A Facile Synthesis of Fluoroalkylisoxazoles

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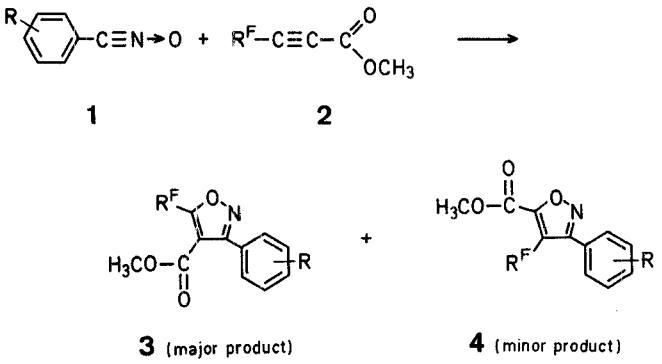
Fluorinated isoxazoles are synthesized from aromatic nitrile oxides and methyl perfluoro-2-alkynoates.

The 1,3-dipolar cycloaddition of nitrile oxides and C—C unsaturated dipolarophiles is a useful method for the synthesis of several heterocyclic compounds having biological properties[1]. Because of the large frontier orbital separations, the dipolarophilic activity of alkynes is usually reduced as compared with that of alkenes[2]. Fluorinated alkynes have been found to be good dipolarophiles as exemplified by the reaction of aromatic nitrile oxides with hexafluoro-2-butyne[3]. However, no 1:1-cycloadduct was isolated from that reaction. We describe here a facile route to fluoroalkylisoxazoles using functionalized fluoroalkynes as dipolarophiles.



1 **2**

3 (major product) **4** (minor product)

Table 1. Yields and Regioselectivity of the Reaction **1** + **2** → **3** + **4**

Product	R	R^F	Yield [%]	Ratio **3**:**4**	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ[ppm] of OCH_3
3a **4a**	H	CF_3	92	90:10	3.20 (s) 3.30 (s)
3b **4b**	H	C_2F_5	94	90:10	3.28 (s) 3.38 (s)
3c **4c**	H	n-C_3F_7	94	90:10	3.27 (s) 3.38 (s)
3d **4d**	2-Cl	CF_3	97	90:10	3.77 (s) 4.00 (s)
3e **4e**	2-Cl	C_2F_5	95	86:14	3.37 (s) 3.57 (s)
3f **4f**	2-Cl	n-C_3F_7	94	88:12	3.33 (s) 3.53 (s)
3g **4g**	4-Cl	CF_3	97	88:12	3.83 (s) 4.00 (s)
3h **4h**	4-Cl	C_2F_5	90	86:14	3.81 (s) 4.00 (s)
3i **4i**	4-Cl	n-C_3F_7	94	88:12	3.80 (s) 4.00 (s)
3j **4j**	4-CH_3	CF_3	92	92:8	3.23 (s) 3.33 (s)
3k **4k**	4-CH_3	C_2F_5	91	89:11	3.87 (s) 3.97 (s)
3l **4l**	4-CH_3	n-C_3F_7	89	89:11	3.87 (s) 4.02 (s)

Table 2. Fluoroalkylisoxazoles (**3a–e**) prepared

Product	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a]	M.S. *m/e*	I.R. ν[cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ[ppm]	^{19}F-N.M.R. (CCl_4/CF_3COOH_{ext}) δ[ppm]
3a	b.p. 109–110°/1	$C_{12}H_8F_3NO_3$ (271.2)	271; 212; 202; 143	1750 (s); 1610 (s); 1220 (s)	3.20 (s, 3H); 6.93–7.20 (m, 5H)	−14.5 (s)
3b	b.p. 94–96°/0.6	$C_{13}H_8F_5NO_3$ (321.2)	321; 290; 202; 143	1750 (s); 1620 (s); 1170 (s)	3.28 (s, 3H); 6.95–7.20 (m, 5H)	6.3 (t, 3F, J = 2 Hz); 37.3 (q, 2F, J = 2 Hz)
3c	b.p. 102–104°/0.6	$C_{14}H_8F_7NO_3$ (371.2)	371; 340; 202; 143	1750 (s); 1620 (s); 1210 (s)	3.27 (s, 3H); 6.92–7.23 (m, 5H)	4.7 (t, 3F, J = 10 Hz); 35.7 (q, 2F, J = 10 Hz); 49.8 (br. s, 2F)
3d	b.p. 113–115°/2	$C_{12}H_7ClF_3NO_3$ (305.6)	305; 270; 177; 111	1750 (s); 1620 (s); 1170 (s)	3.77 (s, 3H); 7.47 (br. s, 4H)	−14.7 (s)
3e	b.p. 101–103°/1	$C_{13}H_7ClF_5NO_3$ (355.7)	355; 270; 177; 111	1750 (s); 1620 (s); 1220 (s)	3.37 (s, 3H); 7.08 (br. s, 4H)	7.5 (t, 3F, J = 2 Hz); 37.3 (q, 2F, J = 2 Hz)
3f	b.p. 116–118°/1	$C_{14}H_7ClF_7NO_3$ (405.7)	405; 320; 177; 111	1750 (s); 1620 (s); 1220 (s)	3.33 (s, 3H); 7.03 (br. s, 4H)	4.3 (t, 3F, J = 10 Hz); 35.0 (q, 2F, J = 10 Hz); 49.7 (br. s, 2F)
3g	m.p. 41–42°	$C_{12}H_7ClF_3NO_3$ (305.6)	305; 236; 177; 111	1750 (s); 1610 (s); 1170 (s)	3.83 (s, 3H); 7.37–7.47 (m, 4H)	−15.7 (s)
3h	m.p. 49–50°	$C_{13}H_7ClF_5NO_3$ (355.7)	355; 236; 177; 111	1750 (s); 1600 (s); 1220 (s)	3.81 (s, 3H); 7.40–7.73 (m, 4H)	4.7 (t, 3F, J = 2 Hz); 35.5 (q, 2F, J = 2 Hz)
3i	m.p. 68–69°	$C_{14}H_7ClF_7NO_3$ (405.7)	405; 236; 177; 111	1750 (s); 1600 (s); 1220 (s)	3.80 (s, 3H); 7.40–7.73 (m, 4H)	2.0 (t, 3F, J = 10 Hz); 33.7 (q, 2F, J = 10 Hz); 47.8 (br. s, 2F)
3j	b.p. 106–108°/1	$C_{13}H_{10}F_3NO_3$ (285.2)	285; 216; 157; 91	1750 (s); 1620 (s); 1170 (s)	1.75 (s, 3H); 3.23 (s, 3H); 6.53–7.07 (m, 4H)	−13.0 (s)
3k	m.p. 42–43°	$C_{14}H_{10}F_5NO_3$ (335.2)	335; 216; 157; 91	1750 (s); 1620 (s); 1220 (s)	2.43 (s, 3H); 3.87 (s, 3H); 7.18–7.65 (m, 4H)	7.0 (t, 3F, J = 2 Hz); 37.7 (q, 2F, J = 2 Hz)
3l	m.p. 50–51°	$C_{15}H_{10}F_7NO_3$ (385.2)	385; 216; 157; 91	1740 (s); 1620 (s); 1220 (s)	2.47 (s, 3H); 3.87 (s, 3H); 7.20–7.67 (m, 4H)	3.0 (t, 3F, J = 10 Hz); 34.5 (q, 2F, J = 10 Hz); 48.8 (br. s, 2F)

[a] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.17, F ± 0.47, except for **3b** (F + 0.99) and **3k** (F + 0.89).

The reaction of aromatic nitrile oxides (**1**) with methyl perfluoro-2-alkynoates (**2**) gave products **3** contaminated with 8–14% of **4** (Table) which was easily removed by column chromatography on silica gel. The ratios **3**:**4** were estimated by integration of the methoxy signals in the ^{1}H-N.M.R. spectra. On the basis of the data of similar compounds[4], we assume that the OCH_3 signals of compounds **3** are shifted upfield while those of compounds **4** are shifted downfield. The structures of all products were ascertained by their M.S., I.R., and N.M.R. spectra and by their microanalyses which were satisfactorily consistent with the calculated values.

5-Perfluoroalkyl-4-methoxycarbonyl-3-aryl-1,2-oxazoles (3) (+ Regioisomers 4); General Procedure:

To a solution of a methyl perfluoro-2-alkynoates (**2**; 7.5 mmol)[5] and an arylhydroximic acid chloride (5 mmol) in absolute ether (25 ml) is slowly added triethylamine (6 mmol) at 0 °C within 1 h. The mixture is stirred at 0 °C for 6 h, then warmed to room temperature, and triethylamine hydrochloride is filtered off. After removal of the solvent the residue is distilled under reduced pressure to give products **3** and **4** (in all cases ~ 9:1). The major regioisomer **3** is separated by column chromatography on silica gel using petroleum ether (30–60 °C) as eluent.

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