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ETHYL PENTAFLUOROPROPANETHIOATE: A USEFUL PENTAFLUOROPROPIONYLATING AGENT FOR AMINES AND ALCOHOLS

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SUMMARY

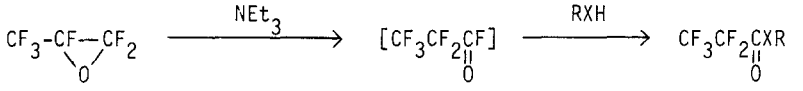
Ethyl pentafluoropropanethioate, prepared by treating ethanethiol with hexafluoro-1,2-epoxypropane in the presence of triethylamine, was found to be a convenient pentafluoropropionylating agent for amines and alcohols.

INTRODUCTION

Trifluoroacetylated amines and alcohols are known to be useful derivatives for characterization and separation of the parent amines and alcohols [1,2]. The sensitivity of several perfluoroacyl derivatives of amines and amino acids in gas chromatographic analyses has been studied by several workers [3 - 7], revealing that in general, pentafluoropropionyl (PFP) derivatives are more sensitive than the corresponding trifluoroacetyl (TFA) derivatives. For instance, Pollok [3] reported that for the separation of amino acids by gas chromatography, the retention time of N-PFP derivatives is 36% less than that of the N-TFA derivatives, with almost equivalent separation. Parr et al. [5] reported that in the case of leucine esters, the highest volatility among various N-perfluoroacyl, such as TFA, PFP, HFB (heptafluorobutyryl) and PDFO (pentadecafluoro-octanoyl) derivatives, was obtained by the N-PFP derivatives. We have also found that the PFP derivatives of free amino acids are more useful for glc separation than TFA derivatives [8].

The usefulness of these properties of PFP derivatives of amines and alcohols makes worthy of report a practically useful reagent for pentafluoropropionylation.

We had already revealed that amines and alcohols can be pentafluoropropionylated by treating them with hexafluoro-1,2-epoxypropane (HFPO) in the presence of triethylamine [9].



(X = NH, O)

N-PFP derivatives of amino acids were prepared by a similar method [8]. However, since HFPO has a very low boiling point (-27 °C) and is toxic, it is troublesome to handle and a pressure vessel must be used for the reaction. Thus, it was thought to convert this strong pentafluoropropionylating agent into a convenient liquid derivative, still possessing sufficient reactivity with amines and alcohols. As is well known, thioesters of carboxylic acids are thermodynamically unstable and they sometimes cause transacylation of amines and alcohols [10]. This tendency was reported to be especially strong for a series of perfluoroacyl derivatives [11]. As a liquid reagent with a suitable boiling point, ethyl pentafluoropropanethioate prepared from ethanethiol and HFPO, was applied to transacylation of amines and alcohols and it was proved that this thioester can be used as a convenient pentafluoropropionylating agent.

RESULTS AND DISCUSSION

Intermolecular transacylation

In order to elucidate the trans-pentafluoropropionylating ability towards amines, alcohols, and thiols, pentafluoropropionyl derivatives of propanol and propanethiol were allowed to react in acetonitrile with an equimolar amount of propylamine and with propylamine or propanol respectively. Qualitative and quantitative analysis of the reaction products was easily done by ^{19}F NMR, as shown in Table 1. Thus, the signals of the CF_2 groups of the pentafluoropropionylated amine, alcohol, and thiol were readily distinguished from each other by their chemical shifts, and the amounts of these compounds in the reaction mixture were determined from their signal intensities.

The transfer of a pentafluoropropionyl group from the ester or thioester to the amine proceeded rapidly and exothermically. Yields of amides after reaction for 0.5 h at room temperature were quantitative. In contrast, the perfluoroacyl transfer from thioester to alcohol occurred very slowly, but was accelerated by addition of a base. Thus, when an equimolar amount of triethylamine was added, pentafluoropropionyl ester was obtained in excellent yield. These results are shown in Table 2.

TABLE 1

The ^{19}F NMR chemical shifts[a] for $CF_3CF_2\overset{\overset{O}{\|}}{C}-XC_3H_7$

X	CF_2	CF_3
NH	+45.4	+6.2
O	+44.3	+6.4
S	+42.3	+5.3

a) ppm upfield from ext. CF_3CO_2H in acetonitrile

TABLE 2

Trans-perfluoroacylation

$$R_f\overset{\overset{O}{\|}}{C}XR + RYH \xrightarrow[MeCN]{r.t.,\ 0.5\ h} R_f\overset{\overset{O}{\|}}{C}YR + RXH$$

($R_f = C_2F_5$; $R = C_3H_7$; X, Y = S, O, or NH)

Reactants		Product	Yield
$R_fC(O)XR$	RYH	$R_fC(O)YR$	%[a]
$R_fC(O)SR$	RNH_2	$R_fC(O)NR$	95
$R_fC(O)OR$	〃	〃	93
$R_fC(O)SR$	ROH	$R_fC(O)OR$	10 (92)[b]

a) Based on ^{19}F nmr signal intensities.

b) Equimolar triethylamine was added.

Pentafluoropropionylation of amines and alcohols with ethyl pentafluoropropanethioate

From results obtained above, we noted that thioesters of pentafluoropropionic acid, prepared from thiol and HFPO, could be used as a pentafluoropropionylating agent for amines and alcohols Ethyl pentafluoropropanethioate was considered to be the most convenient because it is a comparatively stable liquid with a suitable boiling point (b p. 103 ^{o}C [12]), and ethanethiol (b.p 35 ^{o}C) generated by the reaction could be easily removed from the reaction mixture. Experimental results of pentafluoropropionylation using this reagent were summarized in Table 3

Reactions of ethyl pentafluoropropanethioate with aliphatic amines or amino acid esters proceeded smoothly in diethyl ether at room temperature, and the respective amides were isolated in good yields. However, with aromatic amines, the reaction was sluggish and needed assistance by heating in the presence of a catalytic amount of acid. Primary alcohols reacted in the acetonitrile triethylamine system, giving good yields of pentafluoropropionyl esters. For secondary alcohols, the reaction was retarded by steric effects and yields were poor even after refluxing. t-Butyl alcohol and phenol did not react.

EXPERIMENTAL

Ethyl pentafluoropropanethioate

A mixture of ethanethiol (6.20 g, 0 10 mol), triethylamine (5 05 g, 0.05 mol) and dry diethyl ether (50 ml) was placed in a glass pressure vessel and cooled to - 70 ^{o}C. Liquefied HFPO (18 3 g, 0.11 mol) was then introduced into the vessel and the whole was brought to room temperature. After stirring 1 h at this temperature, the reaction mixture was poured into water. The organic layer was separated, washed with water, and dried over magnesium sulfate. Fractional distillation gave the thioate (17 7 g, 85%), b.p. 102 - 103 ^{o}C [12].

N-Butyl pentafluoropropionamide

Ethyl pentafluoropropanethioate (2.08 g, 10 mmol) was added dropwise into a solution of butylamine (0.73 g, 10 mmol) in dry diethyl ether (10 ml) with cooling. After stirring the mixture for 0.5 h at room temperature, the solvent and formed ethanethiol were evaporated. The resulting oily

product was subjected to distillation under reduced pressure, giving pure N-butyl pentafluoropropionamide (1.95 g, 89%), b.p. 55 - 56 °C/ 2 mmHg.

Ethyl N-(pentafluoropropionyl)glycinate

Into a mixture of ethyl glycinate hydrochloride (1.40 g, 10 mmol), triethylamine (1.01 g, 10 mmol) and acetonitrile (10 ml), ethyl pentafluoropropanethioate (2.08 g, 10 mmol) was added and the whole was stirred for 0.5 h at room temperature. The reaction mixture was poured into water, and the oily material was extracted with diethyl ether. After the extract was dried ($MgSO_4$), solvent was removed and the residual product was distilled to give ethyl N-(pentafluoropropionyl)glycinate (2.37 g, 95%), b.p. 113 - 114 °C/ 17 mmHg.

Pentafluoropropionanilide

One drop of concentrated sulfuric acid was added to a mixture of ethyl pentafluoropropanethioate (2.50 g, 12 mmol) and aniline (0.93 g, 10 mmol). The mixture was heated with stirring at 100 °C for 1 h, and evaporated till dry. The remaining solid was recrystallized from hexane giving pure pentafluoropropionanilide (2.01 g, 84%), m.p. 98 - 99 °C.

Benzyl pentafluoropropionate

To a solution of ethyl pentafluoropropanethioate (2.08 g, 10 mmol), benzyl alcohol (1.08 g, 10 mmol) in acetonitrile (5 ml), triethylamine (1.01 g, 10 mmol) was added at room temperature. After 1 h of stirring, the reaction mixture was poured into water. The oily layer was separated and dried over $MgSO_4$, and after removal of ethanethiol, was subjected to distillation. Benzyl pentafluoropropionate (2.15 g, b.p. 80 - 81 °C/ 21 mmHg) was obtained in 85% yield.

Isopropyl pentafluoropropionate

A mixture of ethyl pentafluoropropanethioate (2.08 g, 10 mmol), isopropyl alcohol (0.60 g, 10 mmol), triethylamine (1.01 g, 10 mmol) and acetonitrile (5 ml) was refluxed for 2 h and worked up similarly. Fractional distillation gave (150 g, 51%) of isopropyl pentafluoropropionate, b.p. 87 - 88 °C.

TABLE 3

Pentafluoropropionylation of amines and alcohols

C_2F_5COSEt + RZH ⟶ C_2F_5COZR + EtSH

RZH	Reaction Conditions			C_2F_5COZR	
	Solv.	Temp. (^oC)	Time (h)	Yield (%) (Isolated)	Bp ^oC/mmHg[a] [Mp ^oC]
EtOH	MeCN	r.t.	1	80	75-76 (75-76)[b]
n-PrOH	MeCN	r.t.	1	88	83-84/544 (nc)[c]
$PhCH_2OH$	MeCN	r.t.	1	85	80-81/21 (nc)[c]
i-C_3H_7OH	MeCN	refl.	2	51	87-88 (86.5/741)[d]
$C_6H_{11}OH$	MeCN	refl.	2	55	75-76/47 (155)[e]
n-$PrNH_2$	Et_2O	r.t.	0.5	93	75.5-76/20 (nc)[c]
n-$BuNH_2$	Et_2O	r.t.	0.5	89	55-56/2 (48/1)[f]
$C_6H_{11}NH_2$	Et_2O	r.t.	0.5	95	[89-90] (nc)[c]

Et_2NH	Et_2O	r.t.	0.5	84	68-69/25 (67-69/25)[g]
Gly-OEt	Et_2O	r.t.	0.5	95	113-114/17 (nc)[c]
L-Iso-OEt	Et_2O	r.t.	0.5	93	95-96/6[c),h]
L-Pro-OEt	Et_2O	r.t.	0.5	95	85.5-86.5/17 (nc)[c),i]
$PhNH_2$	——	100	1[j]	84	[98-99] (97.5-98.5)[k]
$p\text{-}MeC_6H_4NH_2$	——	100	1[j]	80	[111.5-112] (nc)[c]

a) The values in parentheses are those reported in the literatures.

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c) New Compound : The microanalysis was satisfactory agreement to the calculated value.

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h) $[\alpha]_D^{20}$ $+122^o$ ($Cl.O.Et_2O$) i) $[\alpha]_D^{20}$ -300^o ($Cl.O.Et_2O$)

j) Catalytic amount of conc. H_2SO_4 was added.

k) R. L. Pannley, D. Yamashiro and R. G. Taborsky, J. Org. Chem., 24, 1706 (1959).

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