A SITE- AND REGIO-SPECIFIC ROUTE TO PERFLUOROALKYLISOXAZOLES

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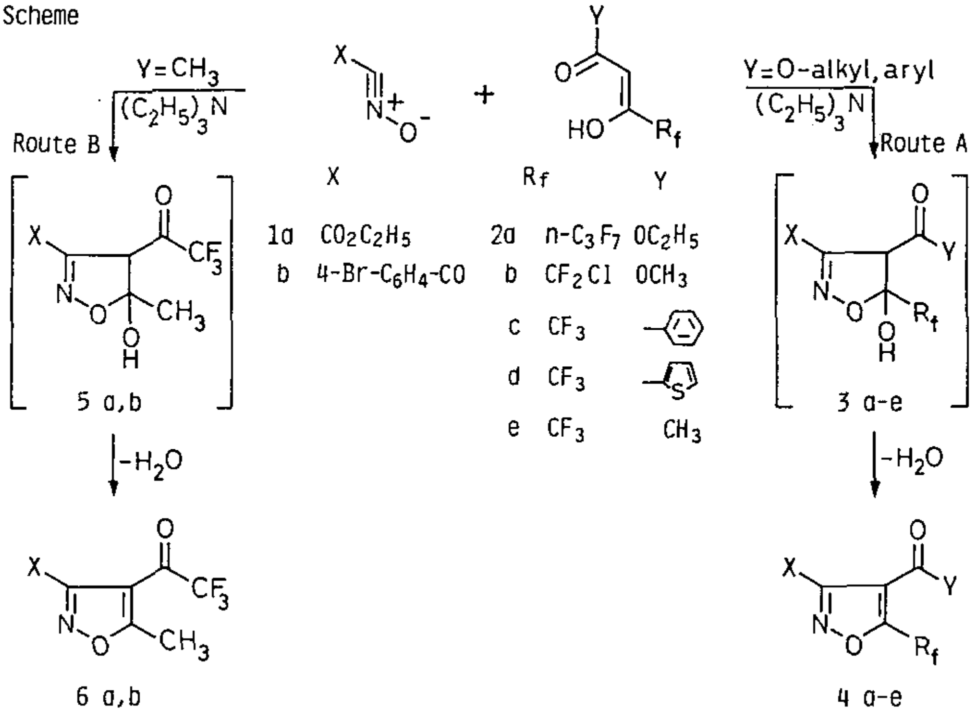
Abstract---The 1,3-cycloaddition reaction of nitrile oxides (**1**) to ß-perfluoroalkyl-ß-dicarbonyl compounds (**2**) affords regio- and site-selectively either 5-perfluoroalkylisoxazoles (**4**) or 4-trifluoroacetylisoxazoles (**6**) according to the nature of dipolarophiles (**2**).

Fluoroalkyl substituted aromatic and heteroaromatic compounds are the target of consistent synthetic efforts as a consequence of their useful properties.[1a] Heteroaromatic rings are usually obtained through cyclization of a properly functionalized fluoroaliphatic precursor.[1b] In most cases these cyclizations are not regioselective and mixtures of isomers are formed.[2]

Here we describe a site- and regio-specific synthesis of 5-perfluoroalkylisoxazoles (**4**) and 4-trifluoroacetylisoxazoles (**6**).

Fluorination shifts the keto-enol equilibrium towards the enol form[3] and in fact ß-dicarbonyl compounds (**2**) are mainly or exclusively in their enol form. It has been suggested that this is the reason for which ethyl 4,4,4-trifluoroacetoacetate reacts with nitrones when ethyl acetoacetate does not.[4] However, when ß-fluoroalkyl-ß-keto esters (**2a,b**) were treated with nitrile oxides (**1**) (generated *in situ* from corresponding chlorooximes by treatment with triethylamine in toluene or tetrahydrofuran) a sluggish cycloaddition reaction occurred and desired isoxazoles were formed in low yields. By simply employing the triethylammonium salts of these ß-keto esters the 5-perfluoroalkylisoxazoles (**4a,b**) were formed cleanly (Scheme).[5] Under the same reaction conditions 1,1,1-trifluoro-2,4-butandiones (**2c-d**), carrying a benzoyl- or 2-thenoyl- residue on C-4, afforded exclusively the 5-trifluoromethylisoxazoles (**4c-e**). Surprisingly, 1,1,1-trifluoro-2,4-pentanedione

Scheme



(**2e**) afforded 4-trifluoroacetylisoxazoles (**6a,b**).[6]
In all cases, compounds (**4**) or (**6**) were formed with complete regioselectivity and were isolated in good yields (Table).
A more or less concerted cycloaddition of 1,3-dipoles (**1**) to the carbon-carbon double bond of enolates of (**2**) occurs[7] to give 5-perfluoroalkyl-5-hydroxy-2-isoxazolines (**3**) or 5-alkyl-5-hydroxy-2-isoxazolines (**5**).
Dehydration of similar 5-perfluoroalkylisoxazolines is reported to occur only in refluxing benzene[8] while 5-alkylisoxazolines lose water spontaneously.[7] Dehydration of our compounds took place very easily. Isoxazoles (**4**) and (**6**) were exclusively isolated and intermediate formation of 2-isoxazolines (**3**) and (**5**) was not detected.
For all the ß-dicarbonyl compounds that we have employed, the preferred enol form is the one reported in the Scheme, i. e. the carbonyl group adjacent to the perfluoroalkyl chain enolizes preferencially.[9] The unique exeption is the 1,1,1-trifluoro-3-(2-thenoyl)acetone (**2d**) for which the enolized carbonyl group is adjacent to the thienyl residue.[10] Formation of 5-perfluoroalkylisoxazoles (**4**) implies that nitrile oxides (**1**) react, with complete regioselectivity, only on the enol form depicted in the Scheme (Route A). The same regioselectivity has been reported for the cycloaddition reaction of nitrile oxides to ethyl acetoacetate and benzoylacetone.[11] The frontier-

Table. Yields and Selected Spectral Data of Compounds (**4a-e**), (**6a,b**).[a]

Compound No.	X	Y	R_f	Yield (%)	^{19}F Nmr[b]	^{13}C Nmr[b] C-4	C-5 ($^2J_{C,F}$)
4a	$CO_2C_2H_5$	OC_2H_5	$n-C_3F_7$	78	-81.5;-113.5; -127.4	117.0	157.3(31.4)
4b	4-Br-C_6H_4-CO	OCH_3	CF_2Cl	75	-53.1	112.4	162.6(37.7)
4c	$CO_2C_2H_5$	C_6H_5	CF_3	81	-63.9	120.2	157.2(44.0)
4d	$CO_2C_2H_5$	2-C_4H_3S	CF_3	86	-63.8	119.9	157.2(44.0)
4e	4-Br-C_6H_4-CO	2-C_4H_3S	CF_3	76	-63.5	120.8	156.5(44.0)
6a[c]	$CO_2C_2H_5$	CH_3	CF_3	74	-70.6	113.2	173.6
6b[c]	4-Br-C_6H_4-CO	CH_3	CF_3	70	-76.1	111.9	176.5

[a] A solution of the chlorooxime (2.5 mmol) in tetrahydrofuran (2.0 ml) was added dropwise to a stirred solution of the fluorinated ß-dicarbonyl compound **2** (12.5 mmol) and triethylamine (2.09 ml, 15 mmol) in the same solvent (10 ml). After 36 h at room temperature a usual work-up and a flash-chromatographic purification afforded products **4** or **6** in pure form. [b] Solvent $CDCl_3$; internal standards: Me_4Si and $CFCl_3$; chemical shifts: δ (ppm); *J*: Hz. [c] Reported chemical shifts are referred to the compounds having the carbonyl group on C-4 in the keto form; the compounds showed however a marked proclivity for becoming hydrated (gem diol): (**6a**), ^{19}F Nmr δ: -88.2 ppm; (**6b**), ^{19}F Nmr δ: -88.0 ppm.

orbital models[4,12] or Coulombic and dipole-dipole interactions in the perturbation equation[13] can be used to rationalize the observed regioselectivity.

Differently, the reaction on 1,1,1-trifluoro-2,4-pentanedione (**2f**) involves, again with complete regioselectivity, exclusively the enol form in which the carbonyl adjacent to the methyl group is enolized (Route B).[14] Formation of 4-trifluoroacetylisoxazoles (**6a,b**) clearly shows the ability of a perfluoroalkyl residue to direct the course of a 1,3-dipolar cycloaddition. Routes A and B have the same regioselectivity as in both cases the positive site of dipole **1** reacts with the α carbon of the ß dicarbonyl system. However, the two Routes occur with different site-selectivity as they involve either of the two possible enol forms of the dicarbonyl compound. The difference between Ruote A and Route B is connected with the differencial effect on the reaction of a *perfluoro-*

alkyl group compared with *aroyl* (Route A) or *acyl* (Route B) residues. The reported approach for the synthesis of fluorinated isoxazoles appears to be particularly attractive as both (**1**) and (**2**) are easily available starting materials. Furthermore, the substitution pattern of isoxazoles (**4**) is quite similar to that present on the isoxazole ring of some semisynthetic penicillins (e. g. oxacillin).[7]

REFERENCES AND NOTES

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5. Structures were determined from nmr data and chemical correlation. ^{13}C Nmr of compounds (**4**) showed a singlet in the typical region of C-4 and a quartet, or triplet, ($^{3}J_{C,F}$ = 40 Hz ca.) in the region of C-5 (see Table). Furthermore, reduction of (**4c**) with sodium borohydride in THF afforded 4-hydroxybenzyl-3-hydroxymethyl-5-trifluoromethyl-isoxazole: ^{1}H Nmr δ: 4.33 and 4.70 (d each, J = 13 Hz, 1H each, OCH_2C-3), 6.17 (br s, 1H, OCHC-4), 7.25 - 7.45 (m, 5H, C_6H_5); ^{19}F Nmr δ: -63.0 ppm.
6. Structures were assigned by observing that in ^{13}C Nmr spectra C-4 and C-5 appeared as singlets and the carbonyl group attached to C-4 appeared as a quartet (^{13}C Nmr δ: (**6a**): 176.5 (q, $J_{C,F}$ = 37.7 Hz); (**6b**): 176.1 (q, $J_{C,F}$ = 37.7 Hz).
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14. When ß-diketones (**2c-f**) were employed without forming their triethylammonium salts the same regioselectivity was observed, but much lower yields were obtained.

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