2-(Trifluoroacetyloxy)pyridine as a Mild Trifluoroacetylating Reagent of Amines and Alcohols

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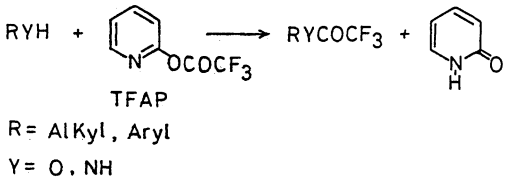
A new trifluoroacetylating reagent, 2-(trifluoroacetyloxy)pyridine (**TFAP**), was prepared by the reaction of 2-pyridinol and trifluoroacetic anhydride. **TFAP** has been found to be effective in the trifluoroacetylation of aliphatic and aromatic amines and alcohols including phenol under mild conditions. The reaction of *p*-nitrophenol with **TFAP** in ether gave the hydrogen-bonded complex between the phenol and 2-pyridone. This reagent has also been shown to be useful for the intramolecular dehydration of aldehyde oximes and amides to give nitriles in high yields.

Trifluoroacetylation is a valuable reaction for the protection or activation of functional groups in organic synthesis and biochemistry. The reaction is also very often used in gas-chromatographic analysis of amines and alcohols. Though trifluoroacetic anhydride,[1] *N*-(trifluoroacetyl)imidazole,[2] *N*-methylbis-(trifluoroacetyl)amine,[3] or *S*-ethyl trifluorothioacetate[4] have been available for the reaction, some of them have disadvantages. The most widely used trifluoroacetic anhydride is volatile and sensitive to moisture; in addition, it needs a base to remove the liberated acid. *N*-(trifluoroacetyl)imidazole is hard to handle because of its high sensitivity against moisture.

We have previously shown that the ester between 2-pyridinol and trifluoromethylsulfonic acid, 2-(trifluoromethylsulfonyloxy)pyridine (**TFOP**) is a useful reagent for the condensation of carboxylic acid and arene to give acylarene, in which the trifluoromethylsulfonylation of carboxylic acid with **TFOP** was assumed.[5] Analogously, we have prepared the ester between 2-pyridinol and trifluoroacetic acid, 2-(trifluoroacetyloxy)pyridine (**TFAP**). We now wish to report an application of TFAP to a trifluoroacetylating reagent of amines and alcohols.[6] The preparation of nitriles by the reaction of aldehyde oximes and amides with TFAP will also be reported.



Scheme 1.

Results

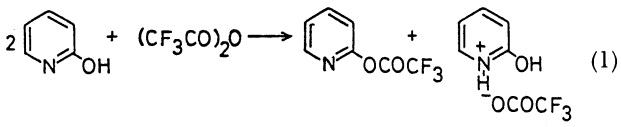
Synthesis of TFAP. The new reagent, **TFAP**, was

Table 1. Trifluoroacetylation of Amines, Alcohols, and Phenols with **TFAP**

Run	Product	Reaction[a] time/h	Isolated yield/%	Bp/°C/mmHg or (Mp/°C)	IR(ν/cm^{-1}) ν_{CO}
1	Cyclohexyl-NHCOCF$_3$	0.5	93	(92—93)	1695
2	Hexyl-NHCOCF$_3$	0.5	95	114—115/9	1705
3	Phenyl-NHCOCF$_3$	0.5	93	(89—90)	1715
4	4-Nitrophenyl-NHCOCF$_3$	0.5	93	(151—152)	1750
5	4-Methylphenyl-NHCOCF$_3$	0.5	90	(111—113)	1710
6	1-Naphthyl-NHCOCF$_3$	1.0	95	(101—103)	1710
7	Diphenyl-NCOCF$_3$	0.5	99	(71—73)	1715
8	Pentyl-OCOCF$_3$	0.5	99	140—141/760	1795
9	Isopentyl-OCOCF$_3$	0.5	93	119—120/760	1796
10	Hexyl-OCOCF$_3$	1.0	95	141—142/760	1790
11	Cyclohexyl-OCOCF$_3$	0.5	99	145/760	1788
12	Benzyl-OCOCF$_3$	0.5	98	175/760	1795
13	4-Methylbenzyl-OCOCF$_3$	1.0	99	184—185/760	1785
14	Phenyl-OCOCF$_3$	2.0[b]	98	60—61/46	1804
15	4-Chlorophenyl-OCOCF$_3$	2.0[b]	95	84—85/40	1805
16	4-Nitrophenyl-OCOCF$_3$	1.0	[c]		
17	2-Hydroxyphenyl-NHCOCF$_3$	1.0	99	(160—161)	1693
18	4-Hydroxyphenyl-NHCOCF$_3$	1.0	99	(167—169)	1700
19	2-Hydroxy-5-chlorophenyl-NHCOCF$_3$	1.0	94	(217—219)	1690
20	3-Hydroxy-5-methylphenyl-NHCOCF$_3$	1.0	94	(191—192)	1695

a) Carried out in an ether solution at 20 °C. b) Carried out in boiling ether. c) The hydrogen-bonded complex between *p*-nitrophenol and 2-pyridone was obtained.

prepared by the reaction of two equivalents of 2-pyridinol with trifluoroacetic anhydride in a tetrahydrofuran solution in good yield.



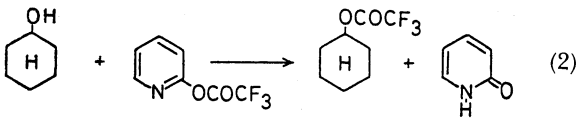
(1)

This compound has not appeared in the literature, despite its simple structure. It is a stable, colorless liquid which does not freeze at the ice-salt temperature and has a high boiling point. Physical data is given in the experimental section.

Trifluoroacetylations with TFAP. Trifluoroacetylations with **TFAP** were carried out by stirring the solution of a substrate and **TFAP** (in a molar ratio of 1 : 1.1, respectively) in ether. The results are summarized in Table 1. Trifluoroacetylated products were identified by a comparison of their IR spectrum or the retention time of GLC with those of the authentic compounds prepared from the reaction of the corresponding substrate with trifluoroacetic anhydride.

Various alkylamines and arylamines readily reacted with **TFAP** at a room temperature to give the corresponding *N*-trifluoroacetyl amines in satisfactory yields. The amines with low nucleophilicity, such as *p*-nitroaniline and diphenylamine, also underwent the trifluoroacetylation at room temperature.

By means of a similar procedure, alcohols and phenols were allowed to react with the reagent. The trifluoroacetylation of alcohols easily proceeded in an ether solution at the room temperature. When the reaction mixture of cyclohexanol and **TFAP** in ether was cooled to 0 °C, white crystals were yielded from the solution, and identified as 2-pyridone by its IR and ^{1}H NMR spectra (Eq. 2).



(2)

The reaction of phenols required a longer time and higher temperature than that for alcohols. Compounds containing both the hydroxyl and amino groups in a molecule were selectively trifluoroacetylated at the amino group. For example, *p*-aminophenol reacted with **TFAP** to give *p*-(trifluoroacetylamino)phenol in a quantitative yield.

The reagent failed to trifluoroacetylate *p*-nitrophenol. A white solid was separated out upon stirring a mixture of *p*-nitrophenol and **TFAP** in ether at room temperature. In the IR spectrum of this solid, a broad absorption band over 3250—2500 cm^{-1} and peaks due to the carbonyl (1660 cm^{-1}) and nitro groups (1590 and 1343 cm^{-1}) were observed. The ^{1}H NMR spectrum in $CDCl_3$ at 50 °C has four peaks, δ=7.60 (t, 1H), 7.49 (d, 1H), 6.72 (d, 1H), and 6.45 (d, 1H), which are similar to those for the ring protons of 2-pyridone,[7] in addition to the two doublets from a *p*-nitrophenol frame. The broad signals were recognized over a region of δ=6.0—7.0 on the ^{1}H NMR, of which intensity corresponded to two protons. The solid is soluble in water, methanol, and dimethyl sulfoxide (**DMSO**) to give a light-yellow colored solution, which seems to indicate the regeneration of *p*-nitrophenol. The ^{1}H NMR spectrum in DMSO-d_6 at 50 °C is consistent with that of a mixture of 2-pyridone and *p*-nitrophenol, in which the protons of the hydroxyl group and the lactam NH function are observed at δ=10.92 and 11.64 respectively. Thus, the white solid was identified as the hydrogen-bonded complex between *p*-nitrophenol and 2-pyridone, as shown in scheme 2. The same complex was obtained by stirring a mixture of 2-pyridinol and *p*-nitrophenol in ether at room temperature.

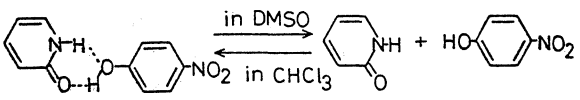
Nitrile Synthesis from Aldehyde Oximes or Amides with TFAP. The treatment of aldehyde oximes with **TFAP** in boiling tetrahydrofuran gave nitriles. The results are shown in Table 2.

A variety of aldehyde oximes were subjected to reacting with **TFAP** to afford the corresponding

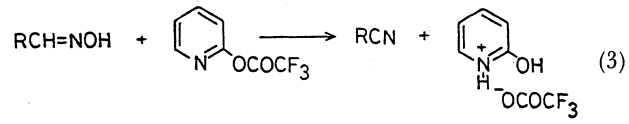
Table 2. Nitrile Synthesis by the Reaction of Aldehyde Oximes or Amides with **TFAP**

Run	R of Nitrile (RCN)	Yield of Nitrile/%		Bp/°C/mmHg or (Mp/°C)		IR(ν/cm^{-1})
		From Oxime[a] (RCH=NOH)	From Amide[b] ($RCONH_2$)	Found	Reported[21]	ν_{CN}
1	Pentyl	Quant.	—	163/760	164/760	2224
2	Hexyl	—	91	180/760	183—184/760	2240
3	Cyclohexyl	—	Quant.	185/760	184—185/760	2230
4	2-Furyl	89	—	146/760	146—148/760	2220
5	Phenyl	90	72	191/760	191/760	2210
6	*p*-Tolyl	94	91	(24—27)	(26—28)	2210
7	*m*-Tolyl	—	77	211/760	210—212/760	2210
8	*p*-Chlorophenyl	Quant.	90	(91—93)	(94—96)	2210
9	*m*-Chlorophenyl	—	77	(40—41)	(39—42)	2210
10	*o*-Chlorophenyl	Quant.	—	(45—46)	(43—44)	2225
11	*p*-Nitrophenyl	97	61	(145—149)	(146—149)	2220
12	Styryl	91	85	(16—18)	(18—20)	2220

a) Carried out in boiling tetrahydrofuran for 2—6 h. b) Carried out in boiling acetonitrile for 5 h.



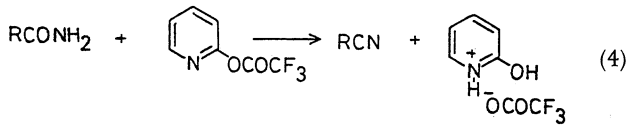
Scheme 2.



(3)

nitriles in satisfactory yields (Eq. 3).

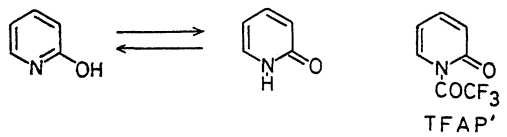
The use of the reagent has been extended to the intramolecular dehydration of amides, which are more difficult to dehydrate than aldehyde oximes. The reaction was carried out by heating a mixture of amide and **TFAP** in acetonitrile under reflux. The results are given in Table 2. Aliphatic amides as well as benzamides having a variety of substituents have been converted to the corresponding nitriles in good isolated yields (Eq. 4).



(4)

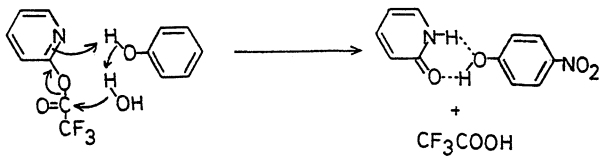
Discussion

2-Pyridinol has a well-known tendency to form 2-pyridone, as shown in scheme 3.[8] Therefore, although the other structure, i.e., the amide form (**TFAP'**), can be drawn for the reaction product of 2-pyridinol with trifluoroacetic anhydride, there are no peaks, indicating the amide form on the IR and ^{1}H NMR spectra.



Scheme 3.

An acyl group of 2-(acyloxy)pyridine can be predicted from the above tautomerism to behave as a good electrophile. In fact, Imoto and coworkers have reported that 2-(acetyloxy)pyridine reacts with amines and alcohols in boiling tetrahydrofuran to give the corresponding acetamides and alkyl acetates, respectively.[9] Dutta and Morley reported the use of 2-pyridyl ester of *N*-acyl amino acids in peptide synthesis.[10] We also previously reported that 2-(acyloxy)-pyridines are effective for the acylation of activated arenes in trifluoroacetic acid.[11] Now, **TFAP** has been shown to be useful for the trifluoroacetylation of amines and alcohols involving phenols. The reaction of *p*-nitrophenol with **TFAP** did not give the desired trifluoroacetylated products but, rather, the molecular complex between the phenol and 2-pyridone. The complex may be formed by the reaction of *p*-nitrophenol and 2-pyridone, which was generated by a reaction with a trace amount of water contained in the reaction system, as shown in scheme 4.[12]



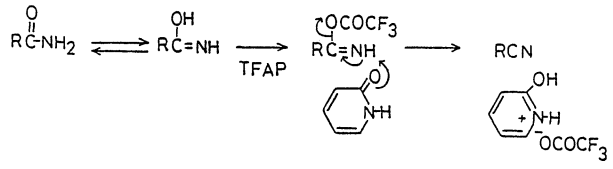
Scheme 4.

In contrast to *N*-(trifluoroacetyl)imidazole,[13] **TFAP** seems to have no enough reactivity to trifluoroacetylate the hydroxyl group of *p*-nitrophenol, which is strongly deactivated by nitro group. The reagent showed a high chemoselectivity in the reaction of aminophenols to give a trifluoroacetylamino compound.

Many methods have been known for converting aldehyde oximes into nitriles, but some of them have disadvantages, such as vigorous reaction conditions, tedious work-up procedures, unsatisfactory yields, or the requirement of unusual reagents. Among them, *N*-(trifluoroacetyl)imidazole (previously reported by us) is a good reagent for the reaction in the light of the fact that this reagent allows the dehydration of aldehyde oximes under neutral conditions without any additives.[15] However, the reagent is sensitive to moisture due to its high reactivity.

Some methods have been reported for the conversion of amides into nitriles. Recent developed procedures for the reaction include diphosphorus tetraiodide,[16] Vilsmeier reagent,[17] cyanuric chloride/*N*,*N*-dimethylformamide,[18] triethoxydiiodophosphorane,[19] and trifluoroacetic anhydride.[20] However, these reagents still have some disadvantages regarding difficulty in handling or unsatisfactory yields.

At present, **TFAP** has been found to be useful for the nitrile synthesis from aldehyde oximes and amides. In the reactions of these substrates with **TFAP**, the trifluoroacetylation of the substrates seems to first take place to give the corresponding *O*-trifluoroacetyl compound, followed by an elimination of trifluoroacetic acid by the generated 2-pyridone, resulting in the formation of nitrile and 2-hydroxypyridinium trifluoroacetate (Scheme 5).



Scheme 5.

In conclusion, the new reagent, **TFAP**, which can be easily obtained from 2-pyridinol and trifluoroacetic anhydride, has been found to be useful for trifluoroacetylating a variety of amines and alcohols. This reagent is mild and easy to handle compared to trifluoroacetic anhydride and *N*-(trifluoroacetyl)imidazole. It is also effective regarding the intramolecular dehydration of aldehyde oximes and amides to afford nitriles.

Experimental

Measurements: Melting and boiling points are uncorrected. The IR spectra were recorded on a Hitachi EPI-S2 model infrared spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL-FX 270 FT-NMR spectrometer with tetramethylsilane as the internal standard. GLC analysis was carried out on a Hitachi GC Model 163 gas chromatograph equipped with a hydrogen flame ionization detector and a stainless-steel column (length 3 m, i.d., 3 mm) packed with 3% Dexil 300 GC on Chromosorb W.

Preparation of TFAP: To a solution of 2-pyridinol (25 g, 0.263 mol) in dry tetrahydrofuran (60 ml), trifluoroacetic anhydride (27.6 g, 0.132 mol) dissolved in tetrahydrofuran (20 ml) was added slowly at 0—5 °C over 0.5 h. Then, the reaction mixture was stirred for 1 h at room temperature and heated under reflux for 4 h; the solvent was then removed under reduced pressure. The residue was distilled under reduced pressure to give TFAP (21.76 g, 87% yield); bp 81—82 °C/21 mmHg, 92 °C/42 mmHg, 79 °C/20 mmHg, 69 °C/14 mmHg (1 mmHg≈133.322 Pa); IR (neat) 1810, 1472, 1175, and 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.43 (d, 1H, J=3.4 Hz), 7.89 (td, 1H, J=1.5, 7.8 Hz) ,7.35 (t, 1H, J=6.1 Hz), and 7.19 (d, 1H, J=8.3 Hz). Found: C, 43.99; H, 2.11; H, 7.12%. Calcd for $C_7H_4F_3NO_2$: C, 43.85; H, 2.24; N, 7.33%.

Trifluoroacetylation: A typical procedure will be described for the reaction of cyclohexanol. To a solution of cyclohexanol (1.00 g, 10 mmol) in dry ether (3 ml), a solution of **TFAP** (2.10 g, 11 mmol) in dry ether (4 ml) was added. The mixture was stirred at room temperature for 0.5 h and, then cooled by ice water. The resulting precipitate was removed by filtration and washed with ether. The combined filtrate was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give cyclohexyl trifluoroacetate (1.95 g, quantitative yield). The above-obtained precipitate was identified as 2-pyridone (mp 104—106 °C); IR (KBr) 3200—2800 (br), 1650, 1240, 1100, and 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.45—7.52 (m, 1H), 7.29—7.42 (m, 1H), 6.60 (d, 1H, J=9.2 Hz), 6.30 (t, 1H, J=6.7 Hz).

Reaction of *p*-nitrophenol with TFAP: A solution of **TFAP** (0.300 g, 1.57 mmol) dissolved in ether (10 ml) was added to a mixture of *p*-nitrophenol (0.218 g, 1.57 mmol) and ether (10 ml). Within a few minutes, a white solid separated out. After stirring for 2 h at room temperature, the resulting solid was filtered and washed with ether to give a solid with the mp of 147—148 °C (0.333 g, 91% yield). The recrystallization of the solid from chloroform gave crystals with the mp of 149—150 °C; IR (KBr) 3250—2500 (br), 1660, 1590, 1495, 1343, 1290, 1115, 843, and 780 cm^{-1}; ^{1}H NMR ($CDCl_3$ at 50 °C) δ=8.13 (d, 2H, J=9.2 Hz), 7.60 (t, 1H, J=8.6 Hz), 7.49 (d, 1H, J=6.1 Hz), 6.92 (d, 2H, J=9.2 Hz), 6.72 (d, 1H, J=9.2 Hz), and 6.45 (t, 1H, J=7.7 Hz); MS *m/z* (rel intensity) 139 (80), 123 (20), 109 (40), and 95 (100). Found: C, 56.25; H, 4.51, N, 11.82%. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30, N, 11.96%.

A mixture of 2-pyridinol (0.149 g, 1.57 mmol) and *p*-nitrophenol (0.218 g, 1.57 mmol) was stirred in ether at a room temperature for 2 h to give a complex with the mp of 146—148 °C (0.363 g, 99% yield). This compound was ascertained to be the same as the compound mentioned above, by the IR spectrum.

Nitrile Synthesis from Aldehyde Oximes: A typical procedure for converting aldehyde oximes into nitriles is described for the reaction of benzaldehyde oxime. To a solution of benzaldehyde oxime (0.50 g, 4.1 mmol) in dry tetrahydrofuran (6 ml), **TFAP** (0.86 g, 4.5 mmol) in tetrahydrofuran (4 ml) was added. After the mixture was heated under reflux for 2 h, it was cooled in an ice-water bath; the resulting precipitate was removed by filtration and washed with ether (30 ml). The combined filtrate was worked up as usual to obtain benzonitrile (0.38 g, 90% yield).

Nitrile Synthesis from Amides: A typical procedure will be described for the synthesis of *p*-chlorobenzonitrile from *p*-chlorobenzamide: To a solution of *p*-chlorobenzamide (0.2 g, 1.28 mmol) in acetonitrile (3 ml), **TFAP** (0.368 g, 1.93 mmol) was added. The reaction mixture was heated under reflux for 5 h. The solvent was then removed upon obtaining about one third of the volume under reduced pressure; this mixture was poured into ice-water. The resulting solid was filtered, washed with water, dried and purified by flush chromatograhy over silica gel with chloroform to give *p*-chlorobenoznitrile (0.159 g, 89% yield, mp 88—89 °C).

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