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Simple Synthesis of Some Pentafluoropropenyl Derivatives of Pyrimidine and Purine Based on Addition−Elimination Reaction

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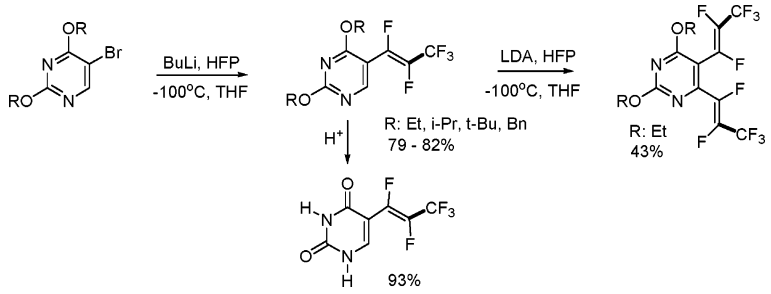

Various pentafluoropropenyl derivatives of pyrimidine and purine bases have been obtained in good to high yield. The procedure involves the reaction of appropriate lithium derivatives prepared from both electron-rich and electron-poor pyrimidines, with the hexafluoropropene at a low temperature, via an addition−elimination process. Organolithiums of pyrimidine and purine bases give addition−elimination products as E/Z mixtures, whereas the products of the reaction of lithium amide of protected inosine with hexafluoropropene contain traces of an addition product as well as the stable perfluoroenamine. The methodology proposed allows a series of perfluorovinyl nucleobases to be obtained quickly and conveniently.

Introduction

Much effort has been devoted to developing new and efficient ways of synthesizing fluorinated compounds because of their interesting properties in applied chemistry and biochemistry.[1] Our interest has been focused on perfluorovinyluracil derivatives and their analogues.[2] They are particularly attractive in regard to their potent biological activities. It has been shown that pyrimidine[3] as well as purine[4] derivatives having unsaturated carbon substituents attached to the ring show significant cytostatic and antiviral activity. In particular, 5-halogenovinyluracils and their nucleoside analogues are characterized by significant and selective biological activities.[5] 5-(2-Bromovinyl)-uracil (BVU) and 5-(2-bromovinyl)-2′-deoxyuridine (BVDU) are effective antiviral agents for herpes simplex virus type 1 (HSV-1,[5a,c] Figure 1). Recently synthesized [2-fluoro-2-(hydroxymethyl)cyclopropylidene]methylpyrimidines exhibit a marked activity against HSV-1 and varicella zoster virus (VZV).[5f]

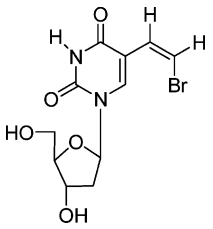

FIGURE 1. BVDU as a selective inhibitory agent for HSV-1.[5a]

(1) (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier: Amsterdam, 1982. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996.

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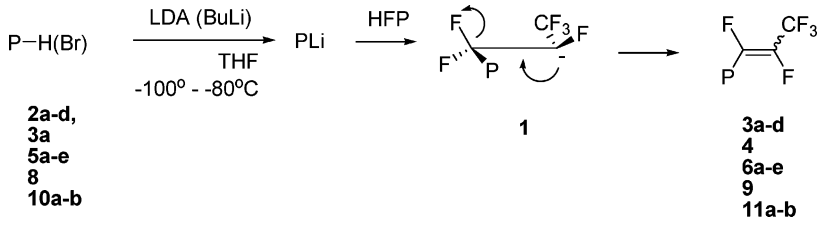
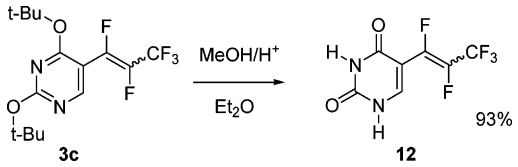
SCHEME 1 [a]



[a] Addition−elimination reactions of various lithiated pyrimidines and purines, PLi, with HFP where P−H(Br) is the appropriate pyrimidine, purine, or pyrimidine bromide.

SCHEME 2



We report herein a simple synthesis of various pentafluoropropenyl pyrimidines via C(5) or C(6) lithiation followed by an addition−elimination reaction with hexafluoropropene (HFP). The classical route to fluoroolefins of the type RCF═CFX, where X, CF_3, and R are aryl or heteroaryl, involves reactions of HFP with aryl Grignard reagents in sealed glass tubes.[6] Alternatively, the fluoroolefins have been prepared by the palladium-catalyzed cross-coupling of perfluoroalkenylzinc reagents with aryl and heteroaryl halides.[7] We also applied this strategy for selected purine derivatives. To the best of our knowledge, only a few examples have been described of the preparation of purine derivatives functionalized with a halogenoalkenyl substituent.[5f,8]

Results and Discussion

Reactions of various lithiated derivatives of either electron-rich or electron-poor pyrimidines with HFP afforded, except in a few cases, the corresponding pentafluoroalkenyl derivatives in moderate to good yields (Scheme 1, Table 1). Thus, the treatment of compounds **2a**−**d**, **3a**, and **5a**−**e** in THF at either −100 °C or −80 °C with butyllithium or LDA generated a solution of the appropriate organolithium to which HFP was added. A standard workup gave pentafluoropropenyl products as mixtures of E and Z isomers. We did not observe any traces of the addition products; the intermediate carbanions **1** exclusively eliminated fluoride to afford products of vinyl substitution. The scope of this method is illustrated and summarized in Table 1.

The E and Z isomers of all synthesized pyrimidines appeared as one spot in TLC analysis using different solvent systems. However, pentafluoropropenyl stereoisomers were easily differentiated by ^{19}F NMR spectroscopy. For aromatic fluoroalkenes with the CF_3CF═CF fragment the trans coupling constant $^3J_{FF}$ is much greater than the cis $^3J_{FF}$.[7b,9] Typical ranges for the couplings in these systems are shown in Figure 2. Chemical shifts of the fluorine atoms connected to the double bond of E isomers also differed significantly from those of Z isomers. Because of such distinctive differences in the values of these coupling constants and chemical shifts, the assignment of all fluorines in the pentafluorovinyl system can be easily established.

2,4-Dialkoxy-5-bromopyrimidines **2a**−**d**, irrespective of the bulkiness of the alkoxy substituent, gave high yields of the pentafluoropropenyl derivatives (entry one). Therefore, the steric bulk of the substituents does not play an important role, and the stability of generated organolithiums arises from the well-known ortho effect of the alkoxy group.[10] Both benzyl and *tert*-butyl derivatives can be easily converted into a fluorinated derivative of C(5) substituted uracil. Particularly, an acidic deprotection of **3c** occurred easily under mild conditions to give uracil **12** in excellent yield (Scheme 2). The steric hindrance at C(5) in compound **3a** significantly reduces the ability of the generated C(6) organolithium to act as a nucleophile, giving olefin **4** in 43% yield. The reaction gave a mixture containing the possible four isomeric products which are rotameric. This led to highly complex NMRs; however, we were able to identify the main products as EE and EZ isomers.

The organolithiums obtained from electron-poor pyrimidines **5a**,**b** gave pentafluoropropenyl derivatives **6a**,**b** in satisfactory yields. However, in contrast to the other derivatives, compound **5a** reacts with HFP to give almost exclusively E isomers, and this enhanced stereoselectivity does not depend on the temperature of the reaction. An increase in temperature from −100 °C to −80 °C upon the addition of HFP (see conditions in entry 3) gave the same E/Z ratio as the addition−elimination product. Generally, the E selectivity could be explained by analyzing the conformations of carbanion **1** leading to the corresponding olefins. The elimination of fluoride from two possible transition states, A and B, of carbanion **1** gives Z and E isomers, respectively.[11] In the state leading to the E isomer, bulky pyrimidyl and CF_3 groups are aligned favorably (anti positions)

(5) (a) Jones, A. S.; Rahim, S. G.; Walker, R. T.; De Clercq, E. *J. Med. Chem.* **1981**, *24*, 759−760. (b) Coe, P. L.; Harnden, M. R.; Jones, A. S.; Noble, S. A.; Walker, R. T. *J. Med. Chem.* **1982**, *25*, 1329−1334. (c) De Clercq, E.; Desgranges, C.; Herdewijn, P.; Sim, I. S.; Jones, A. S.; McLean, M. J.; Walker, R. T. *J. Med. Chem.* **1986**, *29*, 213−217. (d) Ashida, N.; Watanabe, Y.; Miura, S.; Kano, F.; Sakata, S.; Yamaguchi, T.; Suzutani, T.; Machida, H. *Antiviral Res.* **1997**, *35*, 167−175. (e) Onishi, T.; Mukai, C.; Nakagawa, R.; Sekiyama, T.; Aoki, M.; Suzuki, K.; Nakazawa, H.; Ono, N.; Ohmura, Y.; Iwayama, S.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **2000**, *43*, 278−282. (f) Zhou, S.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Drach, J. C.; Matsumi, S.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 6964−6972.

(6) Dmowski, W. *J. Fluorine Chem.* **1981**, *18*, 25−30.

(7) (a) Gillet, J. P.; Sauvetre, R.; Normant, J. F. *Synthesis* **1986**, *7*, 538−543. (b) Heinze, P. L.; Burton, D. J. *J. Org. Chem.* **1988**, *53*, 2714−2720. (c) Morken, P. A.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 1167−1172.

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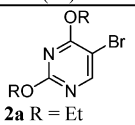
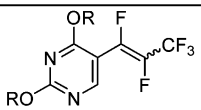
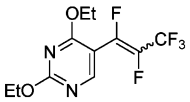
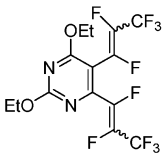
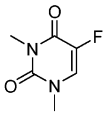
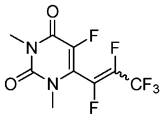
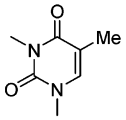
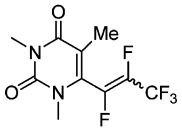
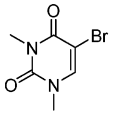
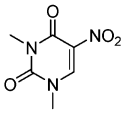
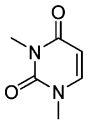
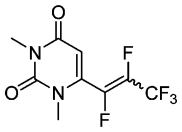
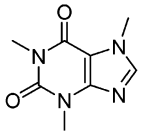
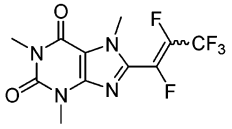
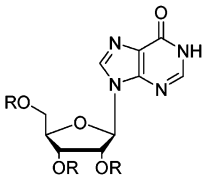
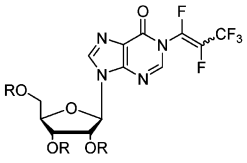
(9) Koroniak, H.; Palmer, K. W.; Dolbier, W. R., Jr.; Zhang, H.-Q. *Magn. Res. Chem.* **1993**, *31*, 748−751.

(10) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Ple, N.; Turck, A.; Queguiner, G.; Glassl, B.; Neunhoeffer, H. *Liebigs Ann. Chem.* **1993**, *6*, 583−585.

(11) Chambers, R. D.; Fuss, R. W.; Spink, R. C. H.; Greenhall, M. P.; Kenwright, A. M.; Batsanov, A. S.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, *10*, 1623−1638.

TABLE 1. Addition−Elimination Reactions of Organolithiums Generated from Appropriate Purine and Pyrimidine Bases (2−10) with HFP.

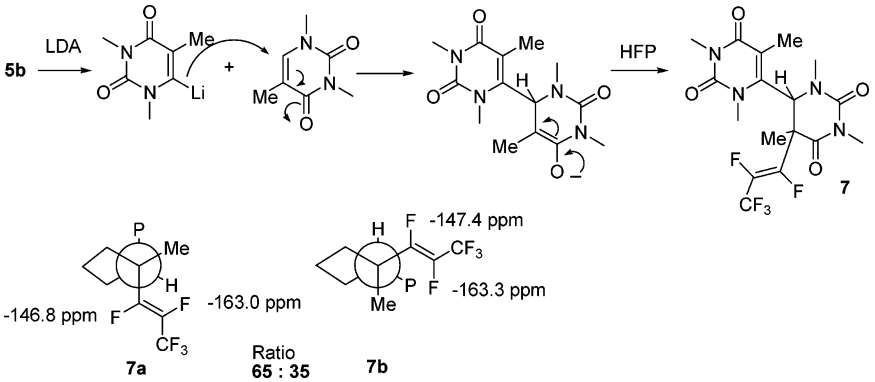
Entry	Reactant P-H (Br)	Conditions	Pentafluoropropenyl product	Yield (%)	E/Z ratio
1	 **2a** R = Et **2b** R = i-Pr **2c** R = t-Bu **2d** R = Bn	BuLi, -100°C	 **3a** R = Et **3b** R = i-Pr **3c** R = t-Bu **3d** R = Bn	81 80 79 82	70/30 68/32 73/27 72/28
2	 **3a**	LDA, -100°C	 **4**	43	a complex mixture
3	 **5a**	LDA, -100°C LDA -80°C	 **6a**	59 54	90/10
4	 **5b**	LDA, -80°C LDA, -100°C	 **6b** (and a side product **7**)	47 of **6b** 15 of **7** 25 of **6b** 23 of **7**	74/26 76/24
5	 **5c**	BuLi, -80°C	no addition-elimination product	-	-
6	 **5d**	LDA, -80°C	no addition-elimination product	-	-
7	 **5e**	LDA, -80°C	 **6e**	< 4	a mixture
8	 **8**	LDA, -80°C	 **9**	17	70/30
9	 **10a** R = Ac **10b R** = Bz	LDA, -80°C	 **11a** R = Ac **11b** R = Bz	20[a] 73	80/20 76/24

[a] ^{19}F NMR yield

and free of steric interaction, whereas in the state leading to the Z isomer, the groups are in syn positions (Figure 3).

Unexpectedly, there is a significant competition reaction of the organolithium derived from **5b**, slightly dependent on temperature (entry 4). Compound **6b** arises from the addition−elimination route. The second product **7** found is a result of 6−6′ dimerization, via the nucleophilic addition of the organolithium to the C(6) center of a second molecule of pyrimidine to give an intermediate enolate which then undergoes an addition−elimination process with HFP. The reaction of the precursory enolate with HFP shows the total stereoselectivity and that stereoisomer E was obtained exclusively. The optional

SCHEME 3 [a]



[a] Proposed mechanism of dimerization of compound **5b** and simplified structures of products **7a**,**b**.

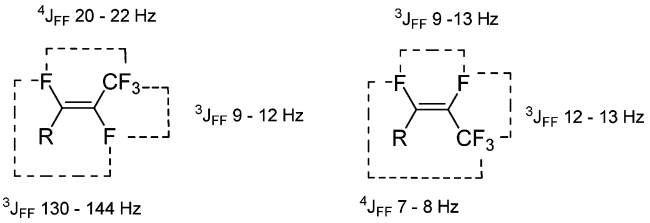


FIGURE 2. Typical coupling constants in pentafluoropropenyl-substituted aromatics.[7b,9]

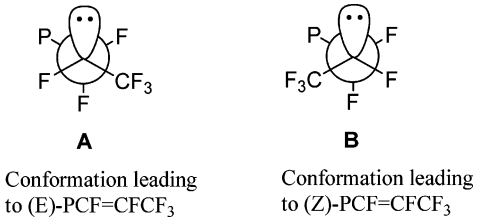


FIGURE 3. Two possible transition states of carbanion **1**.

6−5′ dimerization is excluded because of the absence of vicinal coupling between F and C(6)−H. The structure of compound **7** was confirmed by the ^{19}F NMR and ^{1}H NMR spectrum and by mass spectrometry. Moreover, the detailed analysis of ^{19}F NMR spectra showed that **7** is a mixture of **7a**,**b** which show little difference in chemical shifts. The ratio is 65:35 and is most likely in favor of the **7a** structure (Scheme 3). Attempted reactions of **5c**,**d** with HFP failed; compound **5e** gave traces of the product desired. Treatment of **5d** with LDA at −80 °C, followed by HFP addition, furnished only the 6−6′ dimerization product of this compound (22% yield) without the formation of any pentafluoropropenyl derivative. A comparison of the reactivity of compounds **5b**,**d** leads to an unexpected result, as the lithium derivative of **5b** is the most nucleophilic of the pyrimidines studied, and thus this derivative and not the lithium derivative of **5d** should give dimer quicker, that is, before the HFP addition. Isolation of 1,3-dimethyluracil after acidification of the reaction mixture in the reaction of compound **5c** indicated a formation of organolithium of **5c** which is not sufficiently nucleophilic to react with HFP.

These results prompted us to test the performance of this method on selected purine bases. The obtained C(8) organolithium of **8** and the lithium amide of **10a** reacted with HFP to give the corresponding pentafluoropropenylpurines in poor yields. Comparatively low yields of purine derivatives **9** and **11a** resulted from a low solubility of the substrates and, therefore, from ineffective lithiation of **8** and **10a**. The yield of pentafluoropropenyl inosine **11b** was improved to 73% by using different acyl protecting groups which increased the solubility of **10b**. However, in contrast to the reactions of organolithiums with HFP, some amount of an addition product was observed. Compound **11b** was stable and did not hydrolyze, like fluoroenamines, after the addition of water. Perfluorinated enamines are readily hydrolyzed by being exposed to moist air; they react easily with water to give, in addition−elimination sequences, the corresponding amide and hydrogen fluoride.[12]

Conclusion

We have shown that various pyrimidine and purine derivatives bearing a pentafluoropropenyl group are obtained by the addition−elimination reaction of appropriate organolithiums or lithium amides with HFP in up to 82% yield. Perfluoropropenyl analogues of nucleic acid bases and particularly perfluoropropenyl nucleic acid bases have been prepared in a straightforward way using commercially available HFP.

Experimental Section

General experimental details can be found in Supporting Information.

Representative Procedure: 2,4-Dibenzyloxy-5-(perfluoroprop-1-enyl)pyrimidine (3d). To a stirred solution of *n*-BuLi (1.5 mmol) in anhydrous THF (20 mL) at −100 °C was added dropwise a solution of compound **2d** (1 mmol). The reaction mixture was kept for 30 min at this temperature before a solution of HFP (approximately 3 mmol) in 5 mL of THF was added using a Carrius tube. This mixture was kept at the above temperature for an additional 30 min and then allowed to warm to room temperature over a period of 3 h. The solution was evaporated to dryness under reduced pressure, and 10 mL of water was added. The aqueous solution was extracted with CH_2Cl_2 (2 × 30 mL), and the combined extract was dried over Na_2SO_4. Solvent was removed, and the crude product **3d** was separated by column chromatography (silica gel, hexane, a gradient of hexane/CH_2Cl_2, CH_2Cl_2) to give a mixture of E/Z alkenes. Colorless solid, mp 48−51 °C; yield 346 mg (82%). Anal. Calcd for $C_{21}H_{15}N_2O_2F_5$: C, 59.72; H, 3.58; N, 6.63. Found: C, 59.49; H, 3.49; N, 6.60. IR (KBr) ν: 1720 m (CF═CF), 1685 m, 1648 m, 1598 s, 1553 s, 1435 s, 1361 s, 1207 s, 1145 s cm^{-1}. MS (EI) *m*/*z*: (M^+) 422. HRMS: calcd for $C_{21}H_{15}N_2O_2F_5$, 422.10538; found, 422.10845. ^{1}H NMR ($CDCl_3$):

(12) (a) Li, X.; Pan, H.; Jiang, X. *Tetrahedron Lett.* **1987**, *28*, 3699−3702. (b) Dolbier, W. R., Jr.; Rong, X. X. *J. Org. Chem.* **1997**, *62*, 1576−1577.

δ 5.46−5.50 (m, 4H), 7.36−7.48 (m, 10H), 8.28 (isomer Z) and 8.41 (isomer E) (s, 1H). ^{19}F NMR ($CDCl_3$), isomer E δ −66.6 (dd, ^3J = 11 Hz, ^4J = 22 Hz, 3F), −135.1 (dq, ^3J = 141 Hz, ^4J = 22 Hz, 1F), −164.0 (dq, ^3J = 141 Hz, ^3J = 11 Hz, 1F); isomer Z δ −66.0 (dd, ^3J = 8 Hz, ^4J = 14 Hz, 3F), −110.6 (m, 1F), −149.0 (m, 1F).

Supporting Information Available: Procedures for the preparation of compounds **3a**−**d**, **4**, **6a**,**b**,**e**, **7**, **9**, **11a**,**b**, and **12**; characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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