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SELECTIVITY IN THE SYNTHESIS OF FLUORINATED HETEROCYCLES FROM α,β-UNSATURATED PERFLUOROACYL DERIVATIVES (OR THEIR SYNTHETIC EQUIVALENTS) AND 1,2-BIS-NUCLEOPHILES.

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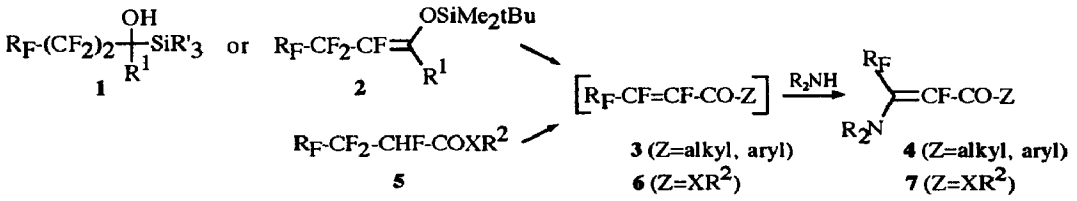
Abstract . Reactions of vicinal diamines, aminoalcohols, aminothiols with synthetic equivalents of perfluoroenones **3** or α,β-unsaturated perfluoroesters **6** gave regiospecifically new five member (imidazo or oxazolidines) or seven member fluorinated heterocycles (dia or thiazepines).

We have recently reported that 1-aryl-1-trialkylsilyl-perfluoroalkanols **1**[1] and 1-alkyl-1-trialkylsilyloxy perfluoroalk-1-enes **2**[2] are useful synthons which can be considered as equivalents of enones **3**.[3] Compounds **1** and **2** react with amines as easily as the enone **3** to yield the corresponding β-enaminones **4**.[2,4] Similarly we have reported earlier the synthesis of β-enaminoesters **7**[5] from esters of α,β-unsaturated perfluoroacids **6** generated in situ from α-hydro perfluoroalcanoates **5**.[6] In all these reactions, primary amines gave also the β-iminotautomer which is often more stable than the β-enamino tautomer and in most cases can be separated.



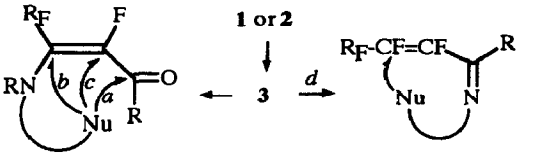
These enamino/imino derivatives are usually formed as intermediates in the reaction pathway leading to heterocycles from β-diketones or β-ketoesters.[7] Heterocycles in general, fluorinated ones in particular, are widely involved in the structure of bioactive molecules having applications in agricultural and medicinal chemistry. Therefore it was interesting to study the reaction of our synthons with bis-nucleophilic amines in order to have access, if a cyclocondensation step follows the formation of the β-enamino/β-imino intermediate, to an heterocycle bearing both a fluorine and a perfluoroalkyl substituent.

Moreover, the fluorine substitution often modifies strongly the charges distribution and/or the frontier orbitals level, so that the second intramolecular nucleophilic attack in the intermediate enaminone is to be expected on the carbonyl carbon but also, for large enough ring size, on the β-carbon.[8] Furthermore, there are in the literature some examples of anti-michael nucleophilic addition on fluorinated enones type substrates.[9]

Thus, the different possible pathways are:

-Michael attack followed by cyclocondensation (path a), Michael (path b), or anti-Michael (path c) cyclisation.

-attack on the carbonyl group followed by cyclocondensation on Cβ (path d).



This paper is devoted to the behaviour of enones **3** (or their synthetic equivalents **1** and **2**) and α,β-unsaturated perfluoroesters **6** (or their synthetic equivalents **5**) with some 1,2-bis-nucleophiles (1,2-diamines, 2-hydroxyamines, and 2-mercaptoamines) from the chemo and regioselectivity point of view. On this occasion, efficient synthesis of new fluorinated heterocycles in the imidazolidine, oxazolidine, diazepine and thiazepine series are reported.

Starting materials

	R^1	R_F
1a, 3a	Ph	C_4F_9
1b, 3b	p-F-Ph	
1c	p-Cl-Ph	
1d	p-MeO-Ph	
2	C_5H_{11}	

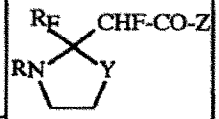
	XR^2	R_F
5a	OCholestanyl	CF_3
5b	SEt	CF_3
5c	OHeptyl	C_5F_{11}

When alcohol **1a** (or the corresponding enone **3a**) or silyl enol ether **2a** were treated in ether at room temperature with 1,2-diaminoethane or N-methyl-1,2-diaminoethane, a smooth reaction took place and the polyfluorinated imidazolidines **8-10** were obtained quantitatively. Similarly, reaction with ethanolamine gave oxazolidines **11-13**[10] (Table I). In no case were traces of diazepine detected. Thus the first step is a chemospecific Michael addition-elimination followed by a regiospecific Michael cyclisation (path b). We have carried out the same reaction with 2-hydro perfluoroesters and thioesters. With the perfluorocrotonic equivalents, **5a** and **5b**, similar reactivity was observed, giving the corresponding imidazolidines **14-16** and oxazolidines **17-18**[10] (Table I). Remarkably, in one case, corresponding to the higher homologue **5c**, a cyclocondensation took place, giving the diazepinone **19**[10] (Table II). This different reactivity owing to the length of the perfluoroalkyl chain remains unexplained, but we can relate this result to the better ability of long chain perfluoroalkyl ketones to accommodate an sp_2 carbon compared with the very easy hydration or hemiketalisation of trifluoromethyl ketones. After the first step, Michael cyclisation leading to a tetrahedral β-carbon would be favored with trifluoromethyl derivatives, whereas cyclocondensation would compete with longer perfluoroalkyl chain.

A more rigid 1,2-diamine must hinder the formation of a five member cycle and favor cyclocondensation (path a). Compounds **1a** and **2a** were reacted with o-phenylenediamine. The reaction needed triethylamine to eliminate HF and was slower according to the weak nucleophilic character of this diamine, but was very clean and gave quantitatively the expected benzodiazepines **20-24**[10] (Table II). A unic tautomer was observed, having the diimine structure. Benzodiazepinones could not be obtained in similar conditions from esters **5**, even in the presence of triethylamine. We had already observed that aromatic amines are not nucleophilic enough to give the β-fluorine substitution.[5] Such a benzodiazepinone has been reported: it has been prepared by treating an α-hydro-β-keto perfluoroester with o-phenylenediamine in acidic medium.[11] Reaction of o-aminothiophenol gave also regiospecifically the benzothiazepine **25**. A primary Michael attack by the thiol function was

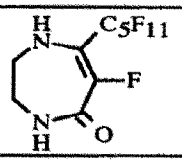
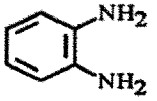
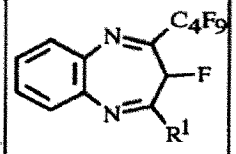
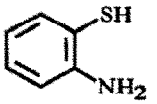
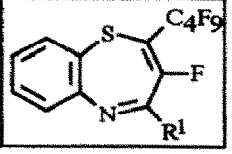
confirmed by ^{1}H- and ^{19}F-NMR monitoring of the reaction which indicated the disappearence of the β-fluorine and SH signals at the beginning of the reaction. In contrast to reported results about reaction of β-chloro trifluoromethyl enones,[8] our reaction works in neutral medium and is chemospecific and regiospecific following the path a.

Table I

Starting compound	Bis-nucleophilic reagent	Reaction conditions[a]	Imidazolidine or oxazolidine	Y	R	Z	yield (%)[b]	
1a	$H_2N(CH_2)_2NH_2$	Et_2O, reflux, 4h	**8**	NH	H	Ph	88	
3a	$H_2N(CH_2)_2NH_2$	Et_2O, rt, 3h	**8**	NH	H	Ph	92	
2a	$H_2N(CH_2)_2NH_2$	Et_2O, rt, 8h	**9**	NH	H	C_5H_{11}	94	
1a	$H_2N(CH_2)_2NHMe$	Et_2O, reflux, 4h	**10**	NH	Me	Ph	81[c]	
3a	$H_2N(CH_2)_2NHMe$	Et_2O, rt, 3h	**10**	NH	Me	Ph	88[c]	
1a	$HO(CH_2)_2NH_2$	Et_2O, rt, 4h	**11**	O	H	Ph	91[c]	
1a	$HO(CH_2)_2NHMe$	Et_2O, rt, 4h	**12**	O	Me	Ph	92[c]	
2	$HO(CH_2)_2NHMe$	Et_2O, rt, 3.5h	**13**	O	Me	C_5H_{11}	85[c]	
5a	$H_2N(CH_2)_2NH_2$	THF, reflux, 4h	**14**	NH	H	OCholest	96[c]	
5a	$H_2N(CH_2)_2NHMe$	THF, reflux, 4h	**15**	NH	Me	OCholest	64[c]	
5b	$H_2N(CH_2)_2NH_2$	Acetone, rt, 2h	**16**	NH	H	SEt	54	
5a	$HO(CH_2)_2NH_2$	Acetone, rt, 15h	**17**	O	H	OCholest	46[c]	
5a	$HO(CH_2)_2NHMe$	Acetone, rt, 15h	**18**	O	Me	OCholest	64[c]	

[a] 2 eq with 2, 3a, and 5a,b; 3 eq with 1a. [b] Pure isolated compound. [c] Mixture of diastereomers.

Table II

Starting compound	Bis-nucleophilic reagent	Reaction conditions	Diazepine or thiazepine	R^1	Yield (%)[a]	
5c	$H_2N(CH_2)_2NH_2$	2 eq, THF, 1h	**19**		59	
1a		3 eq + 1 eq Et_3N Et_2O,reflux, 20h	**20**	Ph	92	
1b			**21**	p-F-Ph	82	
1e			**22**	p-Cl-Ph	98	
1d			**23**	p-MeO-Ph	82	
2		2 eq, MeOH, reflux, 15h	**24**	C_5H_{11}	91	
3b		2 eq, Et_2O, rt, 4h	**25**	p-F-Ph	87	

[a] Pure, isolated compound

In conclusion, when reacted with bis-nucleophilic amines, α,β-unsaturated perfluoroacyl compounds exhibit: (i) chemospecific Michael reactivity; (ii) two competitive sites of second nucleophilic attack; (iii) this second nucleophilic attack is regiospecific with bis-nucleophiles studied. These reactions lead to new fluorinated heterocycles in high yield and very mild conditions.

Table III

	1H-NMR (ppm/TMS)	13C-NMR (ppm/TMS)	19F-NMR (ppm/$CFCl_3$)
9	4.82 (d, =50 Hz, Ha)	82.9 (q, 19Hz, Cb); 92.6 (d, 197 Hz, Ca); 208,6 (d, 25 Hz, CO)	-117.8 and -121.5 (2 dm, 280 Hz, $CF_{2\gamma}$); -195.7 (m, CHF)
10	5.60 (minor) and 6.10 (major. isom.) (d, 45 Hz, CHF)	91.7 and 92.8 (d, 196 Hz, C_b)	-194,0 (dq, 46 and 8 Hz)
19	5.92 and 7.25 (br s, NH)	128.2 (m, CR_F); 134.9 (d, 220 Hz, CF); 163.2 (d, 29 Hz, CO)	-153.0 (m, CF)
21	6.35 (d, 45 Hz, CHF)	138.5 (d, 277 Hz, CHF); 140.4 (m, CN); 148.3 (d, 7.5 Hz)	-107.5 (m, ArF); -190.1 (m, CHF)
25		153.1 (d, 301 Hz, CF); 153.6 (m, CS); 157.0 (d, 27 Hz, CN)	-82.8 (m, CF); -107.4 (m, ArF);

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References and notes.

1/ Dondy, B; Doussot, P; Portella, C. *Synthesis*, **1992**, 995-998.

2/ Doussot,P.; Portella.C. *J. Org. Chem.*, **1993**, *58*, 6675-6680.

3/ B. Dondy, C. Portella. *J. Org. Chem.*, **1993**, *58*, 6671-6674.

4/ B. Dondy, P. Doussot, C. Portella. *Tetrahedron Lett.*, **1994**, *35*, 409-412.

5/ C. Portella, M. Iznaden. *J. Fluor. Chem.*, **1991**, *51*, 1.

6/ C. Portella, M. Iznaden. *Tetrahedron*, **1989**, *45*, 6467. M. Muzard, C. Portella. *J. Org. Chem.* **1993**, *58*, 29-31.

7/ Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. *Tetrahedron*, **1987**, *43*, 5171-5186.

8/ Alvernhe, G.; Langlois, B.; Laurent, A.; Le Dréan, I.; Selmi, A. *Tetrahedron Lett.*, **1991**, *32*, 643-646. Laurent, A.; Le Dréan, I.; Selmi, A. *Tetrahedron Lett.*, **1991**, *32*, 3071-3074. Alvernhe, G.; Laurent, A.; Le Dréan, I.; Selmi, A. *Tetrahedron Lett.*, **1993**, *34*, 2483-2486. Alvernhe, G.; Greif, D.; Langlois, B.; Laurent, A.; Le Dréan, I.; Pulst, M.; Selmi, A; Weissenfels, M. *Bull Soc. Chim. Fr.*, **1994**, *131*, 167-172.

9/ Nguyen, T.; Rubinstein, M.; Wakselman, C. *J. Fluorine Chem.*, 1978, *11*, 573-589. Martin, V.; Molines, H.; Wakselman, C. *J. Org. Chem.*,**1986**, *51*, 4082-4083.

10/ All compounds were fully characterized by spectral and microanalysis. Selected NMR data are reported in table III.

11/ Ishikawa, N; Takaoka, A., *European Patent* 133 322 A1, Daikin Industries, Ltd, 1985. *Chem. Abstr.* **1985**,*102*, 185113.

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