The Reactions of 2-Fluoro-1,3,5-trinitrobenzene (FTNB) as a New Condensing Reagent

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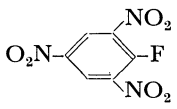
(Received December 13, 1977)

2-Fluoro-1,3,5-trinitrobenzene (FTNB) was found to be a useful new condensing reagent. Various amides, esters and thiocarboxylic *S*-esters were prepared in good yields from carboxylic acids with the reagent.

As has been reported in a preliminary communication,[1] we have examined the reaction of various polynitrohalobenzenes with carboxylic acids in the presence of a base and have found that the readily available 2-fluoro-1,3,5-trinitrobenzene (FTNB) is most reactive for the amide formation. In this paper we wish to report that FTNB is a useful new condensing reagent for the preparation of amides, esters, and thiocarboxylic *S*-esters from carboxylic acids.



FTNB

Preparation of Amides. When triethylamine was added to a mixed solution of an equimolar amount of FTNB and carboxylic acid (**1a—h**) in acetonitrile at room temperature under a nitrogen atmosphere, a facile reaction began immediately; we checked the reaction by means of TLC. The spots of the starting materials, FTNB and carboxylic acid, disappeared, and a new spot of the intermediate appeared. After 1 h twice a molar quantity of aniline was added to the solution at room temperature, the reaction mixture was stirred for 1 h and then worked up to give the corresponding anilide (**2a—h**) in an excellent yield, as is listed in Table 1.

From these results, it will be noted that 2,2-dimethylpropanoic acid (**1e**) produces the initial active intermediate as fast as other carboxylic acids, but that the subsequent nucleophilic reaction of aniline with the intermediate is relatively slow. These differences in reactivity appear to be based on the differences in steric hindrance.

This versatile compound, FTNB, also proved to be an excellent condensing reagent for peptide synthesis, which will be described elsewhere.

Preparation of Esters and Thiocarboxylic S-*Esters.* In order to compare the results with those described above for amides, the same carboxylic acids (**1a—f**) except **1i** were used first and the corresponding benzyl ester derivatives (**3a—f, i**) were prepared. The benzyl group is a useful carboxyl-protecting group because it is easily cleaved by reductions.

The initial step in the formation of the active intermediate from carboxylic acid and FTNB was carried out in a similar manner; however, it was found that the subsequent nucleophilic reaction of benzyl alcohol to the intermediate in the presence of a base was very slow at room temperature. Consequently, the reaction with benzyl alcohol was run by refluxing to give the desired benzyl esters in good yields, as is shown in Table 2.

The low yields or the relatively slow reaction rates in the cases of 2,2-dimethylpropanoic acid (**1e**) and 2-methylpropanoic acid (**1f**) probably reflect the steric

TABLE 1. PREPARATION OF ANILIDES FROM CARBOXYLIC ACIDS AND ANILINE WITH FTNB

FTNB + RCO_2H + Et_3N —(r.t., 1 h, in CH_3CN)→ —(2 $PhNH_2$, r.t., (A))→ RCONHPh

1a—h **2a—h**

	RCO_2H	Time (A)	Isolated yield (%) **2a—h**	Mp (°C)[a]
1a	$PhCH{=}CHCO_2H$	1 h	quant.	151—152
1b	$PhCO_2H$	1 h	93	161—162
1c	$PhCH_2CO_2H$	1 h	88	116—117
1d	Z-Gly-OH	1 h	87	143—144
1e	$(CH_3)_3CCO_2H$	2 days	93	128—131
1f	$(CH_3)_2CHCO_2H$	2.5 h	96	103—105
1g	CH_3CO_2H	1.5 h	82	111—113
1h	$CH_3(CH_2)_{12}CO_2H$	2 h	89	83—84

a) They were in accordance with the values cited in the literatures (see Ref. 2 except for **2d**[3]).

TABLE 2. PREPARATION OF BENZYL ESTERS FROM CORBOXYLIC ACIDS AND BENZYL ALCOHOL WITH FTNB

FTNB + RCO_2H + Et_3N

1a—f, i

—(r.t., 2 h, in CH_3CN)→ —($PhCH_2OH$, base, reflux, (B))→ RCO_2CH_2Ph

3a—f, i

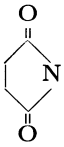
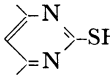
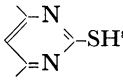
	RCO_2H	Base	Time (B)	Isolated yield (%) **3a—f, i**	$\nu_{C=O}$ (cm^{-1})
1a	$PhCH{=}CHCO_2H$	Et_3N	3 h	89	1710
1b	$PhCO_2H$	Et_3N	3 h	80	1710
1c	$PhCH_2CO_2H$	Et_3N	2 h	91	1730
1d	Z-Gly-OH	Et_3N	2 h	81	1715
1e	$(CH_3)_3CCO_2H$	Et_3N	92 h	27	1725
	$(CH_3)_3CCO_2H$	Et_3N	92 h	42[a]	1725
	$(CH_3)_3CCO_2H$	DBU	92 h	41	1725
1f	$(CH_3)_2CHCO_2H$	Et_3N	20 h	50	1730
	$(CH_3)_2CHCO_2H$	Et_3N	20 h	72[a]	1730
	$(CH_3)_2CHCO_2H$	DBU	20 h	78	1730
1i	$CH_3(CH_2)_6CO_2H$	Et_3N	5 h	95	1735

a) A 1.5 equivalent of benzyl alcohol was used.

Table 3. Preparation of esters of benzoic acid and thiobenzoic *S*-acid

FTNB + $PhCO_2H$ + Et_3N —(r.t., 2 h, in CH_3CN)→ —(RYH (**4a—h**), Et_3N (C))→ PhCOYR (Y=O, S)

5a—h

	RYH	Conditions (C)	Isolated yield (%) **5a—h**	$\nu_{C=O}$ (cm^{-1})
4a	Cl_3CCH_2OH	r.t., 2 h	81	1735
4b	*t*-C_4H_9OH	reflux, 4 h	0	—
4c	*p*-$NO_2C_6H_4OH$	r.t., 5 h	94	1735
4d	C_6Cl_5OH	r.t., 22 h	71	1750
4e		r.t., 30 min	83	1765, 1735
4f	*n*-C_4H_9SH	r.t., 3 h	96	1660
4g	*p*-$CH_3C_6H_4SH$	r.t., 1 h	87	1660
4h	 [a]	r.t., 6 h	64	1670
	 [a]	r.t., 6 h	76[b]	1670

a) A HCl salt was used and neutralized *in situ* with Et_3N.
b) A 1.5 equivalent of **4h** was used.

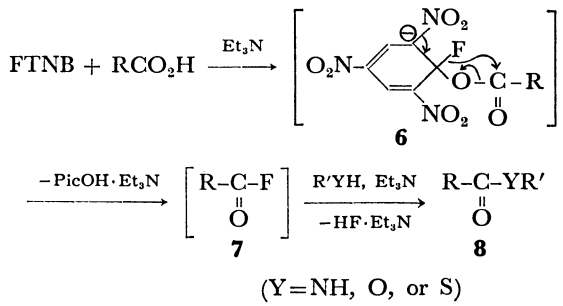
hindrance as well as the formation of 2,2-dimethylpropananilide (**2e**). The use of excess benzyl alcohol or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) as a base was effective in such a case.

Various esters of benzoic acid (**5a—e**) and of thiobenzoic *S*-acid (**5f—h**) were prepared by this reaction; the results are shown in Table 3.

The failure to prepare *t*-butyl benzoate (**5b**) suggests that this reaction is also affected by the steric hindrance of alcohol; the fact that all the reactions (except that of *t*-butyl alcohol (**4b**)) proceeded at room temperature, unlike the case of benzyl alcohol, can be explained on the basis of the high nucleophilicity of the anions produced by the reaction of **4a, c—h** with triethylamine.

The extension of this reaction to macrolide synthesis is in progress.

Mechanism. The probable course of this reaction is illustrated in the following scheme. First, an anionic sigma complex (**6**) is formed *via* the aromatic nucleophilic addition of a carboxylate anion to FTNB, followed by the elimination of the picrate anion to produce an acyl fluoride (**7**), which then reacts with a nucleophile, R'YH, to give the corresponding product (**8**). Support for this scheme was found in the reaction of FTNB with cinnamic acid (**1a**) and triethylamine to isolate cinnamoyl fluoride by sublimation.



(Y=NH, O, or S)

Experimental

All the melting points are uncorrected. The proton NMR spectra were recorded on a JEOL JNM-MH 60 spectrometer. The chemical shifts are reported on the δ scale relative to TMS as the internal standard. The IR spectra were taken with a JASCO IRA-1 diffraction grating infrared spectrometer.

Materials. The acetonitrile used here was distilled according to the usual method and was stored over molecular sieves as a drying agent. 2-Fluoro-1,3,5-trinitrobenzene (FTNB, recrystallized from benzene; mp 127—128 °C [lit,[4] mp 122—123 °C or 130—131.5 °C]) was readily prepared using a modification of the procedure for the nitration of 1-fluoro-2,4-dinitrobenzene by 25% fuming sulfuric acid and fuming nitric acid (sp gr about 1.50). 2-Mercapto-4,6-dimethylpyrimidine hydrochloride was prepared by the reported procedure.[5] Thin-layer chromatography (TLC) and column chromatography were performed on Merck's Kieselgel 60 PF_{254} (Art. 7749) and on Alumina Woelm B (Akt. 1), respectively.

Cinnamanilide (2a). To a mixed solution of FTNB (116 mg, 0.5 mmol) and cinnamic acid (74 mg, 0.5 mmol) in acetonitrile (3 ml) was added an acetonitrile solution (1 ml) of triethylamine (55 mg, 0.55 mmol) at room temperature under a nitrogen atmosphere. After 1 h, a solution of aniline (93 mg, 1 mmol) in acetonitrile (1 ml) was added to the solution, after which the reaction mixture was stirred for an additional hour at room temperature. The solution was then evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and a saturated solution of $NaHCO_3$. The organic layer was further washed with 1M HCl and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The desired product, cinnamanilide, was separated from the residue by preparative TLC (development with 5:3 benzene: ethyl acetate) in a nearly quantitative yield (112 mg, mp 151—152 °C [lit,[2] mp 153 °C]).

In a similar manner, other anilides (**2b—h**) were prepared in excellent yields from the corresponding carboxylic acids and aniline with FTNB. The results are listed in Table 1.

Benzyl Cinnamate (3a). To an acetonitrile solution (3 ml) of FTNB (231 mg, 1 mmol) was added a mixed solution of cinnamic acid (148 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in acetonitrile (5 ml) at room temperature under a nitrogen atmosphere. After this mixture had been stirred for 2 h, a solution of benzyl alcohol (108 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in acetonitrile (4 ml) was added, and the reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was then dissolved in benzene, followed by injection into one end of a short column of basic alumina. The triethylammonium picrate was removed efficiently by elution with benzene. The eluate from the column was condensed, and pure benzyl cinnamate was separated from the residue by prepatative TLC (development with 5:1 benzene: hexane) in an 89% yield (212 mg).

The other examples reported in Tables 2 and 3 were carried out in a similar manner. The spectral data, physical proper-

ties, and analytical data of the products are listed below.

3a: oil, NMR (CCl_4) δ 5.09 (s, 2H), 6.29 (d, 1H, J=17 Hz), 7.22 (m, 10H), 7.56 (d, 1H. J=17 Hz). **3b**: oil, NMR (CCl_4) δ 5.20 (s, 2H), 7.0—7.5 (m, 8H), 7.8—8.1 (m, 2H). **3c**: oil, NMR (CCl_4) δ 3.48 (s, 2H), 4.94 (s, 2H), 7.11 (s, 5H), 7.13 (s, 5H). **3d**: mp 68—70 °C, NMR ($CDCl_3$) δ 3.86 (d, 2H, J=6 Hz), 4.98 (s, 2H), 5.03 (s, 2H), 5.1—5.6 (broad, 1H), 7.21 (s, 10H). **3e**: oil, NMR (CCl_4) δ 1.19 (s, 9H), 4.99 (s, 2H), 7.22 (s, 5H). **3f**: oil, NMR (CCl_4) δ 1.13 (d, 6H, J=7 Hz), 2.46 (h, 1H, J=7 Hz), 4.93 (s, 2H), 7.15 (s, 5H). **3i**: oil, NMR (CCl_4) δ 0.6—1.9 (m, 13H), 2.26 (t, 2H, J=7 Hz), 5.01 (s, 2H), 7.27 (s, 5H).

5a: oil, NMR (CCl_4) δ 4.82 (s, 2H), 7.1—7.6 (m, 3H), 7.8—8.2 (m, 2H). **5c**: mp 139—142 °C (lit,[2] mp 142.5 °C). **5d**: mp 159—160 °C (lit,[2] mp 159—160 °C). **5e**: mp 139—140 °C, NMR (CCl_4) δ 2.86 (s, 4H), 7.3—7.8 (m,3H), 8.0—8.3 (m, 2H).

S-(4,6-Dimethyl-2-pyrimidyl) Thiobenzoate (5h). To a mixed solution of FTNB (231 mg, 1 mmol) and benzoic acid (122 mg, 1 mmol) in acetonitrile (6 ml) was added an acetonitrile solution (2 ml) of triethylamine (101 mg, 1 mmol) at room temperature under a nitrogen atmosphere. After 2 h, a mixed solution of 2-mercapto-4,6-dimethylpyrimidine hydrochloride (265 mg, 1.5 mmol) and triethylamine (253 mg, 2.5 mmol) in acetonitrile (10 ml) was added to the solution, after which the reaction mixture was stirred for an additional 6 h at room temperature. The solvent was removed under reduced pressure; the residue was then dissolved in benzene, followed by injection into one end of a short column of basic alumina. After elution with benzene, the eluate was condensed, and pure **5h** was separated from the residue by preparative TLC (development with 5:1 benzene: ethyl acetate) in a 76% yield (278 mg): mp 74—77 °C (recrystallized from cyclohexane), NMR (CCl_4) δ 2.41 (s, 6H), 6.78 (s, 1H), 7.2—7.5 (m, 3H), 7.7—8.0 (m, 2H). Found: C, 63.90; H, 4.94; N, 11.94%. Calcd for $C_{13}H_{12}N_2OS$: C, 63.92; H, 4.95; N, 11.47%.

The other thiocarboxylic *S*-esters, **5f** and **5g**, were prepared in a similar manner. Their spectral data and physical properties are listed below.

5f: oil, NMR (CCl_4) δ 0.7—1.9 (m, 7H), 2.97 (t, 2H, J=7 Hz), 7.1—7.5 (m, 3H), 7.6—8.1 (m, 2H). **5g**: mp 74—75 °C (lit,[6] mp 75°C).

Cinnamoyl Fluoride. To an acetonitrile solution (3 ml) of FTNB (231 mg, 1 mmol) was added a mixed solution of cinnamic acid (148 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in acetonitrile (5 ml) at room temperature under a nitrogen atmosphere. After the mixture had been stirred for 2 h, the solvent was removed under reduced pressure; then we sublimed cinnamoyl fluoride (102 mg) from the residue *in vacuo* in a 68% yield: mp 30 °C (lit,[7] mp 31—31.5 °C), IR 1782, 1615, 1182, 1092 cm^{-1}; NMR ($CDCl_3$) δ 6.32 (d·d, 1H, J_{HH}=16.2 Hz, J_{HF}=7.2 Hz), 7.44 (m, 5H), 7.82 (d, 1H, J_{HH}=16.2 Hz).

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