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Preliminary note

An efficient and convenient synthesis of 4-polyfluoroalkylated pyrrole-3-carboxylates through 1,3-dipolar cycloaddition reaction of polyfluoro-2-alkynoic acid esters with munchnones

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Abstract

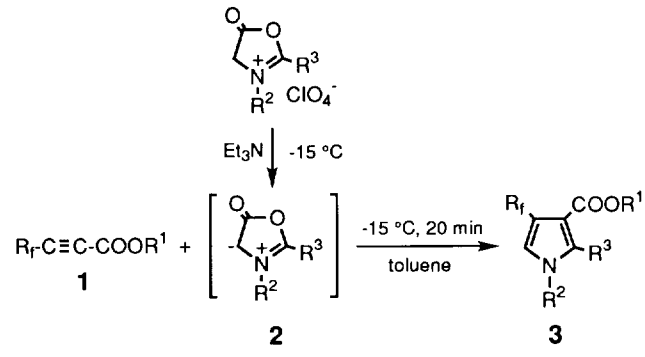
1,3-Dipolar cycloaddition between polyfluoro-2-alkynoic acid esters and 1,3-oxazolium 5-olates (munchnones) readily proceeds in a regiospecific manner under very mild reaction conditions, followed by simultaneous decarboxylation to afford 4-(polyfluoroalkyl)pyrrole-3-carboxylate derivatives in good yield.

Keywords: Synthesis; Polyfluorinated pyrrole carboxylates; Dipolar cycloaddition; NMR spectroscopy; Mass spectrometry

Much attention has been addressed to fluorinated or polyfluoroalkylated heterocyclic compounds because they often exhibit unique biological and physiological activities [1]. One of the most promising approaches to such compounds, particularly five-membered ones, is a 1,3-dipolar cycloaddition reaction in which various types of fluorine-containing dipolarophiles [2–4] [1] and dipolar compounds [5] have hitherto been employed successfully. However, there are merely scattered examples of 1,3-dipolar cycloaddition using polyfluoroacetylenic acids or esters as the dipolarophile [4] which do not necessarily exhibit satisfactory results. Our recent development of a method for preparing polyfluoro-2-alkynoic acids [6] has prompted us to investigate their chemistry as well as their application to the synthesis of polyfluoroalkylated carbocyclic and heterocyclic compounds [7].

In our continuing studies in this area, we have found that the polyfluoro-2-alkynoic acid esters **1** are so highly activated as to undergo regiospecific cycloaddition reaction with 1,3-dipolar compounds such as the munchnones **2** under very mild conditions. Herein we wish to report the results of these studies, which provide a new efficient and convenient tool in the high-yield synthesis of the 1,2-disubstituted 4-(polyfluoroalkyl)pyrrole-3-carboxylic acid esters **3** (Scheme 1).

The starting polyfluoro-2-alkynoic acid esters **1** were prepared by a two-step procedure involving carbonation of magnesium polyfluoroalkylacetylide with carbon dioxide (48%–72% yield) [6] and esterification of the resultant acid with alcohol in the presence of 1–2 equimolar amounts of concentrated sulfuric acid (60%–96% yield), as shown in Scheme 2. Munchnones **2** [8], one of the stabilized azomethine ylides, were employed as 1,3-dipolar components in view of their ready availability from 1,3-oxazolium perchlorates which could be pre-



Scheme 1. Synthesis of the 4-(polyfluoroalkyl)pyrrole-3-carboxylates **3**.

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[1] For fluoroolefins see Ref. [2]. For fluorinated acetylenes see Ref. [3]. For the cycloaddition of polyfluoroacetylenic acids and esters with (a) diazomethane, (b) nitrile oxide, (c) nitron, (d) azide and (e) diazoacetate see Ref. [4].

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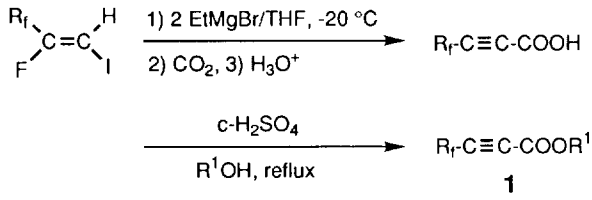

Scheme 2. Synthesis of the polyfluoro-2-alkynoic acid esters **1**.

pared by the reaction of *N*-alkyl (or -aryl)-*N*-acyl-α-amino acids with 60% aqueous perchloric acid [8b].

When ester **1** (R_f=CHF_2, R^1=Me) thus obtained was treated with in-situ generated **2** (R^2=R^3=Ph) at ambient temperature or 0 °C for 20 min, the corresponding adduct **3a** was produced as a single regioisomer in 65%–72% yield, together with a small amount of an unidentified by-product (entries 1–3 in Table 1). Lowering the reaction temperature to −15 °C allowed the reaction to take place cleanly, the formation of by-product being subsequently suppressed and the yield of **3a** being substantially increased (entry 5). Nonpolar solvents such as benzene and toluene were preferred for the reaction. Toluene was more favorable than benzene (entries 1 and 3). The use of acetonitrile as a solvent led to the preferential formation of an undesired adduct between ester **1** and triethylamine [2], i.e. methyl 4,4-difluoro-3-(triethylammonio)-2-butenoate perchlorate [3] (55% yield), the product **3a** being obtained only in 24% yield (entry 4).

As shown in Table 1, various polyfluoro-2-alkynoic acid esters **1** were found to take part readily in the cycloaddition reaction with **2** in a highly regiospecific manner, followed by decarboxylation to afford good yields of the 4-polyfluoroalkylated pyrrole-3-carboxylates **3**. Both the polyfluoroalkyl (R_f) group of **1** and substituents (R^2 and R^3) of **2** did not affect the regiospecificity of the reaction. Very interestingly, the reaction of dimethyl acetylenedicarboxylate with munchnone (R^2=R^3=Ph) under similar conditions gave dimethyl 1,2-diphenyl-pyrrole-3,4-dicarboxylate (**3j**) in 75% yield, whereas the reaction of methyl 2-butynoate hardly occurred and resulted in a quantitative recovery of the starting ester (entries 14 and 15). These facts suggest that the electronic nature of the R_f group is nearly comparable to that of the ester carbonyl group [2e]. Thus, the high efficiency in the reaction between **1** and **2** may be ascribed to strong electron-withdrawal of the R_f group which is capable of decreasing the

[2] The addition reaction of propynoic acid esters with trimethylammonium salts has been reported [9].

[3] $CHF_2(Et_3N^+)C$=$CHCOOMe \cdot ClO_4^-$: m.p. 86–88 °C IR (KBr disk) (cm^{-1}): 1730 (C=O); 1670 (C=C). ^{1}H NMR (DSS, D_2O) δ: 1.31 (9H, t, J=7.1 Hz); 3.75 (6H, q, J=7.1 Hz); 3.84 (3H, s); 7.04 (1H, s); 7.20 (1H, t, J=51.0 Hz) ppm. ^{19}F NMR (TFA, D_2O) δ: −36.4 (2F, d, J=51.0 Hz) ppm. MS (SIMS) *m/z* (rel. intensity): 571 (3); 236 (100).

Table 1
Synthesis of 4-(polyfluoroalkyl)pyrrole-3-carboxylates **3** via 1,3-dipolar cycloadditions between esters **1** and munchnones **2** [a]

Entry No.	R_f	R^1	R^2	R^3	Product	Yield [b] (%)	HRMS (*m/z*) Found	(Calc.)	^{19}F NMR δ [c] (*J*, Hz) (ppm)
1	CHF_2	Me	Ph	Ph	**3a**	65 [d]			
2	CHF_2	Me	Ph	Ph	**3a**	71 [e]			
3	CHF_2	Me	Ph	Ph	**3a**	72 [f]			
4	CHF_2	Me	Ph	Ph	**3a**	24 [g]			
5	CHF_2	Me	Ph	Ph	**3a**	81	327.1066	(327.1072)	−31.7 (dd, J=56.5, 1.5)
6	CHF_2	Me	Ph	*p*-$NO_2C_6H_4$	**3b**	65	372.0918	(372.0922)	−32.3 (dd, J=56.5, 1.7)
7	CHF_2	Me	Ph	*p*-ClC_6H_4	**3c**	78	361.0666	(361.0682)	−31.8 (dd, J=56.5, 1.7)
8	CHF_2	Me	Ph	*p*-MeC_6H_4	**3d**	61	341.1220	(341.1228)	−31.7 (dd, J=56.5, 1.5)
9	CHF_2	Me	Ph	*p*-$MeOC_6H_4$	**3e**	57	357.1183	(357.1177)	−32.1 (dd, J=56.5, 1.5)
10	CHF_2	Me	Me	Ph	**3f**	57	265.0910	(265.0915)	−31.1 (dd, J=56.2, 1.5)
11	CHF_2	Me	Ph	Me	**3g**	78	265.0907	(265.0915)	−31.8 (dd, J=56.2, 1.3)
12	CF_3	n-hexyl	Ph	Ph	**3h**	89	415.1757	(415.1760)	20.7 (d, J=1.1)
13	$H(CF_2)_3$	Me	Ph	Ph	**3i**	74	427.1001	(427.1008)	−24.0 (t, J=6.3), −50.5 (dt, J=5.9, 6.3), −57.7 (dtt, J=51.8, 6.3, 6.3)
14	COOMe	Me	Ph	Ph	**3j**	75	335.1164	(335.1158)	
15	Me	Me	Ph	Ph	no reaction				

[a] Unless otherwise noted, the reaction was carried out in toluene at −15 °C for 20 min (see text).
[b] Yields refer to pure isolated products.
[c] Expressed in ppm downfield from external trifluoroacetic acid (TFA).
[d] Performed in benzene at 0 °C for 20 min.
[e] Conducted in toluene at room temperature for 20 min.
[f] Carried out in toluene at 0 °C for 20 min.
[g] Performed in acetonitrile at −15 °C for 20 min.

energy of the lowest unoccupied molecular orbital in **1**. In support of this view, the HOMO/LUMO energies for 4,4-difluoro-2-butynoic acid methyl ester and 2-butynoic acid methyl ester have been calculated as −12.1/−8.1 and −12.2/−7.8 eV, respectively, by the extended Hückel MO method.

A typical experimental procedure for the reaction of **1** with munchnone **2** was as follows. Methyl 4,4-difluoro-2-butynoate (**1**; $R_f = CHF_2$, $R^1 = Me$) (0.128 g, 0.96 mmol), 2,3-diphenyl-5-oxo-1,3-oxazolinium perchlorate (0.405 g, 1.20 mmol) and dry toluene (2 ml) were placed in a three-necked flask which had been purged with argon. To this mixture was added triethylamine (0.152 g, 1.50 mmol) dropwise over 30 min with cooling to −15 °C using an ice methanol slush bath. After being stirred at the same temperature for 20 min, the reaction mixture was quenched with water (50 ml), followed by extraction with chloroform (30 ml × 3) and drying over anhydrous $MgSO_4$. The solvents were removed in vacuo to leave an oily residue which was purified by column chromatography on silica gel using hexane/EtOAc (3:1) as eluent to give analytically pure methyl 1,2-diphenyl-4-(difluoromethyl)pyrrole-3-carboxylate (**3a**) (0.253 g, 81%). Spectroscopic (^1H and ^{19}F NMR, IR and MS) and analytical data for the products were in good accord with the assigned structures. In particular, their regiochemical assignment was made on the basis of the fact that long-range coupling [2c] between the C(5) hydrogen and the fluorine atoms of the difluoromethyl or trifluoromethyl group appeared in the ^1H and/or ^{19}F NMR spectra of **3a–h**, as listed in Table 1. The other results of the reactions are summarized in Table 1, together with some spectral data of products **3**.

In summary, polyfluoro-2-alkynoic acid esters **1** have been shown to react regiospecifically with stabilized azomethine ylides such as munchnones **2** under extremely mild conditions, providing 4-(polyfluoroalkyl)pyrrole-3-carboxylic acid derivatives **3** in high yield. The present reaction could serve as a simple and effective method for the synthesis of a variety of such polyfluoroalkyl-containing nitrogen heterocyclic compounds.

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