ (5 ml). b) Compound **2a** (5 mmol) and **4** (5 mmol) were treated in H_2O (5 ml)–$CHCl_3$ (5 ml). c) Isolated yields.

Table 2. Benzoylation of Phenols, Acids, and Amines with **3a**[a]

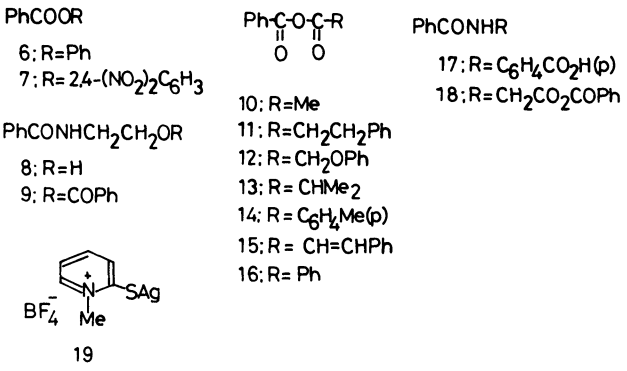
Substrate	Base[b]	Product(s)	Yield/%
Sodium *p*-nitrophenoxide		**5a**	81
Phenol	NaOH	**6**	82
2,4-Dinitrophenol	NaOH	**7**	73
Sodium Acetate		**10**	83[c] (59)
3-Phenylpropionic acid	$NaHCO_3$	**11**	82[c] (62)
Phenoxyacetic acid	$NaHCO_3$	**12**	79[c] (63)
Isobutyric acid	NaOH	**13**	61[c] (21)
Toluic acid	NaOH	**14**	91[c] (23)
Cinnamic acid	NaOH	**15**	66[c]
2-Aminoethanol	NaOH	**8**	75[d]
p-Aminobenzoic acid	$NaHCO_3$	**17**	79
Glycine	$NaHCO_3$	**18**	19

a) Prepared in situ from **1** and **2a** in $CHCl_3$–H_2O. The reaction mixture was stirred for 1.5 h at room temperature, except for the case of sodium *p*-nitrophenoxide (2 h). b) Equimolar amount of base was used. c) Estimated by ^1H NMR spectroscopy; figures in parentheses showed the yields isolated as the corresponding anilides; besides the anilides, benzanilide was obtained in 6, 18, trace, 26, and 55% yields, respectively, from **10**—**14**. d) Small amounts (5%) of dibenzoyl derivative **9** was isolated.

presence of an equimolar amount of sodium hydrogencarbonate or sodium hydroxide afforded the corresponding mixed acid anhydrides in moderate to good yields (Table 2). Furthermore addition of sodium hydroxide to a chloroform-water solution of **1** and **2a** yielded benzoic anhydride (**16**) in 79% yield. This reaction should involve hydrolysis of **2a**, followed by nucleophilic attack of the benzoic acid thus produced on **3a**. Under the same conditions, but in the absence of **1**, hydrolysis of **2a** occurred predominantly to give benzoic acid together with small amounts of benzoic anhydride and benzoyl chloride.

When **3a** was similarly treated with trifluoroacetic acid, only the hydrolysis was observed. This is reasonable because benzoic trifluoroacetic anhydride was hydrolyzed within 10 min by stirring it in a benzene-water solution.

Reaction of *p*-aminobenzoic acid with **3a** gave the *N*-benzoyl derivative **17** in 75% yield, whereas benzoylation of glycine yielded the *N,O*-dibenzoyl derivative **18** (19%), which was partially converted into *N*-benzoylglycine during column chromatography or recrystallization.



An aqueous solution of sodium *p*-nitrophenoxide (**4**) was added to a chloroform–water solution of **1** and isobutyryl chloride, giving the ester **5b** in 63% yield based on isobutyryl chloride. Similar reaction of **4** with acetyl chloride provided the acetate **5c** in 44% yield. Under the same conditions, but in the absence of **1**, the acetate **5c** could not be obtained.

In order to obtain some information about the partition of **3** between chloroform and water as well as the stability of **3**, the following ^1H NMR spectral investigation was performed. (i) In a NMR sample

Table 3. The Ratios of **3** to **1** in Chloroform-*d* and Partition of **3** between Chloroform-*d* and Deuterium Oxide

Acyl(Sulfonyl) chloride	Product	The ratios of **3** to **1**+**3**/% in $CDCl_3$[a]	The estimated amount of **3**/%[b] in $CDCl_3$		in D_2O	
			After 5 min	After 2 h	After 5 min	After 2 h
PhCOCl	**3a**	22 (δ=4.80)[c]	0	0	77	71
$Me_2CHCOCl$	**3b**	16 (δ=4.65)[c]	0	0	49	11[d]
AcCl	**3c**	18 (δ=4.65)[c]	0	0	28	3[d]
EtOCOCl	**3d**	49 (δ=4.88)[c]	4.0	3.4	53	58
p-$MeC_6H_4SO_2Cl$		0	0	0	0	0

a) In the absence of D_2O: Calculated by method (i). b) Calculated by method (ii). c) The chemical shift of the 1-methyl signal of **3**. d) Most acyl chloride was hydrolyzed, since strong signals of the methyl groups of isobutyric acid and acetic acid were observed, respectively.

tube, **1** (0.2 mmol) and acyl chloride (0.2 mmol) were dissolved in $CDCl_3$ (0.2 ml) and the reaction was monitored by ^1H NMR spectroscopy; the ratio of **1** and **3** was calculated on the basis of area-ratios due to the 1-methyl signal of **1** (δ=4.00) and that of **3** (see, Table 3). (ii) After 1 h, D_2O (0.2 ml) was added to the sample tube and the ratios of **1** to **3** in both the layers were determined by comparing the integration of the methyl signals due to **1** and **3** with that of toluene (added as an internal standard). The results are shown in Table 3. The salts **3a—c** were formed immediately and equilibrated with the starting material within 10 min, whereas formation of **3b** was slow and even after 1 h, equilibrium was not attained. Under the same conditions, however, *p*-toluenesulfonyl chloride did not afford the corresponding salt. The salts **3a** and **3d** were fairly stable in an aqueous layer, but the salt **3c** was sensitive to water. In accord with expectation, the stability of **3b** stood between **3a** and **3c**.

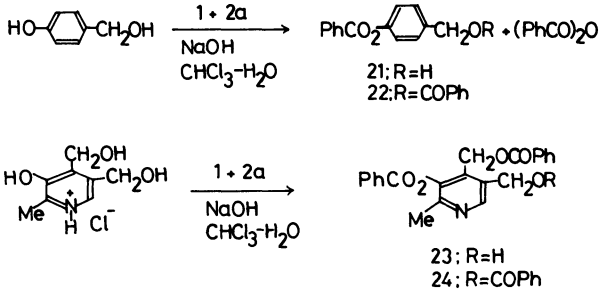
Treatment of sodium *p*-nitrophenoxide with ethyl chloroformate in the presence of **1** afforded the carbonate **5d** in 32 and 70% yields, respectively, after 1.5 h and 5 h. In the absence of **1**, however, the carbonate **5d** formed in 61% yield after 5 h.

Several attempts to purify **3a** failed, mainly owing to its reversibility in solution. Therefore, the counter ion was changed to a less nucleophilic tetrafluoroborate. After reflux of an acetonitrile solution of **1** and **2a** for 2 h, silver tetrafluoroborate was added to give water-insoluble precipitates. Its IR and/or ^1H NMR spectra indicated the absence of a carbonyl group, but the presence of a *N*-methyl group (δ=4.07, DMSO-d_6) and the characteristic absorption band for tetrafluoroborate (1000—1150 cm^{-1}). The same compound was obtained by treatment of **1** with silver tetrafluoroborate, as judged by IR spectroscopy. From these results the product was tentatively assigned to **19**.

The intending tetrafluoroborate **20a** was prepared by *N*-ethylation of 2-benzoylthiopyridine with triethyloxonium tetrafluoroborate in 85% yield. The salt **20a** is fairly stable at room temperature even in an open vessel and is soluble in chloroform as well as in water. Similar treatment of 2-isobutyrylthiopyridine and 2-acetylthiopyridine afforded the corresponding salts **20b** and **20c** as a syrup, respectively. The latter two salts gradually turned yellow even in a desiccator over phosphorus pentaoxide and they were soluble in water but insufficiently soluble in chloroform. By this route water-soluble acylating agents could be synthesized from carboxylic acid, since 2-acylthiopyridines were prepared by treatment of the corresponding carboxylic acid with 2-pyridinethiol in the presence of di-2-pyridyl sulfide-triphenylphosphine[5] or dicyclohexylcarbodiimide.[6]

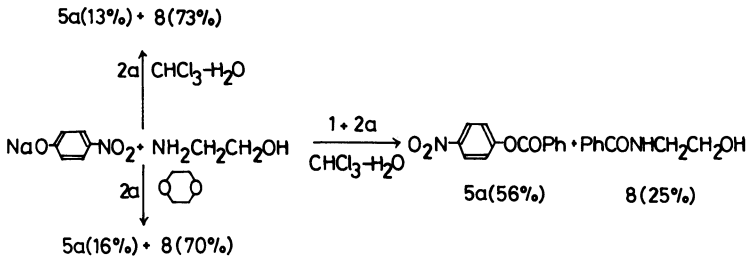
Treatment of the phenoxide **4** with the salts **20a—c** in water yielded the corresponding esters in 95, 80, and 73% yields, respectively.

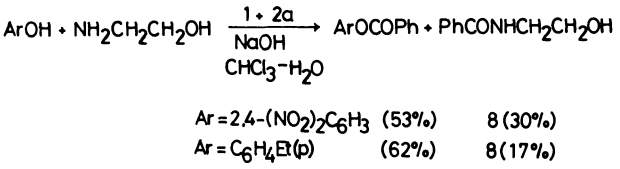
Addition of an equimolar amount of 1 M sodium hydroxide and either methanol or benzyl alcohol to a chloroform–water solution of **1** and **2a** gave the corresponding esters in only 2.4 and 10% yields, respectively. These results suggested that it may be possible to achieve selective benzoylation of the phenolic hydroxyl group, if the compounds have both alcoholic and phenolic hydroxyl groups. In fact benzoylation of *p*-hydroxybenzyl alcohol with **3a** afforded *p*-(hydroxymethyl)phenyl benzoate (**21**) (49%) and dibenzoate **22** (3%).[7] Similar reaction of pyridoxol hydrochloride gave 3,α^4-dibenzoate **23** in 36% yield. Since migration of the acyl group from C-3 to C-4 was known to occur,[8] two equimolar amounts of **3a** were used; the yield of **23** was raised to 75%, together with the perbenzoate **24** (7%).



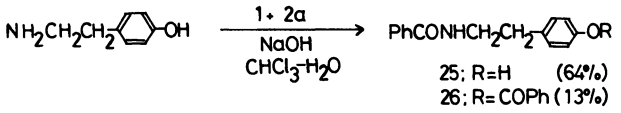
Addition of an equimolar amount of sodium *p*-nitrophenoxide and 2-aminoethanol to **3a** (generated in situ) provided the benzoate **5a** and benzamide **8**

(isolated as the acetate) in 56 and 25% yields, respectively. On the other hand, in the absence of **1** similar heterogeneous or homogeneous reactions with **2a** gave **5a** and **8** in 13 and 73% or 16 and 70% yields, respectively. In similar competitive reactions between 2-aminoethanol and 2,4-dinitrophenol or *p*-ethylphenol, predominant benzoylation of phenolic hydroxyl groups was also observed in the presence of **1**.





Contrary to the competitive reactions described above, benzoylation of tyramine, having both amino and phenolic hydroxyl groups in the same molecule, with **3a** preponderant gave the *N*-benzoyl derivative **25** (64%) together with the *N,O*-dibenzoyl derivative **26** (13%) and unreacted tyramine (11%, recovery).[9]



Such a difference may be explained as follows. The amino group might be more reactive than the phenoxide ion towards **3a**. Benzoylation of phenoxide ion, however, should be entropically favorable, since the phenoxide ion could become the counter ion of the pyridinium salt, but 2-aminoethanol could not. But, in the case of tyramine, which should be captured as the counter ion of pyridinium salt, such an entropical predominance seems to be negligible and the more reactive amino group would be preferentially benzoylated.

Experimental

General. All melting points are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM-360A Spectrometer in $CDCl_3$ and D_2O solution with tetramethylsilane and DSS, respectively, as an internal standard. IR Spectra were determined with a Hitachi 285 Infrared Spectrophotometer. Column chromatography was performed on silica gel (Wako, C-300). The organic solutions were dried over magnesium sulfate and distilled under reduced pressure.

2-Benzoylthio-1-methylpyridinium Chloride (3a). A solution of 1-methyl-2(1*H*)-pyridinethione (**1**) (1.81 g, 14.5 mmol) and benzoyl chloride (**2a**) (2.04 g, 14.5 mmol) in acetonitrile (15 ml) was heated under reflux for 2 h and cooled at room temperature. Addition of diethyl ether to the mixture caused hygroscopic precipitates; ^{1}H NMR ($CDCl_3$) δ=4.00 (s, N-Me), 4.80 (s, N^+-Me), 6.70 (d, pyridine ring proton at 6), and 7.10—8.85 (m, ring protons); ^{1}H NMR (D_2O) δ=4.05 (s, N-Me), 4.37 (s, N^+-Me), 7.35—8.80 (m, ring protons), and 9.18 (d, pyridinium ring proton at 6). Attempts to purify the precipitate failed. The ^{1}H NMR spectrum in $CDCl_3$ showed that the salt **3a** attained an equilibrium with the starting material (**3a**:**1**=ca. 1:4).

Benzoylation of Sodium *p*-Nitrophenoxide with 3a. (a) The precipitate of **3a** (61 mg) and sodium *p*-nitrophenoxide (**4**) (37 mg, 0.23 mmol) was dissolved in water (2 ml). After being stirred for 30 min at room temperature, the mixture was extracted with chloroform. The extracts were combined and evaporated. The residue was chromatographed with dichloromethane to afford 28 mg (50%) of *p*-nitrophenyl benzoate (**5a**). (b) To an ice-cooled solution of the pyridinethione **1** (126 mg, 1.01 mmol) and benzoyl chloride (142 mg, 1.01 mmol) in chloroform (5 ml) was added water (5 ml) and the mixture was stirred for 5 min. After addition of **4** (163 mg, 1.01 mmol) at 0 °C, the mixture was stirred for 2 h at room temperature and extracted with chloroform. Similar processing as described above afforded 199 mg (81%) of **5a**.

Benzoylation of Phenol. To a solution of **1** (136 mg, 1.09 mmol) and benzoyl chloride (153 mg, 1.09 mmol) in chloroform (5 ml) was added water (3 ml) and the mixture was stirred for 5 mim and cooled with ice-water. A solution of phenol (103 mg, 1.09 mmol) in water (8 ml) containing 1 M NaOH (1.09 ml) was added over 15 min and the mixture was stirred for an additional 1.5 h at room temperature and then extracted with chloroform. The combined extracts were dried, and evaporated to a syrup, which was chromatographed with dichloromethane, to give 178 mg (82%) of phenyl benzoate (**6**).

Similar treatment of 2,4-dinitrophenol (201 mg, 1.09 mmol) gave 2,4-dinitrophenyl benzoate (**7**) in 73% (229 mg) yield.

Benzoylation of 2-Aminoethanol. Similar treatment of 2-aminoethanol (67 mg, 1.1 mmol) described for the pre-

paration of **6** afforded a syrup, which was chromatographed with chloroform, to give successively 17 mg (7%) of benzoic anhydride, 15 mg (5%) of the *N,O*-dibenzoyl derivative **9**, and 38 mg (21%) of the *N*-benzoyl derivative **8**. The residue obtained by evaporation of the aqueous layer was extracted with chloroform and the extracts were evaporated to give 83 mg of **8** (total yield 67%).

Typical Procedure for the Preparation of Acid Anhydride; Acetic Benzoic Anhydride (10): To an ice-cooled solution of **1** (179 mg, 1.43 mmol) and **2a** (201 mg, 1.43 mmol) in chloroform (10 ml) were added 5 ml of water and the solution was stirred for 5 min. To the mixture was added sodium acetate (117 mg, 1.43 mmol) at 0 °C. After being stirred for 1.5 h at room temperature, the mixture was extracted with chloroform and the combined extracts were dried, and evaporated to a syrup. The yield of acetic benzoic anhydride (83%) was deduced on the basis of signals due to the 1-methyl group of **1** (δ=4.00) and the acetyl group of **10** (δ=2.35). In its spectrum, the acetyl signals of acetic acid (δ=2.09) and acetic anhydride (δ=2.20) were negligible. Purification by column chromatography with benzene provided 61 mg (26%) of **10**, together with 87 mg (50%) of benzoic acid. Sublimation of the anhydride was found to be unsuitable because of the co-sublimation of **1**. To a chloroform solution (2 ml) of the crude product was added aniline (133 mg, 1.43 mmol). The mixture was kept for 3.5 h at room temperature, diluted with chloroform and washed successively with dilute HCl, aq $NaHCO_3$, and water, dried, and evaporated. The syrup was chromatographed with dichloromethane to yield acetanilide (114 mg, 59%) and benzanilide (17 mg, 6%).

Similar treatment of the acid, except for the addition of an equimolar amount of sodium hydrogencarbonate, afforded the corresponding acid anhydride. The estimated yield of benzoic 3-phenylpropionic anhydride (**11**) (based on the ethylene signals at δ=3.00) and benzoic phenoxyacetic anhydride (**12**) (methylene signals at δ=4.91) were 82 and 79%, respectively.

Similar treatment of the acid, except for the use of sodium hydroxide instead of sodium hydrogencarbonate, provided benzoic isobutyric anhydride (**13**) (61%, methyl signals at δ=1.36 and 1.25), benzoic *p*-toluic anhydride (**14**) (91%, methyl signal at δ=2.45), benzoic cinnamic anhydride (**15**) (66%, signals of olefinic proton at δ=6.70 and 6.43).

Benzoic Anhydride (16). To a stirred solution of **1** (1.12 mmol) and **2a** (1.12 mmol) in 10 ml of chloroform was added 4 ml of water at room temperature and the solution was stirred for 5 min. To the solution was added over 5 min 1 M NaOH (1.12 ml) and the mixture was stirred for 1.5 h and extracted with chloroform. The extracts were evaporated and the residue was chromatographed with chloroform, to give 100 mg (79%) of **16**.

Benzoylation of *p*-Aminobenzoic Acid and Glycine. Similar treatment of *p*-aminobenzoic acid (196 mg, 1.43 mmol) described for the preparation of **11** afforded 259 mg (75%) of **17**.

Glycine (107 mg, 1.43 mmol) was similarly benzoylated. After chromatography with dichloromethane, the *N,O*-dibenzoyl derivative **18** was isolated in 77 mg (19%); IR (KBr) 1810, 1655, and 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.42 (4H, s, $-CH_2-$), 7.35—7.75 and 7.90—8.25 (10H, m, 2×Ph). Purification of **18** failed because of partial hydrolysis to *N*-benzoylglycine during recrystallization from benzene.

Acylation of Sodium *p*-Nitrophenoxide. (a) To an ice-cooled solution of **1** (120 mg, 0.96 mmol) and isobutyryl chloride (102 mg, 0.96 mmol) in chloroform (5 ml) and water (5 ml) was added sodium *p*-nitrophenoxide (**4**) (155 mg, 0.96 mmol). After being stirred for 1 h at room temperature, the mixture was extracted with chloroform. The combined extracts were dried, and evaporated. The residue was chromatographed with chloroform to give 126.4 mg (63%) of **5b**.

(b) Similar treatment of acetyl chloride (75 mg, 0.96 mmol) with **4** (0.96 mmol) afforded 76 mg (44%) of *p*-nitrophenyl acetate (**5c**).

Ethyl *p*-Nitrophenyl Carbonate (5d). Similar treatment of ethyl chloroformate (104 mg, 0.96 mmol) with **4** as described above gave **5d** in 32% yield. When the reaction time was extended to 5 h, the yield was raised to 70%.

Similar treatment in the absence of **1** for 5 h afforded **5d** in 61% yield.

Attempt at Preparation of 20a by Exchange of the Counter Ion. Compound **1** (2.06 mmol) and **2** (2.06 mmol) was stirred for 5 min in chloroform (10 ml)–water (10 ml) and the organic layer was drawn off. To the aqueous layer was added silver tetrafluoroborate (2.06 mmol). After filtration of the precipitates, the filtrate was freeze-drying to give 230 mg of hygroscopic powder; IR (KBr) 1620, 1540, 1490, 1420, 1400, 1260, 1050, 760, and 700 cm^{-1}.

The same product, as judged from IR spectroscopy, was obtained by treatment of **1** with silver tetrafluoroborate.

2-Benzoylthio-1-ethylpyridinium Tetrafluoroborate (20a). A suspension of benzoic acid (3.66 g, 30 mmol) and 2-pyridinethiol (3.33 g, 30 mmol) in dry ethyl acetate (18 ml) was cooled with ice–ethanol (ca. −12 °C). To the solution was added over 10 min a solution of dicyclohexylcarbodiimide (6.18 g, 30 mmol) in dry ethyl acetate (15 ml) with stirring. After being cooled at ambient temperature, the mixture was kept overnight at room temperature . After filtration, the filtrate was evaporated and the residue was purified by bulb to bulb distillation, bp 145 °C (oven temperature)/0.1 Torr (1 Torr=133.322 Pa), to afford 5.03 g (78%) of 2-benzoylthiopyridine. The same compound was also prepared from sodium 2-pyridinethiolate with benzoyl chloride.[10]

To an ice-cooled solution of triethyloxonium tetrafluoroborate (190 mg, 1 mmol) in dichloromethane (1 ml) was added a solution of 2-benzoylthiopyridine (210 mg, 0.98 mmol) in dichloromethane (1.5 ml) with stirring. The mixture was stirred overnight at room temperature and filtered (14 mg of a precipitate was obtained, which had no ethyl group). The filtrate was washed with diethyl ether (decantation). Reprecipitation from acetone–diethyl ether afforded 276 mg (85%) of **20a**, mp 79—80 °C; IR (KBr) 1695, 1600, 1490, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.58 (3H, t, J=7.0 Hz, Et), 4.90 (2H, q, Et), 7.35—8.90 (8H, m, Ph and H-3, H-4, and H-5 of the pyridine ring), and 9.36 (1H, d, J=7.0 Hz, H-6 of the pyridine ring). Found: C, 50.38; H, 4.17; N, 4.22; S, 9.98%. Calcd for $C_{14}H_{14}NOSBF_4$: C, 50.78; H, 4.26; N, 4.23; S, 9.68%.

1-Ethyl-2-isobutyrylthiopyridinium Tetrafluoroborate (20b). Similar treatment of isobutyrylthiopyridine with triethyloxonium tetrafluoroborate as described above afforded a syrup. It was partially purified by repeated decantation with dichloromethane–diethyl ether (ca. 70%), but complete purification was unsuccessful, because it

gradually turned yellow in a desiccator containing phosphorus pentaoxide, IR(KBr) 1740 and 1060 cm^{-1}; ^1H NMR (CD_3COCD_3) δ=1.36 (6H, d, J=7.0 Hz, $CHMe_2$), 1.68 (3H, t, J=7.0 Hz, Et), 3.30 (1H, m, $CHMe_2$), 5.03 (2H, q, Et), 8.30—9.05 (3H, m, ring protons), and 9.51 (1H, q, ring proton).

2-Acetylthio-1-ethylpyridinium Tetrafluoroborate (20c). Similar treatment of 2-acetylthiopyridine with triethyloxonium tetrafluoroborate gave **20c** as a syrup in ca. 88% yield, which also gradually turned yellow and failed to purify, IR (KBr) 1745, 1615, and 1060 cm^{-1}; ^1H NMR (CD_3COCD_3) δ=1.62 (3H, t, J=7.0 Hz, Et), 2.82 (3H, s, COMe), 4.98 (2H, q, Et), 8.22—9.05 (3H, m, ring protons), and 9.47 (1H, q, ring proton).

Acetylation of Sodium *p*-Nitrophenoxide with 2-Acylthio-1-ethylpyridinium Tetrafluoroborate. To a stirred solution of **20a** (166 mg, 0.53 mmol) was added sodium *p*-nitrophenoxide (81 mg, 0.50 mmol). After being stirred for 1 h at room temperature, the mixture was extracted with chloroform and the extracts were evaporated. The syrup was chromatographed with chloroform, to afford the ester **5a** in 95% yield.

Similar treatment of **20b** and **20c** with sodium *p*-nitrophenoxide provided the corresponding esters **5b** and **5c** in 80 and 73% yields, respectively.

Benzoylation of *p*-Hydroxybenzyl Alcohol. To an ice-cooled solution of **1** (2.86 mmol) and **2a** (2.86 mmol) in chloroform (10 ml) was added 10 ml of water and the mixture was stirred for 10 min. To the solution was added over 20 min a solution of *p*-hydroxybenzyl alcohol (355 mg, 2.86 mmol) and 1 M NaOH (2.86 ml) in 10 ml of water. After being stirred for 1.5 h at room temperature, the mixture was extracted with chloroform and the extracts were dried and evaporated. The residue was chromatographed with dichloromethane, to give successively benzoic anhydride (22% based on **2a**), *p*-(hydroxymethyl)phenyl benzoate (**21**) (320 mg, 49%), and *p*-[(benzoyloxy)methyl]phenyl benzoate (**22**) (29 mg, 3% based on the alcohol).

Benzoylation of Pyridoxol. Similar treatment of pyridoxol hydrochloride (588 mg, 2.86 mmol) as described above, but using two equimolar amounts of NaOH, yielded 389 mg (36%) of 3,α^4-dibenzoate (**23**). When two equimolar amounts of **1** and **2a** were used, the yield of **23** was raised to 75%, together with the tribenzoate **24** (7%).

Hydrogen chloride was bubbled into a solution of **23** in methanol–diethyl ether to give white crystals of the salt of **23**, mp 151—152 °C (lit, 152—153 °C).[8] The tribenzoate was recrystallized from ethanol; mp 120—121 °C (lit, 122 °C).[11]

Competitive Benzoylation between 2-Aminoethanol and Sodium Phenoxide. (a) In the Presence of 1. To a solution of **1** (1.96 mmol) and **2a** (1.96 mmol) in chloroform (10 ml) was added over 15 min a solution of sodium *p*-nitrophenoxide (**4**) (1.96 mmol) and 2-aminoethanol (1.96 mmol) in 10 ml of water at room temperature. After being stirred for an additional 1 h, the mixture was extracted with chloroform and the extracts were evaporated to a syrup, which was chromatographed with dichloromethane, to give 267 mg (56%) of **5a**. To the residue obtained by evaporation of the aqueous layer was added acetic anhydride (10 ml) and 0.5 ml of BF_3 etherate and the mixture was stirred overnight. After conventional work up, the residue was chromatographed with chloroform, to provide 101 mg (25%) of 2-(benzamido)ethyl acetate. An analytical sample was prepared by recrystallization from cyclohexane, mp 50—51 °C; IR(KBr) 3350 (NH), 1715 (CO), 1617 and 1513 cm^{-1} (NHCO). Found: C, 63.78; H, 6.36; N, 6.70%. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76%.

(b) In the Absence of 1. To a solution of **4** (1.96 mmol) and 2-aminoethanol (1.96 mmol) in 10 ml of water was added benzoyl chloride (**2a**) (1.96 mmol) in 10 ml of dichloromethane and the mixture was stirred for 24 h. Processing as described above afforded the ester **5a**, amide **8**, and 2-(benzamido)ethyl acetate in 13, 52, and 21% yields, respectively.

Similar benzoylation in 1,4-dioxane afforded **5a**, **8**, and 2-benzamidoethyl acetate in 16, 40, and 30% yields, respectively.

To a solution of **1** (2.07 mmol) and **2a** (2.07 mmol) in chloroform (20 ml)–water (4 ml) at ca. 5 °C was added an aqueous solution (24 ml) of 2,4-dinitrophenol (2.07 mmol), sodium hydroxide (2.07 mmol), and 2-aminoethanol (2.07 mmol). After being stirred for 1.5 h, the mixture was worked up as described above, to give the ester **7** (53%) and 2-(benzamido)ethyl acetate (30%).

Similar competitive reaction of 2-aminoethanol (2.02 mmol) and *p*-ethylphenol yielded *p*-ethylphenyl benzoate (62%) and 2-benzamidoethyl acetate (17%).

The possibility of benzoyl migration from *p*-nitrophenyl benzoate to 2-aminoethanol was excluded as follows. To a chloroform solution of **5a** (2.23 mmol) was added an aqueous solution (10 ml) of 2-aminoethanol (2.23 mmol) and the solution was stirred for 24 h. The organic layer separated was evaporated to afford the unchanged **5a** in 95% yield.

Benzoylation of Tyramine. To a solution of **1** (0.97 mmol) and **2a** (0.97 mmol) in chloroform (10 ml) was added a solution of tyramine (133 mg, 0.97 mmol) containing 1 M NaOH (0.97 ml) in water (10 ml) at room temperature. After being stirred for 1 h, the mixture was diluted with chloroform. The organic layer was washed with water and evaporated to a syrup, which was chromatographed with chloroform, to give 44 mg (13%, based on tyramine) of the dibenzoate **26** as the first fraction, mp 171—172 °C (lit, 172 °C).[12] The second fraction (150 mg, 64%) was the *N*-benzoyl derivative **25**, which was recrystallized from acetonitrile, mp 163—164 °C (lit, 162 °C).[13]

The aqueous layer was evaporated and the residue (870 mg) was acetylated to give 24 mg (11%) of the *N,O*-diacetyl derivative of tyramine, which was isolated by column chromatography with chloroform. The acetate was recrystallized from benzene, mp 97—98 °C; IR (KBr) 3300 (NH), 1770 and 1760 (CO), and 1643 (NHCO) cm^{-1}. Found: C, 64.86; H, 6.81; N, 6.29%. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33%.

The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References

1) For example, I. S. Kleiner and J. M. Orten, "Biochemistry," 7th ed., ed by C. V. Mosby, Saint Louis (1966), p. 385.

2) For reviews on the onium salts of aza-arenes: T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **18**, 707 (1979).

3) Preparation of **3a** and benzoylation of some acids, amines, and phenols with **3a** had been reported in a preliminary form; M. Yamada, Y. Watabe, T. Sakakibara, and R. Sudoh, *J. Chem. Soc., Chem. Commun.*, **1979**, 179.

4) If the acylation was slow, hydrolysis of acyl chloride should be the major reaction path, since these reactions compete each other.

5) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).

6) K. Lloyd and G. T. Young, *J. Chem. Soc. C*, **1971**, 2890.

7) Since *p*-hydroxybenzyl alcohol was insufficiently soluble in both water and chloroform, the alcohol was partially recovered under the employed conditions.

8) W. Korytryk and B. Paul, *J. Org. Chem.*, **32**, 3791 (1967).

9) When tyramine and *N,O*-dibenzoyltyramine were kept for 1 h in chloroform or for 3 h in acetone or ethanol, no change was observed in TLC, suggesting that intermolecular benzoyl migration was negligible.

10) S. Ueno, S. Asakawa, and E. Imoto, *Nippon Kagaku Zassi*, **89**, 101 (1968).

11) T. Matukawa, *J. Pharm. Jpn.*, **60**, 551 (1940).

12) E. F. Gale, *Biochem. J.*, **34**, 846 (1949).

13) G. Barger, *J. Chem. Soc.*, **95**, 1123 (1909).