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SYNTHESIS OF FLUORINATED ENYNES AND DIENES VIA 1-BROMO 2-FLUORO ALKENES

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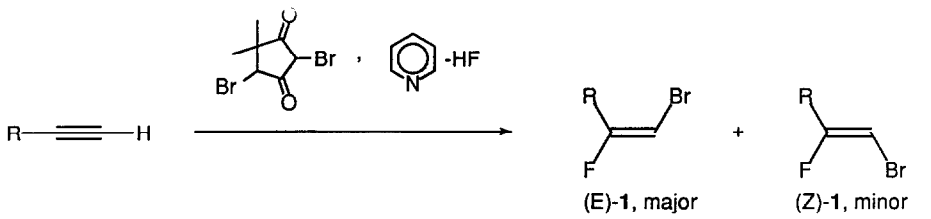
Abstract – A stereospecific synthesis of fluorinated enynes and dienes was performed through palladium-catalyzed condensation of 1-bromo-2-fluoroalkenes, synthesized either through "BrF" addition to the corresponding alkynes or through bromine addition and HBr elimination on fluoroesters, with monosubstitued alkynes or alkenes.

Preparation of enynes and dienes fluorinated at selected positions allows the synthesis of a variety of fluorinated compounds, often interesting for their potential biological activity[1,2a]. We have recently described an access to 2-fluoro-1-en-3-ynes using 1-bromo-1-fluoroalkenes[3]. We now report syntheses of 1-bromo-2-fluoroalkenes and their palladium-catalyzed condensations with alkenes and enynes leading to 1-fluoro dienes and enynes. Palladium-catalyzed reactions of halogenofluoroalkenes with organozinc compounds have recently been used to synthesize several difluorinated dienes[2] and enynes[4]. A few other methods of preparation of monofluorodienes[5] and monofluoroenynes[6] have also been reported.

Addition of the elements of BrF to alkynes is a straightforward method to prepare 1-bromo-2-fluoroalkenes. Such reactions have been performed by using a brominating agent in the presence of fluorohydric acid[7], or more efficiently of HF-pyridine complex[8] (in the case of BrF addition to alkenes, HF-triethylamine has also been used[9]). Our attempts of reaction of phenylacetylene with N-bromosuccinimide and HF-pyridine complex mainly led to 1,2-dibromostyrene. Use of 1,3-dibromo-5,5-dimethylhydantoïn as a brominating agent gave much better results, as could be expected from the reported results concerning "BrF" addition on alkenes[10].



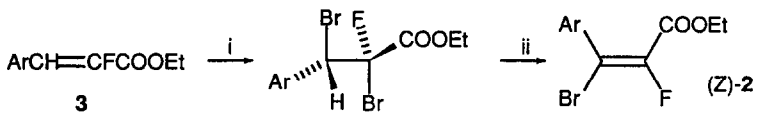
Reaction conditions : DBH 0.5 equiv., w/w 70/30 HF-pyridine complex 1 mL/mmol alkyne, sulfolane, 0°C 10 min then 20°C 20 min.

R	Product	E/Z ratio	Isolated yield	Physical properties
Ph	**1a**	92/8	93%	bp_{18} 102°C
n-C_5H_{11}	**1b**	90/10	65%	bp_{18} 65°C

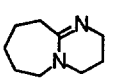
The reaction was totally regioselective leading to the bromine atom on the unsubstituted side of the triple bond and afforded the E isomer with a good stereoselectivity[11]. Use of THF as a solvent instead of sulfolane led mainly to bromine addition.

Synthesis of the disubstituted 1-bromo-2-fluoroalkenes **2** was easily achieved from the corresponding Z unsaturated fluoroesters **3**[12] ; bromination of either E or Z-**3** followed by dehydrobromination under mild conditions (DBU, 20°C) afforded selectively (Z)-**3**[13]. This stereoselectivity was expected from successive anti Br_2 addition and anti HBr elimination on (Z)-**3**. In the case of (E)-**3** it was shown that bromine-catalyzed E to Z isomerization occurred faster than bromine addition, leading to a dibrominated compound identical to that obtained from (Z)-**3**.

Some reported preparations of fluoroalkenes have made a similar use of anti elimination reactions[14].

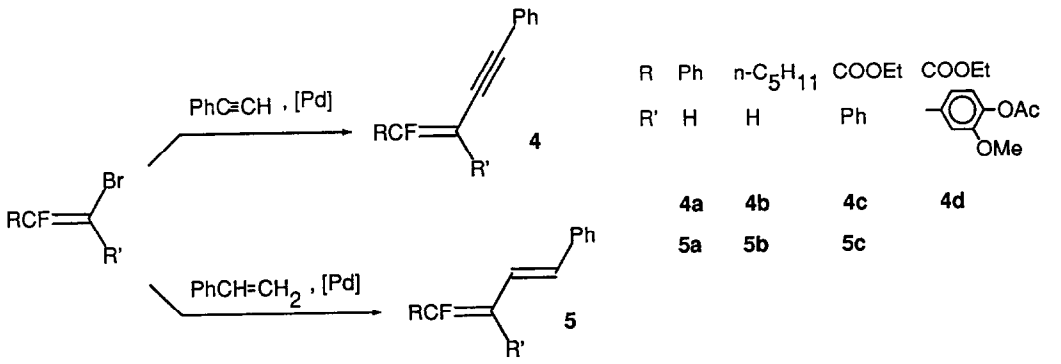


i : Br_2 1.5 equiv., CCl_4, 60°C, 3 h.
ii : DBU 2 equiv, THF, 20°C, 10 mn.

DBU : 

Ar	Product	Z/E ratio	Isolated yield		Physical properties
			Step i	Step ii	
Ph	**2a**	95/5	100%	76%	$bp_{0.01}$ 76°C
3-OMe-4-OAc-Ph	**2b**	98/2	74%	83%	viscous oil, purified by chromatography

The 1-bromo-2-fluoroalkenes obtained by the two methods described above were reacted with styrene or phenylacetylene in the presence of palladium acetate[15] :



Reaction conditions : alkene or alkyne 1-2 equiv., $Pd(OAc)_2$ 0.02 equiv., PPh_3 0.04 equiv., triethylamine, reflux, 3 h.

Starting materials	(E/Z ratio)	Product (E/Z ratio)	Isolated yield[a]
PhC≡CH	**1a** (92/8)[b]	**4a** (92/8)	83%
	1b (90/10)	**4b** (90/10)	74%
	2a (5/95)[c]	**4c** (40/60)	68%
	2b (2/98)[c]	**4d** (45/55)	63%
$PhCH=CH_2$	**1a** (92/8)	**5a** (86/14)	71%
	1b (90/10)	**5b** (82/18)	82%
	2a (5/95)	**5c** (26/74)	95%

[a] column chromatography.
[b] reaction run in n-butylamine instead of triethylamine.
[c] This reaction required harder conditions : $Pd(OAc)_2$ 0.05equiv., 15 h refluxing. Fluoroesters (E) and (Z)-**3**, resulting from reduction of **2a**, were obtained as byproducts.

As could be expected from literature[16] the palladium-catalyzed reactions of styrene involved exclusively the hydrogen atom trans to the phenyl group. The stereochemistry of the fluorinated double bond was retained for bromofluoroalkenes **1**; with Z-**2** substrates a mixture of E and Z isomers was obtained, due to isomerization of the initially formed E product in the reaction medium. In the latter case use of stannic derivatives of alkenes and alkynes should improve the selectivity by allowing milder reaction conditions.

References and notes

1 J. T. Welch, Tetrahedron, 1987, 43, 3123.

2 (a) F. Tellier, R. Sauvêtre and J.-F. Normant, J. Organomet. Chem. 1989, 364, 17. (b) F. Tellier, R. Sauvêtre and J.-F. Normant, J. Organomet. Chem. 1985, 292, 19. (c) F. Tellier, R. Sauvêtre and J.-F. Normant, J. Organomet. Chem. 1986, 303, 309.

3 S. Eddarir, C. Francesch, H. Mestdagh and C. Rolando, Tetrahedron Lett., in press.

4 (a) F. Tellier, R. Sauvêtre and J.-F. Normant, Tetrahedron Lett. 1986, 27, 3147. (b) Z.-Y. Yang and D. J. Burton, Tetrahedron Lett. 1990, 31, 1369.

5 (a) K. Kondo, S. Cottens and M. Schlosser, Chem. Lett. 1984, 2149. (b) M. Schlosser, R. Dahan and S. Cottens, Helv. Chim. Acta 1984, 67, 284. (c) F. Camps, J. Coll, G. Fabrias and A. Guerrero, Tetrahedron. 1984, 40, 2871.

6 F. Camps, G. Fabrias and A. Guerrero, Tetrahedron. 1986, 42, 3623.

7 R. E. A. Dear, J. Org. Chem. 1970, 35, 1703.

8 G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes and J. A. Olah, J. Org. Chem. 1979, 44, 3872.

9 (a) G. Haufe, G. Alvernhe and A. Laurent, Tetrahedron Lett. 1986, 4449. (b) G. Alvernhe, A. Laurent and G. Haufe, Synthesis 1987, 562.

10 (a) D. Y Chi, D. O. Kiesewetter and J. A. Katzenellenbogen, J. Fluorine Chem. 1986, 31, 99. (b) T. Ando, D. G. Cork, M. Fujita, T. Kimura and T. Tatsuno, Chem. Lett. 1988, 1877.

11 The E or Z configuration of the bromofluorostyrenes **1** was assigned from the $^{3}J_{H\text{-}F}$ coupling constant : 14-18 Hz for a cis H-F coupling, 33-36 Hz for a trans coupling.

12 (a) E. Elkik and C. Francesch, Bull. Soc. Chim. France, 1973, 1277; Bull. Soc. Chim. France, 1973, 1281. (b) G. Etemad-Moghadam and J. Seyden-Penne, Bull. Soc. Chim. France, 1985, 448.

13 The configuration of **2** was assigned using ^{1}H NMR NOE experiment : appearance of NOE on the phenyl group when irradiating the methyl group (which was not the case for the other isomer of **2**) indicated Z configuration.

14 (a) L. Eckes and M. Hanack, Synthesis 1978, 217. (b) A. Baklouti and M. M. Chaabouni, J. Fluorine Chem., 1981, 19, 181.

15 The configuration of **4** and **5** was assigned from $^{3}J_{H\text{-}H}$ and $^{3}J_{H\text{-}F}$ coupling constants, and from correlations between ^{13}C chemical shifts of **2**, **3** and **5**.

16 R. F. Heck, Organic Reactions, 1982, 27, 345.

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