The Preparation of Perfluoroaryl Substituted Isoxazoles *via* Nucleophilic Aromatic Substitution with Lithioalkylisoxazoles

Xiongbing Xia, Gary Knerr and N. R. Natale*

301 Renfrew Hall, Department of Chemistry,
University of Idaho,
Moscow, ID 83843-4144

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The lithioalkylisoxazoles obtained from C-5 lateral metalation of alkylisoxazoles, **1**, add to hexafluorobenzene. When the C-4 substituent was an electron withdrawing tertiary amide moiety, the yields were highest for mono-perfluoroarylation to give 5-pentafluorophenylmethylisoxazoles, **2**.

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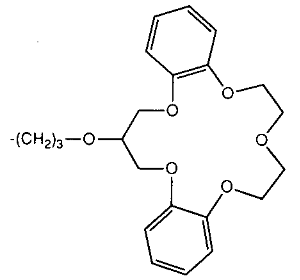
Bioisosteric replacement of functional groups by perfluorinated substituents often has a profound effect on electronic parameters, while introducing little steric perturbation [1,2]. Thus, selective synthetic introduction of perfluoro groups has potential widespread application in medicinal chemistry [3,4]. Our interest in the structure activity relationships of isoxazole containing systems [5,6] demanded the incorporation of such fluorinated functional groups, and we now report that the nucleophilic aromatic substitution reaction of lithioalkylisoxazoles [7-15] with hexafluorobenzene represents a direct entry into this arena.

The reaction of the lithio anion of simple 3,5-dimethylisoxazole, **1a**, with hexafluorobenzene produced four products, **2a-5a** shown in the Scheme, which were separable by flash chromatography [16]. Incorporation of a single electrophile was observed, product **2a**, in modest yield after isolation and purification; as well as double electrophile incorporation. Since the substitution of the first electron withdrawing group increases the acidity of the remaining protons at the C-5 lateral position of the isoxazole, the observation of double electrophile incorporation was not unexpected. What is unique in our experience is that this double electrophile incorporation product **3a**, represented the major reaction product in the quenching of a monovalent anion. Minor amounts of products arising from further attack of lithioalkylisoxazoles on a single perfluoro aryl ring were also observed, **4a** and **5a**, albeit in small amounts. The isolation of **4a** and **5a**, however, underscore the high reactivity of the pentafluoroaryl moiety even after substitution of one fluorine by an isoxazolylmethyl group.

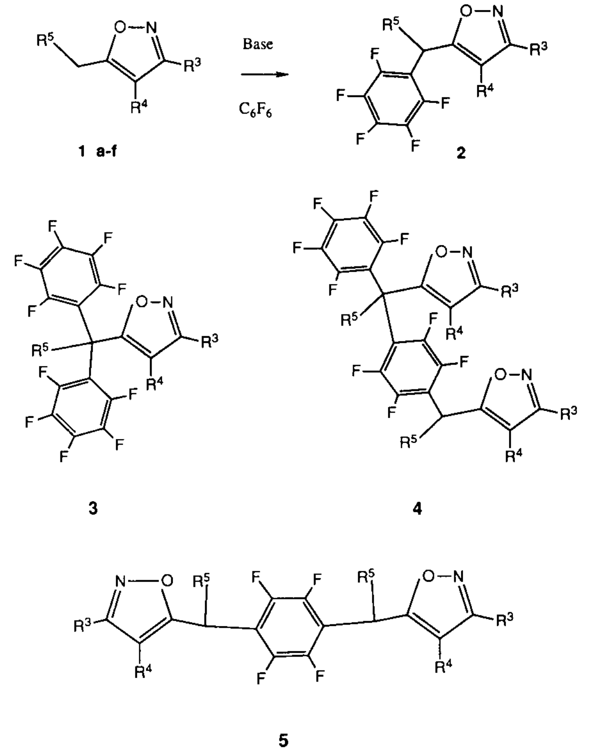
Table 1. Products of Nucleophilic Aromatic Substitution

Entry	R^3	R^4	R^5	Products (% Yield)			
				2	3	4	5
a	CH_3	H	H	20	31	10	3
b	CH_3	H	COOH	18			
c	CH_3	CON(iPr)$_2$	H	42	7		
d	C_6H_5	CON(iPr)$_2$	H	39	24		
e	CH_3	[a]	H	20	4		
f	CH_3	$(CH_2)_3OCH_3$	H	9	7		

[a] R^4 =



Scheme. Products of nucleophilic aromatic substitution of hexafluorobenzene with isoxazolyl lateral anions.



The dianion of 5-carboxymethyl-3-methyl-isoxazole gave good yields of product **2b** after extractive isolation, however, attempted distillation gave rise to complete decar-

Table 2

Characterization Data for Fluoroarylisoxazoles

Entry	mp, °C (tlc, silica gel, R_f, solvent)	^{1}H NMR (deuteriochloroform) 200 MHz δ ppm from TMS	^{19}F NMR 188 NHz δ ppm from carbontrichlorofluoride	Mass Spectrum m/e (%) [a]
2a	58-60 (0.42, hexane: ethyl acetate, 5:1)	5.85 (s, 1H), 4.10 (s, 2H), 2.23 (s, 3H)	-161.7 (m, 2F), -155.1 (t, 1F, J = 22 Hz), -142.7 (m, 2F)	264 (100) [b,c] 181 (16.46) 82 (72.25)
3a	71-73 (0.53, hexane: ethyl acetate, 5:1)	6.07 (s, 1H), 5.81 (s, 1H), 2.27 (s, 3H)	-160.6 (m, 4F), -152.4 (t, 2F, J = 22.4 Hz), -140.5 (m, 4F)	430 (100) [b,c] 388 (13.72) 347 (18.75), 82 (45.12)
4a	(0.22, hexane: ethyl acetate, 5:1)	6.09 (s, 1H), 5.90 (s, 1H), 5.83 (s, 1H), 4.14 (s, 2H), 2.26 (s, 3H), 2.22 (s, 3H)	-160.9 (m, 2F), -152.8 (tt, 1F, J = 22.2, 2.6 Hz), -142 (m, 2F), -141.1 (m, 2F), -140.3 (m, 2F)	507 (100) [b,c] 82 (48.7)
5a	159-159.5 (0.31, hexane: ethyl acetate, 5:1)	5.85 (s, 2H), 4.12 (s, 4H), 2.22 (s, 6H)	-143.1 (s, 4F)	341 (100) [b,c] 82 (85.2)
2b [d]	136-138 (0.3, hexane: ethyl acetate, 5:1)	7.8 (s, 1H), 6.26 (s, 1H), 5.49 (s, 1H), 2.29 (s, 3 H)	-160.7 (m, 2F), -152.5 (t, 1F), -140.6 (m, 2F)	308 (15.4) [b,c]
2c	80-81	4.11 (s, 2H), 3.59 (br m, 2H), 2.21 (s, 3H), 1.27 (br m, 12H)	-161.9 (m, 2F), -154.9 (br s, 1F), -141.8 (m, 2F)	391 (100) [b,c] 84 (22.39)
3c	(0.57 hexane: ethyl acetate, 3:2)	6.15 (s, 1H), 3.58 (br m, 2H), 2.20 (s, 3H), 1.22 (br m, 12H)	-161 (m, 4F), -152.6 (t, 2F, J = 22 Hz), -140.5 (m, 4F)	556 (21.9), 84 (100)
2d	113-114 (0.2, hexane: ethyl acetate, 5:1)	7.33-7.65 (m, 5H), 4.23 (s, 2H), 3.4 (br m, 2H), 0.6-1.4 (br m, 12H)	-161.8 (m, 2F), -154.8 (t, 1F, J = 22 Hz), -141.5 (m, 2F)	453 (100) [b,c], 409 (60.35) $[M\text{-}C_3H_7]^+$, 144 (100)
3d	146-147	7.32-7.61 (m, 5H), 6.23 (s, 1H), 3.3 (m, 2H), 0.6-1.3 (br m, 12H)	-161.3 (m, 4F), -156.3 (t, 2F, J = 22 Hz), -140.7 (m, 4F)	619 (100) [b,c]
2e	118-120	6.78-7.47 (m, 8H), 3.91-4.30 (m, 14H), 3.75 (t, 2H), 2.58 (t, 2H), 2.22 (s, 3H), 1.8 (m, 2H)	-162.3 (m, 2F), -155.9 (t, 1F), -142.5 (m, 2F)	650 (31.3) [b,c] 119 (100)
3e	56-57	6.82-6.99 (m, 8H), 6.15 (s, 1H), 3.86-4.27 (m, 13H), 3.70 (t, 2H), 2.47 (t, 2H), 2.26 (s, 3H), 1.65 (m, 2H)	-161.2 (m, 4F), -153.3 (t, 2F), -140.9 (m, 4F)	816 (68.46) [b,c] 136 (100)
2f	b.p. 135-140, 0.01 mm Hg (0.2 hexane: ethyl acetate, 5:1)	4.04 (s, 2H), 3.32 (t, 2H, J = 6.5 Hz), 3.31 (s, 3H), 2.45 (t, 2H, J = 7.4) 2.19 (s, 3H), 1.7 (m, 2H)	-162.0 (m, 2F), -155.5 (t, 1F), -142.5 (m, 2F)	336 (100) [b,c]
3f	7.6-7.8 (0.31, hexane: ethyl acetate, 5:1)	612 (s.12 (s, 1H), 3.24 (t, 2H, J = 5.8 Hz), 3.26 (s, 3H), 2.29 (t, 2H, J = 7.2 Hz), 2.23 (s, 3H), 1.60 (m, 2H)	-161.1 (m, 4F), -153.1 (t, 2F, J = 22 Hz), -140.9 (m, 4F)	502 (100) [b,c]

[a] Electron Impact, the high mass ion corresponds to the M^+ ion, unless otherwise noted. [b] Chemical Ionization. [c] The high mass ion corresponds to the $[M+1]^+$ ion. [d] IR (potassium bromide): 1739.8 cm^{-1} (ν C=O).

boxylation to **2a**. Silica gel chromatography produced **2b** in pure form, however, the recovered yield of product was low, which we attribute to decarboxylation catalyzed by the silica gel. The efficiency of the reaction appears to improve somewhat when an electron withdrawing group is present in the C-4 position of the isoxazole, as in **1c** and **1d**. In the cases studied, moderate to good yields of perfluoroaryl products were observed, as shown in Table 1. The reactivity of the perfluoroaryl group of **2** and **3** in these cases is probably moderated by a combination of steric and electronic factors. The diisopropylamide functional group is the largest group in the series studied to date. The electron withdrawing amide group may moderate the perfluoroaryl effect somewhat by the competition for electron density by the C-4 substituent, thus, limiting multiple substitution onto the perfluoroaryl group initially introduced. Thus both factors contribute to a lessening of oligomer formation.

The yields were significantly lower for the C-4 crown ether substituent **1e**, and a subsequent control was per-

Table 3

Analytical Data for the Products

Compound	Formula	Analysis, Calcd./Found			
		C	H	N	F
2a	$C_{11}H_6F_5NO$	50.20	2.30	5.32	36.10
		50.18	2.15	5.06	35.93
3a	$C_{17}H_5F_{10}NO$	47.57	1.17	3.26	44.27
		47.58	0.91	3.48	44.29
4a	$C_{22}H_{11}F_9N_2O_2$	52.18	2.19	5.53	33.77
		52.19	1.94	5.44	33.77
5a	$C_{16}H_{12}F_4N_2O_2$	56.47	3.56	8.23	22.33
		56.80	3.41	8.31	22.19
2b	$C_{12}H_6F_5NO_3$ [a]	46.92	1.97	4.56	30.93
		48.91	1.83	4.64	30.50
2c	$C_{18}H_{19}F_5N_2O_2$	55.38	4.91	7.18	24.34
		55.35	4.70	6.89	24.08
3c	$C_{24}H_{18}F_{10}N_2O_2$	51.80	3.26	5.04	34.15
		52.08	3.25	4.92	33.85
2d	$C_{23}H_{21}F_5N_2O_2$	61.06	4.68	6.19	21.00
		61.16	4.72	6.23	20.91
3d	$C_{29}H_{20}F_{10}N_2O_2$	56.31	3.26	4.53	30.72
		56.14	3.31	4.58	30.39
2e	$C_{33}H_{32}F_5NO_7$	61.01	4.97	2.16	14.62
		61.07	5.11	2.27	14.51
3e	$C_{39}H_{31}F_{10}NO_7$	57.43	3.83	1.72	23.29
		57.67	4.07	1.99	21.73
2f	$C_{15}H_{14}F_5NO_2$	53.73	4.21	4.18	28.34
		53.30	4.16	4.01	28.24
3f	$C_{21}H_{13}F_{10}NO_2$	50.31	2.61	2.79	37.90
		50.46	2.57	2.75	37.07

[a] Exact mass Calcd.: 308.0346. Found: 308.0346.

formed with a simple alkyl ether, **1f**, to ascertain whether this was due to the electron donating effect of the group at C-4, or to some chelation effect associated with the crown ether moiety. Since results with **1e** and **1f** were essentially the same, it appears that it is not complexation of the lithium by the macrocycle giving rise to the low yields, but rather the electron donating nature of the substituent.

We shall report on the application of the perfluoroaryl-isoxazole derivatives, in both synthesis and biology, in due course.

EXPERIMENTAL

Commercial reagents were obtained from Aldrich, and purified by crystallization or distillation before use, as appropriate. Reactions involving organometallic reagents were performed under inert atmosphere. Tetrahydrofuran was distilled from sodium and benzophenone. The nmr spectra were obtained on a Bruker AF200 Instrument (200 MHz for ^1H). The ir spectra were obtained on a Digilab FTS-80. Mass spectra were obtained on a VG Micromass 70/70 HS Mass Spectrometer. Combustion Analyses were performed by Desert Analytics, Tuscon, AZ.

Typical Procedure for Metalation and Quenching with Hexafluorobenzene.

To a solution of 3,5-dimethylisoxazole (1.94 g, 20 mmoles) in 100 ml of tetrahydrofuran was added 11 ml of a 1.8 *M* solution of *n*-butyllithium in hexanes, at −78°. After one hour hexafluorobenzene (2.3 ml, 20 mmoles) was added dropwise *via* syring. The reaction mixture was allowed to warm to room temperature, and 200 ml of water was added. The mixture was extracted with chloroform (3 x 50 ml), the combined organic layers washed with water, and dried over anhydrous sodium sulfate. The solution was filtered, and the solvent evaporated under reduced pressure. The products were obtained by flash chromatography on silica gel, using the solvent system listed in Table 2.

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