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5*H*-3-oxa-Octafluoropentanesulfonyl fluoride: a novel and efficient condensing agent for esterification, amidation and anhydridization

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ABSTRACT

The use of 5*H*-3-oxa-octafluoropentanesulfonyl fluoride ($HCF_2CF_2OCF_2CF_2SO_2F$) as a novel and efficient condensing reagent for esterification of carboxylic acids with alcohols and amidation of carboxylic acids with amines in the presence of 1,3-diazabicyclo[5.4.0]-undec-7-ene (DBU) is reported. $HCF_2CF_2OCF_2CF_2SO_2F$ cannot serve as a condensing agent for anhydridization of carboxylic acids, however, $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system can mediate anhydridization of some aromatic carboxylic acids.

1. Introduction

Carboxylic esters, amides and anhydrides are three classes of important organic compounds, which are frequently used in synthetic organic chemistry. Among many useful and reliable esterification, amidation and anhydridization methods available in the literature,[1] the condensation reaction is the most efficient and convenient one, in which a condensing reagent is employed to activate a carboxylic acid followed by the attack of an anion derived from an alcohol, amine or carboxylic acid. To date, a variety of condensing agents for this purpose have been developed.[2–4] For example, *N*,*N*′-carbonyldiimidazole, *N*,*N*′-dicyclohexylcarbodiimide/4-dimethylaminopyridine, 2-halopyridinium salts and di-2-pyridyl carbonate have been widely used as condensing agents to induce esterification, amidation and anhydridization. However, some of them are moisture-sensitive and highly expensive, and sometimes suffer from the formation of reagent-derived by-products (such as urea), which limits their extensive application and gives rise to the searching for the new type of condensing reagents.

Poly(per)fluoroalkanesulfonyl fluoride (R_fSO_2F) is a class of air- and moisture-tolerant and relatively non-toxic reagent. It is also commercially available and cost effective. So far, R_fSO_2F has found wide application in the preparation of aryl sulfonates, alkenyl sulfonates and other fluorinated organic compounds through the reaction of R_fSO_2F with phenols, ketones and alcohols.[5] In many cases involving R_fSO_2F, the by-product is water-soluble poly(per)fluoroalkanesulfonic acid anion, which makes these reactions easy to handle, and more importantly, metal poly(per)fluoroalkanesulfonate is also a kind of superior surface-activating agent.

On the basis of the excellent leaving ability of poly(per)fluorosulfonate anion (in comparison with *p*-toluenesulfonate anion)[6] and the ease of reaction of poly(per)fluoroalkanesulfonyl fluoride with alcohol in the presence of a base, we have studied the reaction of $HCF_2CF_2OCF_2CF_2SO_2F$ (an easily available compound in our hand) with *threo*-diol and hydrogen peroxide (H_2O_2), respectively, in the presence of an organic or inorganic base, resulting in the smooth formation of enantiopure *cis*-epoxide and in situ generation of highly efficient oxidant polyfluoroalkanesulfonic peracid.[5o,p]

With these findings in hand and as a continuation of our project of poly(per)fluoroalkanesulfonyl fluoride-mediated reactions and their application in synthetic organic chemistry, we envisaged that the reaction of $HCF_2CF_2OCF_2CF_2SO_2F$ with carboxylate anion would produce the unstable mixed anhydride (intermediate **A** in Scheme 1) which would be easily attacked by a nucleophile such as an alcohol, an amine or a carboxylic acid anion, resulting in the formation of an ester, amide or anhydride (Scheme 1). Indeed, tosyl chloride and tosylimidazole have been used for this purpose as condensing reagents in esterification of carboxylic acids (or their salts) with alcohol,[3a,7] however, the harsh conditions were employed in these cases.

In order to confirm our idea that $HCF_2CF_2OCF_2CF_2SO_2F$ can be served as a candidate of condensing agent for esterification, amidation and anhydridization, we initially tried the reaction of

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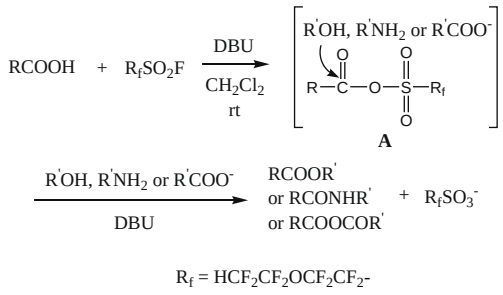


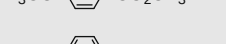
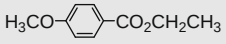
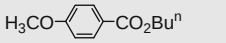
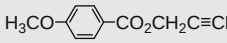
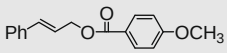
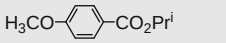
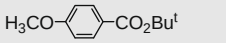
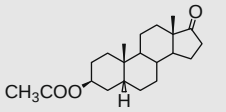
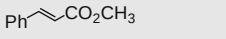
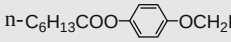
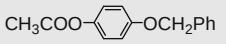
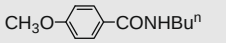
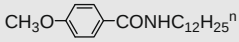
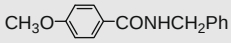
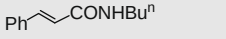
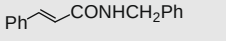
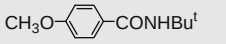
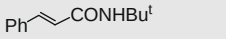
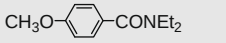
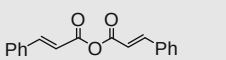
Scheme 1.

p-methoxylbenzoic acid with methanol. The procedure is as follows. The reaction was performed in one-pot procedure in CH_2Cl_2. At room temperature, a solution of *p*-methoxylbenzoic acid and 1,3-diazabicyclo[5.4.0]-undec-7-ene (DBU, 1.0 equiv) in CH_2Cl_2 was stirred for 1 h. Then it was treated with $HCF_2CF_2OCF_2CF_2SO_2F$ (1.0 equiv) and stirred at rt for 12 h. Methanol (10.0 equiv) was added followed by the addition of 2.0 equiv of DBU. After further stirring the resultant mixture at rt for 24 h, we obtained the desired product methyl *p*-methoxybenzoate in 80% yield. However, when *n*-butylamine was used in place of methanol, the desired product *N*-*n*-butyl *p*-methoxybenzamide was obtained only in very low yield. Luckily, after addition of 10.0 equiv of *n*-butylamine and 2.0 equiv of DBU and the reaction run in reflux for 24 h, the yield of *N*-*n*-butyl *p*-methoxybenzamide considerably improved to 75%. Disappointedly, we did not obtain *p*-methoxybenzoic acid anhydride in this way even when the reaction was performed in reflux for 48 h in CH_2Cl_2 or using $PhCH_3$, THF, MeCN or DMF as solvent. Interestingly, if the reaction was carried out according to the procedure described in Section 2 (see the procedure for anhydridization) using $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system as condensing agent, the corresponding *p*-methoxybenzoic acid anhydride was smoothly prepared in 48% yield. Although the yield of symmetrical anhydride is moderate, the selectivity is very high, and no other impurity was found besides the unreacted starting material *p*-methoxylbenzoic acid. These above preliminary results indicated that $HCF_2CF_2OCF_2CF_2SO_2F$ can be used as a novel and efficient condensing agent for esterification and amidation, but not for anhydridization. However, $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system can be used to induce anhydridization.

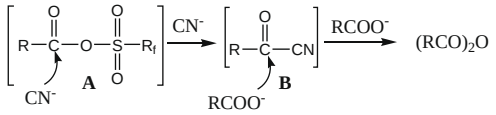
Next, we undertook the investigation on the scope and limitation of esterification and amidation using $HCF_2CF_2OCF_2CF_2SO_2F$ as condensing agent, and of anhydridization mediated by $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system as condensing reagent. A variety of substrates were selected and examined. Experimental results are summarized in Table 1. In most cases, esters and amides were obtained in good to excellent yields, which means that $HCF_2CF_2OCF_2CF_2SO_2F$ is a highly efficient condensing agent for esterification and amidation. For $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system-induced anhydridization reactions, symmetrical aromatic anhydrides were obtained in moderate to good yields.

For primary alcohols and primary allylic alcohols (entries 1–9, 13), the corresponding esters can be prepared in 60–87% yields. For secondary alcohol (entry 10), only low yield of desired product was formed. In the case of sterically hindered tertiary alcohol (entry 11), no desired product was found even after reflux for a prolonged reaction time. However, for the secondary alcohol substrate (entry 12), when reaction was run in reflux in CH_2Cl_2, the yield of desired product can be improved. Phenol derivatives are exceptions and esterification reaction proceeded quite well, as can be seen in entries 14 and 15 in Table 1, and corresponding ester products were produced in 80% and 98% yields, respectively, even in a very short reaction time of 10 min. This might be due to

Table 1
The acylation of alcohols, amines and acids through $HCF_2CF_2OCF_2CF_2SO_2F$ activated carboxylic acids

Entry	Product	Isolated yield (%)
1		80
2		79
3		60
4		82
5	(*E*)-$CH_3CO_2CH_2CH{=}CHPh$	80
6	(*E*)-$CH_3CH_2CO_2CH_2CH{=}CHPh$	82
7	(*E*)-$PhCH{=}CHCH_2OCOCH_2CH_2CH(CH_3)_2$	69
8	*E*-$PhCH{=}CHCH_2OCOC_6H_{13}{}^n$	82
9		42
10		30
11		0
12		76[a]
13		87
14		80[b]
15		98[b]
16		75
17		73
18		78
19		80
20		68
21		15
22		35
23		0
24	(*p*-$CH_3OC_6H_4CO)_2O$	48[c]
25	(*p*-$CH_3C_6H_4CO)_2O$	46[c]
26	$(C_6H_5CO)_2O$	60[c]
27		55[c]

[a] The reaction was run in reflux.
[b] The reaction time is 10 min.
[c] using $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system as condensing agent.



Scheme 2.

the fact that the stronger acidity of hydroxyl group in phenol derivatives resulted in the easier formation of phenol anions which is a strong nucleophile.

For amidation of carboxylic acids with amines, similarly, the structure of amines has a considerable influence on the reaction. In the case of linear primary amines (entries 16–20), amides can be obtained in 68–80% yields. For sterically encumbered branched substrates (entries 21 and 22), only low yields of desired products were formed. The result in entry 23 (no desired product formed) indicates that the secondary amine is not a suitable substrate for this reaction.

Results from entries 24–27 in Table 1 shows that $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system also can efficiently mediate anhydridization of some aromatic carboxylic acids. In all the cases, only desired symmetrical anhydrides were formed and the others were unreacted starting materials carboxylic acids. Unfortunately, $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ system is not applicable to anhydridization of aliphatic carboxylic acids which might be due to the instability of intermediate **B** (see Scheme 2) of aliphatic carboxylic acids. A possible mechanism was put forward to interpret the anhydridization and is shown in Scheme 2. Intermediate **A** (mixed anhydride, see Scheme 1) is first formed and then is attacked by cyanide anion resulting from the reaction of DBU·HF salt with $(CH_3)_3SiCN$ to afford acyl cyanide (intermediate **B**). Cyanide moiety in acyl cyanide is a very good leaving group and the reaction of acyl cyanide with carboxylic acid anion smoothly offers a symmetrical anhydride. The failure of reaction of intermediate **A** with carboxylic acid anion might be due to the weak nucleophility of $RCOO^-$ species and the bulky size of $R_fSO_3^-$ moiety.

In conclusion, a novel and efficient condensing reagent, $HCF_2CF_2OCF_2CF_2SO_2F$, for esterification and amidation is described. It is especially suitable for esterification of carboxylic acids with primary alcohols, primary allylic alcohols and phenol derivatives, and for amidation of carboxylic acids with linear primary amines. High efficiency, mild reaction conditions and air- and moisture-stability are the distinctive advantages for $HCF_2CF_2OCF_2CF_2SO_2F$-induced condensation reactions. In addition, $HCF_2CF_2OCF_2CF_2SO_2F/(CH_3)_3SiCN$ as a new anhydridization condensing agent system was also developed. It can relatively efficiently induce the anhydridization of some aromatic carboxylic acids to produce symmetrical aromatic anhydrides in moderate to good yields. Their application in the preparation of peptides and other interesting target molecules is currently underway in our laboratory.

2. Experimental

2.1. General procedure for esterification, amidation and anhydridization

The reaction was performed in one-pot procedure in CH_2Cl_2. At room temperature, a solution of carboxylic acid (RCOOH) and DBU (1.0 equiv) in CH_2Cl_2 was stirred for 1 h. Then it was treated with $HCF_2CF_2OCF_2CF_2SO_2F$ (1.0 equiv) and stirred at rt for 12 h. Alcohol (R′OH) (2.0–10.0 equiv) was added followed by the addition of 1.5–2.0 equiv of DBU. The resultant mixture continued to stir at rt for 24 h. The workup procedure is simple and just evaporation of volatile ingredients and purification of residue through flash column chromatography were needed.

For the amidation of carboxylic acids (RCOOH) with amines ($R'NH_2$), the procedure is a little bit different from the above one. After addition of 2.0–10.0 equiv of amine ($R'NH_2$) and 1.5–2.0 equiv of DBU, the reaction should be run in reflux for 24 h. The workup procedure is the same as described above.

The procedure for anhydridization: At room temperature, a solution of carboxylic acid (RCOOH) and 1,3-diazabicyclo[5.4.0]-undec-7-ene (DBU, 1.0 equiv) in CH_2Cl_2 was stirred for 1 h. Then $HCF_2CF_2OCF_2CF_2SO_2F$ (0.5 equiv) and trimethylsilyl cyanide (0.5 equiv) were added, respectively, and the resultant mixture continued to stir at rt for 24 h. The workup procedure is the same as described above.

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