

Communication

# Synthesis of 3-perfluoroalkyl-, including 3-trifluoromethyl-, substituted pyrazoles from perfluoroalkylacetylenes

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## Abstract

3-Perfluoroalkylpyrazoles **2** have been prepared in excellent yield by the reactions of perfluoroalkylacetylenes **1** with hydrazine monohydrate under mild conditions.

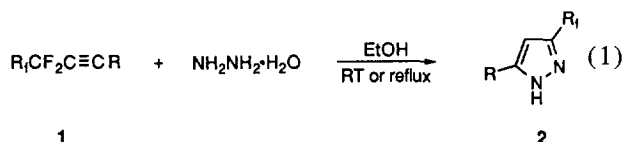
**Keywords:** Perfluoroalkylpyrazoles; Synthesis; Perfluoroalkylacetylenes; Hydrazine; Nucleophilic addition

It is now recognized that the regioselective replacement of hydrogen in an aromatic or heterocyclic system by a perfluoroalkyl group may have a profound influence on the physical and biological properties of such molecules [1]. As a result, considerable effort has been devoted to the development of synthetic methodologies for the preparation of perfluoroalkyl-substituted heterocycles [2]. One such method is based on the use of a building block with a fluorine-containing substituent.

Perfluoroalkylacetylenes have been found to be good electrophiles since the perfluoroalkyl group  $R_f$  significantly enhances the electrophilic character of the triple bond [3]. Use of perfluoroalkylacetylenes for the incorporation of fluorine into molecules and numerous reactions involving their use as either nucleophilic and electrophilic synthons have been described [4]. In particular, nucleophilic additions to perfluoroalkylacetylenes by *N*-nucleophiles [5], *O*-nucleophiles [6], *S*-nucleophiles [7], as well as *C*-nucleophiles [8] and others have been reported. In connection with the preparation of a series of perfluoroalkyl-substituted heterocycles with potential high biological activities, we were interested in examining the interaction of perfluoroalkylacetylenes **1** with dinucleophiles. Here we describe preliminary results on the reaction of perfluoroalkylacetylenes **1** with hydrazine monohydrate leading to the synthesis of 3-perfluoroalkylpyrazoles **2** in excellent yield.

Perfluoroalkylacetylenes **1** reacted smoothly with hydrazine monohydrate under reflux in ethanol to give 3-perfluoroalkylpyrazoles **2** as the sole product [Eq. (1)]. The spectral

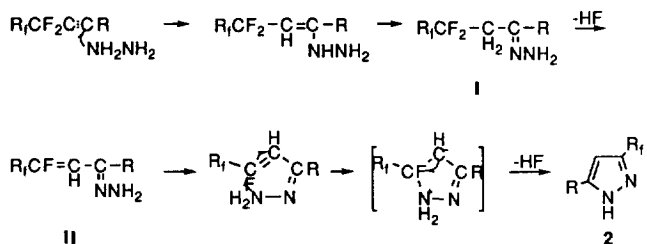
data for **2** indicate that the perfluoroalkyl group of the product is one carbon atom less than that of the starting material.



Examination of the reaction conditions showed unequivocally that at least 3 equiv. of hydrazine monohydrate were essential for the complete conversion of the perfluoroalkylacetylenes.

On the basis of this fact [3,9], this reaction is assumed to proceed via nucleophilic attack of hydrazine monohydrate on perfluoroalkylacetylenes to give a hydrazone intermediate **I**, which eliminates hydrogen fluoride to form the intermediate **II**. Such intramolecular nucleophilic addition, followed by elimination of another molecular hydrogen fluoride to give the 3-perfluoroalkylpyrazoles, occurs as shown in Scheme 1.

In a typical procedure, hydrazine monohydrate (35 mmol) was added to a solution consisting of 10 mmol of 3,3,4,4,5,5,6,6,6-nonafluoro-1-phenyl-1-hexyne,  $CF_3(CF_2)_3C\equiv$



Scheme 1.

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Table 1  
Preparation of 3-perfluoroalkylpyrazoles (2)

Entry No.	Acetylenes		R	Conditions <sup>a</sup>		Time (h)	Products <sup>b</sup>	M.p. (°C)	Yield (%) <sup>c</sup>
	R <sub>1</sub>	R <sub>2</sub>		Temp. (°C)					
1	F(CF <sub>2</sub> ) <sub>3</sub>	Ph (1a)	Ph	reflux	4	2a	93-94	96	
2	Cl(CF <sub>2</sub> ) <sub>3</sub>	Ph (1b)	Ph	reflux	6	2b	90-92	95	
3	F(CF <sub>2</sub> ) <sub>5</sub>	Ph (1c)	Ph	reflux	6	2c	72-73	98	
4	CF <sub>3</sub>	Ph (1d)	Ph	reflux	4	2d [11]	120-121	94	
5	CF <sub>3</sub>	CH <sub>2</sub> OH (1e)	CH <sub>2</sub> OH	25	3	2e [12]	115-116	95	
6	CF <sub>3</sub>	CH(OH)Me (1f)	CH(OH)Me	25	4	2f [12]	93-94	92	
7	CF <sub>3</sub>	C(OH)Me <sub>2</sub> (1g)	C(OH)Me <sub>2</sub>	reflux	4	2g [12]	150-151	94	
8	Cl(CF <sub>2</sub> ) <sub>3</sub>	CH <sub>2</sub> OH (1h)	CH <sub>2</sub> OH	25	3	2h [13]	118-119	95	
9	Cl(CF <sub>2</sub> ) <sub>3</sub>	CH <sub>2</sub> OH (1h)	CH <sub>2</sub> OH	reflux	0.5	2h [13]		90	
10	Cl(CF <sub>2</sub> ) <sub>5</sub>	CH <sub>2</sub> OH (1i)	CH <sub>2</sub> OH	25	4	2h [13]	170-172	96	
11	Cl(CF <sub>2</sub> ) <sub>3</sub>	H (1j)	H	25	6	1j [14]	66-68	89	
12	Cl(CF <sub>2</sub> ) <sub>5</sub>	H (1k)	H	25	6	1k [14]	52-54	90	

<sup>a</sup> All reactions were carried out in ethanol with 3-4 equiv. of hydrazine monohydrate being employed.

<sup>b</sup> All new compounds were characterized by mass spectrometry, IR, <sup>1</sup>H NMR, <sup>19</sup>F NMR spectroscopy and microanalysis.

<sup>c</sup> Isolated yield.

CPh, (1a) in 20 ml of 95% ethanol. The reaction mixture thus obtained was heated to reflux for 2 h, then cooled and diluted with water (40 ml). The resulting precipitate was collected by filtration and purified by recrystallization from petroleum ether to give 3-heptafluoropropyl-5-phenylpyrazole (2a)<sup>1</sup>.

Representative examples are summarized in Table 1. The reaction can be applied to a wide variety of perfluoroalkylacetylenes and the yields are invariably high. The substitution pattern at skeletal atoms 3 and 5 of the pyrazole ring can be altered by choosing the appropriate perfluoroalkylacetylenes. Therefore, this reaction can serve as a convenient route to 3-perfluoro-alkyl substituted pyrazole derivatives emerging as a new kind of fluorine-containing compound possessing high biological activities such as herbicides, fungicides, insecticides, etc [10]. Based on the supposed reaction mechanism, we envisage that this method may have great potential for further application to other dinucleophiles for preparing perfluoroalkylated heterocycles. This study is in progress.

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<sup>1</sup> Compound 2a: M.p. 92.5-94.0 °C. <sup>19</sup>F NMR (CD<sub>3</sub>COCD<sub>3</sub>/TFA) δ: 4.0 (s, 3F); 33.9 (s, 2F); 50.9 (s, 2F) ppm. <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>/Me<sub>4</sub>Si) δ: 7.03 (s, 1H); 7.43 (m, 3H); 7.77 (m, 2H) ppm. IR (KCl) ν (cm<sup>-1</sup>): 3100, 1580; 1480; 1360; 1120; 710. MS m/z (%): 312 (M<sup>+</sup>, 58.50); 313 (M<sup>+</sup> + 1, 8.30); 293 (8.45); 193 (M<sup>+</sup> - C<sub>2</sub>F<sub>5</sub>, 100.00); 164 (21.25); 115 (16.50); 77 (10.00). Satisfactory elemental analyses were obtained for 2a.

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