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Communication

A new and concise method for the synthesis of 5-trifluoromethylisoxazoles

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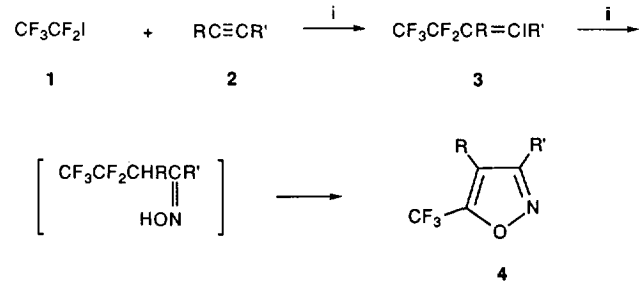
Abstract

A highly effective synthesis of a series of 5-trifluoromethylisoxazoles **4** from pentafluoroethyl iodide (**1**) and various alkynes **2** by a two-step sequence is described.

Keywords: Synthesis; Trifluoromethylisoxazoles; Pentafluoroethyl iodide; Alkynes; NMR spectroscopy; Mass spectrometry

Isoxazoles play interesting roles in medicinal and agricultural chemistry [1]. Moreover, they are precursors of several functional groups by ring modification and cleavage [2,3]. Although numerous synthetic routes to isoxazoles have been reported [3,4], the syntheses of trifluoromethylated isoxazoles are few and not regiospecific. From a biological point of view, fluorine substitution can often confer unique properties on a molecule and trifluoromethylated heterocyclic compounds have received an increasing amount of attention because of their enhanced biological activities and various applications to materials sciences [5]. However, the lack of synthetic methodologies for the preparation of trifluoromethylated heterocycles has hampered developments along these lines. Fluoroalkylisoxazoles are mainly prepared by the 1,3-dipolar cycloaddition of nitrile oxide to acetylenes or 1,3-dicarbonyl derivatives [6]. However, only the aromatic nitrile oxides are readily available, while the non-aromatic ones are unstable and dimerize to fluroxanes. Furthermore, the more common precursors of nitrile oxides, the hydroximoyl chlorides are severe skin irritants and the preparation of fluorine-containing starting material is tedious. Another route to the formation of fluoroalkylisoxazoles is the cyclocondensation of α, β-unsaturated carbonyl derivatives with hydroxylamine, which, however, leads to the formation of a mixture of isomers [7]. Here we report some preliminary results on a new versatile route to the synthesis of 5-trifluoromethylisoxazoles in high yields from the readily obtainable adduct **3** of pentafluoroethyl iodide with alkynes.



Scheme 1. Reagents and conditions: (i) $Na_2S_2O_4/NaHCO_3$, CH_3CN/H_2O, 0 °C; (ii) $NH_2OH \cdot HCl$, K_2CO_3, $EtOH/H_2O$, 60 °C or reflux.

The 1:1 adducts **3** of pentafluoroethyl iodide (**1**) with alkynes **2** can be readily prepared by known methods [8]. Compounds **3** were found to react smoothly with hydroxylamine to give 5-trifluoromethylisoxazoles **4**, which may proceed through an oxime intermediate formed by the nucleophilic addition of hydroxylamine to the adducts **3** (Scheme 1).

The following is a typical procedure: K_2CO_3 (2.76 g, 20 mmol) was added in portions to a stirred solution of 1-iodo-1-phenyl-3,3,4,4,4-pentafluoro-1-butene, $CF_3CF_2CH=CIPh$, (**3a**), (3.48 g, 10 mmol, $E+Z$ mixture) and hydroxylamine hydrochloride (1.04 g, 15 mmol) in a mixture of ethanol (15 ml) and water (4 ml) at room temperature. The resultant reaction mixture was stirred and heated to reflux for several hours, poured into water (20 ml) and extracted with diethyl ether (2×40 ml). The combined diethyl ether layers were washed with water and dried over Na_2SO_4. After removal of the diethyl ether, the residue was purified by column chromatography on silica gel (petroleum ether as

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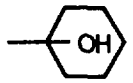
Table 1
Preparation of 5-trifluoromethylisoxazoles (4)

Entry No.	Alkene (3)		Conditions [a]		Product [b] (4)	^{19}F NMR δ (ppm) [e]	Yield [c] (%)
	R	R′	Temp. (°C)	Time (h)			
1	H	Ph (**3a**)	reflux	6	**4a**	−13.3	95
2	H	Ph (**3a**)	reflux	14	**4a**	−13.3	96 [d]
3	H	CH_2OH (**3b**)	60	10	**4b**	−13.0	80
4	H	$CH(OH)CH_3$ (**3c**)	60	8	**4c**	−12.8	87
5	H	$C(OH)Me_2$ (**3d**)	60	8	**4d**	−13.0	91
6	CH_2OH	CH_2OH (**3e**)	60	8	**4e**	−13.2	80
7	H	$CH(OH)^nPr$ (**3f**)	60	8	**4f**	−13.6	82
8	H	$CH(OH)^iPr$ (**3g**)	60	6	**4g**	−13.5	84
9	H	CH(OH)CH=CHMe(E) (**3h**)	60	6	**4h**	−13.2	78
10	H	 (**3i**)	65	6	**4i**	−13.2	88
11	H	$n\text{-}C_6H_{13}$ (**3j**)	reflux	10	**4j**	−13.0	90
12	H	CH(OH)Ph (**3k**)	65	8	**4k**	−13.2	88
13	H	$CH(OH)C_6H_4Cl$-*o* (**3l**)	60	8	**4l**	−12.1	85
14	H	$CH(OH)C_6H_4OMe$-*p* (**3m**)	65	6	**4m**	−12.7	84
15	H	$CH_2CH(OH)Ph$ (**3n**)	65	10	**4n**	−13.6	88

[a] All reactions were carried out in $EtOH/H_2O$ (3:1 in volume) using 1.2–2.0 equiv. of $NH_2OH \cdot HCl$ and 4–5 equiv. of K_2CO_3.
[b] All compounds are new and satisfactory spectral and microanalytical data were obtained.
[c] Isolated yield based on compound **3**.
[d] The reaction was carried out in $MeOH/H_2O$ (4:1 in volume).
[e] Downfield designated as negative with trifluoroacetic acid (δ 0.00 ppm) as an external standard.

eluent) to give 2.02 g (95%) of 3-phenyl-5-trifluoromethylisoxazole (**4a**) [1]. The ^{19}F NMR of **4a** revealed only a single peak δ −13.3 ppm and suggested a trifluoromethyl group (not a pentafluoroethyl group). The ^{13}C NMR spectrum showed a substituted isoxazole ring δ 103.5 (s, C_4); 159.4 (q, J_{C-F} = 42.1 Hz, C_5); 162.7 (s, C_3) ppm, suggesting that the trifluoromethyl group is substituted at the C_5 position of the isoxazole ring [9], which was further supported by its MS spectrum m/z = 213 (M^+, 69); 144 ($M^+ - CF_3$, 100); 116 ($M^+ - CF_3CO$, 24) [10].

Representative examples are summarized in Table 1. Using this methodology, the 3,4-substituents on the isoxazole ring can be varied by choosing an appropriate alkyne as the starting material. The reaction proved to be quite general for various alkynes. With both non-functionalized alkynes and functionalized alkynes, the yields of the 5-trifluoromethylisoxazoles are invariably excellent. Hence, this reaction represents a convenient route to CF_3-substituted isoxazole derivatives with a variety of substitution patterns at C_3 and C_4.

In conclusion, a new, useful and practical method for the regiospecific synthesis of 5-trifluoromethyl-substituted isoxazoles obtained ultimately from pentafluoroethyl iodide and alkynes in two steps has been established. The readily availability of the starting material, the simplicity of the experimental procedures and the high yields obtained make this approach a useful route to a variety of 5-trifluoromethylisoxazoles. Synthetic application of these functionalized building blocks for preparing trifluoromethylated organic compounds of biological interest and further studies on the generality of this process for the synthesis of other heteroaromatic compounds are being pursued.

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[1] Compound **4a**: M.p. 75–76 °C. Analysis: Calc. for $C_{10}H_6NF_3O$: C, 56.35; H, 2.8; N, 6.57; F, 26.74%. Found: C, 56.40; H, 2.70; N, 6.49; F, 27.04%. ^{19}F NMR ($CDCl_3/CF_3COOH$) δ: −13.3(s) ppm. ^{1}H NMR ($CDCl_3$/Me_4Si) δ: 7.80 (m, 2H); 7.47 (m, 3H); 6.98 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ: 103.5 (s, C_4); 118.0 (q, J_{C-F} = 268.4 Hz, CF_3); 127.0 (s), 127.5 (s), 129.3 (s), 131.0 (s), 159.4 (q, J_{C-F} = 42.1 Hz, C_5); 162.7 (s, C_3) ppm. IR (KCl) (cm^{-1}): 1600; 1580; 1460; 1440; 1340; 1200–1100. MS m/z (%): 213 (M^+, 69.71); 214 (M^+ + 1, 8.71); 144 ($M^+ - CF_3$, 100.00); 116 ($M^+ - CF_3CO$, 24.90); 77 (Ph^+, 51.95); 89 (11.67); 67 (CF_3^+, 5.98); 51 (21.41).

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