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A Versatile Synthesis of Fluorinated Uracils in Solution and on Solid-Phase

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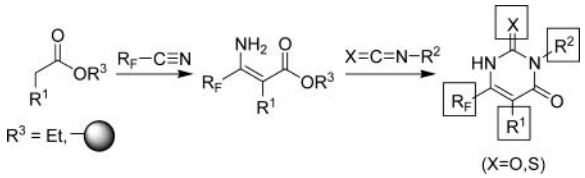
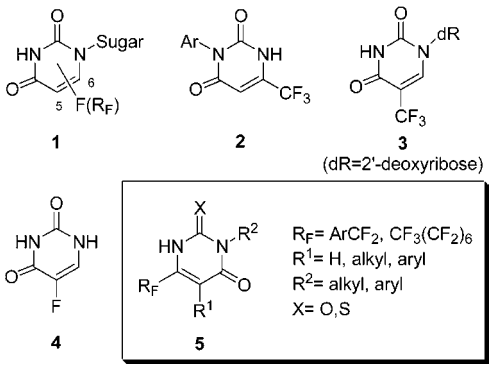
ABSTRACT



An efficient and convenient two-step synthesis of new fluorinated uracils is described. The first step involves the condensation of an ester enolate with a fluorinated nitrile to furnish fluorinated *β*-enamino esters. In turn, these compounds react with organic isocyanates or isothiocyanates to give C-6 fluorinated uracils or thiouracils, respectively, in excellent yields. This synthesis has been successfully adapted to solid-phase conditions with high diversity, thereby facilitating the creation of small (thio)uracil libraries.

The design of antimetabolites with structures similar to those of nucleosides and nucleotides has become a very attractive field of research due to the essential role that nucleic acids play in metabolic processes. The structures can be modified to affect the base ring, the sugar, or both. For some time now, analogues of nucleosides have been successfully used as antineoplasic and antiviral agents.[1] In this particular area, much attention has been devoted to the preparation of nucleosides with pyrimidinic bases and their derivatives, especially uracils with fluorinated groups in positions 5 or 6 of the ring (see structure **1** below). While compounds in which the substituent appears on C-5 have applications as antitumoral agents,[2] those in which it appears on C-6 are used mostly as herbicides (see *N*-aryl-6-trifluoromethyluracil **2** below), insecticides, and acaricides.[3,4]

One important example of a fluorinated nucleoside is Trifluridine (5-trifluoromethyl-2′-deoxyuridine, **3**), a potent inhibitor of thymidylate synthase,[1] which has been used as an antiviral agent against *Herpes simplex* infections. Modifications to the nitrogen base of this compound give rise to other significant antimetabolites which are generally active only after their in vivo conversion to nucleotides. A representative example is 5-fluorouracil **4**, which displays potent anticarcinogenic activity.[1]



Combinatorial chemistry has become a powerful tool for the discovery of new bioactive compounds.[5] Solid-phase

† X-ray analysis.

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(2) Ozaki, S. *Med. Res. Rev.* **1996**, *16*, 51−86.

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(4) Yagi, K.; Akimoto, K.; Mimori, N.; Miyake, T.; Kudo, M.; Arai, K.; Ishii, S. *Pest Manag. Sci.* **2000**, *56*, 65−73.

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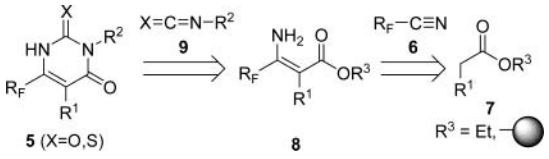
organic synthesis is now widely accepted as a key methodology for the preparation of large numbers of potentially bioactive compounds without tedious and time-consuming purification steps. For this reason, the development of new strategies for carbon−carbon and carbon−nitrogen bond formation on solid support has become a necessity.[6] Moreover, the solid-phase synthesis of organofluorinated compounds has been studied only infrequently, in stark contrast with that of nonfluorinated compounds.

In this paper,[7] we describe a novel and efficient synthetic strategy for the preparation of C-6 fluoroalkylated uracils **5** from fluorinated nitriles **6** and esters **7** via the corresponding fluorinated β-enamino esters **8** (Scheme 1, retrosynthetic analysis) with both solution- and solid-phase techniques.

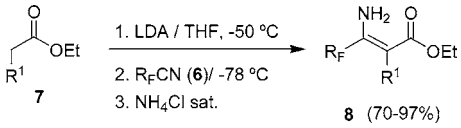
Scheme 1



In our synthesis, one aliphatic (**6c**) and two aromatic (**6a**, **6b**) fluorinated nitriles were used as starting materials. While perfluorooctanenitrile (**6c**), is commercially available, **6a** (2,2,difluoro-3-phenylethanenitrile)[8,9] and **6b** (2,2,difluoro-3-α-naphthylethanenitrile)[9] were prepared by slightly modifying[10] procedures previously described in the literature.

In the first step of our synthesis, fluorinated nitriles **6** were transformed into their corresponding fluorinated β-enamino esters through reaction with enolates of esters **7**. Although this reaction, known as the Blaise reaction when performed with zinc enolates,[11] has been previously used with nonfluorinated nitriles, it often displays serious drawbacks; in most cases, the yields are only low to moderate and the reaction itself is not general in that its result is often dependent on the structures of the reactants.[12] In contrast, fluorinated nitriles **6** reacted smoothly and consistently, affording excellent yields (Table 1) to give β-enamino esters **8**.

Table 1. Results for the Preparation of Fluorinated β-Enamino Esters **8** from Nitriles **6** and Esters **7**



entry	6	7	R^1	R_F[a]	8	yield (%)[b]
1	**6a**	**7a**	H	$CF_2C_6H_5$	**8a**	97
2	**6a**	**7b**	CH_3	$CF_2C_6H_5$	**8b**	87
3	**6a**	**7c**	C_6H_5	$CF_2C_6H_5$	**8c**	93
4	**6b**	**7a**	H	$CF_2(\alpha\text{-}C_{10}H_7)$	**8d**	70
5	**6c**	**7a**	H	$CF_3(CF_2)_6$	**8e**	91

[a] α-$C_{10}H_7$ = α-naphthyl. [b] Yields for purified products.

Specifically, esters **7** (R^3 = Et) were treated with 1.25 equiv of LDA at −50 °C to afford their enolates, which were then condensed with various fluorinated nitriles **6** at −78 °C, which gave β-enamino esters **8** in yields ranging from 70 to 97% (Table 1) after hydrolysis. The method appears to be general, with all compounds appearing exclusively in the enamino form. In this fashion, a variety of compounds **8** was prepared (see Table 1).

In the second step, the β-enamino esters **8** were condensed with either isocyanates or isothiocyanates to furnish the corresponding uracils. First, compounds **8** were treated with 1.8 equiv of NaH in DMF at 0 °C for 30 min after which time 1.2 equiv of the iso(thio)cyanates **9** were added. This led to the N-acylation of the enamine, which then underwent a cyclization to yield the (thio)uracils **5**. The yields were varied; when isocyanates were used, the corresponding uracils were obtained in good yields (64−90%, Table 2), whereas the thiouracils were obtained in somewhat lower yields (64−70%). All in all, 20 new fluorinated (thio)uracils **5** were easily prepared in only two steps and in high yields from fluorinated nitriles **6**, esters **7**, and iso(thio)cyanates **9**.

Compound **5q**, the structure of which displays interesting potential for coupling reactions, could not be prepared by merely brominating the corresponding uracil **5a**. Rather, the preparation of this compound required a brominated enamino ester (entry 17, Table 2), which was prepared by brominating the corresponding enamino ester **8a** with NBS.[13]

The structure of these compounds was confirmed through X-ray diffraction analysis of **5e** (Figure 1, ORTEP diagram).

The high yields of this two-step synthesis and the ease with which diversity can be introduced into the molecule led us to believe that this process might be a good candidate for solid-phase methodology. The diversity can be introduced into groups R^1 (from different esters), R^2 (from different iso(thio)cyanates), R_F (from different fluorinated nitriles), and X (using either an isocyanate or an isothiocyanate). This greatly facilitates the creation of small libraries of fluorinated uracils for their subsequent biological evaluation. To the best of our knowledge, there is only one recent precedent of the

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(6) For recent reviews, see: (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (b) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

(7) Presented in part (FLUO0006) at the 226th ACS National Meeting, Sept 7−11, 2003, New York.

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(9) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883−2887.

(10) We obtained improved chemical yields for **6b** (91 vs 61%) using 2.2 equiv of Deoxofluor (dimethoxyethylaminotrifluorosulfurane) at room temperature for 24 h instead of DAST. See: Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048−7054.

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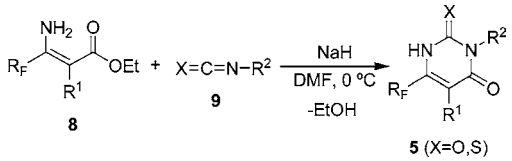
(12) (a) Hiyama, T.; Kobayashi, K. T. *Tetrahedron Lett.* **1982**, *23*, 1597−1600. (b) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833−3835. (c) Lee, A. S.-Y.; Cheng, R.-Y. *Tetrahedron Lett.* **1997**, *38*, 443−446.

(13) Fustero, S.; Salavert, E.; Sanz-Cervera, J. F.; Román, R.; Fernández-Gutiérrez, B.; Asensio, A. *Lett. Org. Chem.* **2004**, *1*, 93−98.

Table 2. Results for the Reaction of Compounds **8** with Iso(thio)cyanates **9**



entry	R_F	R^1	R^2	X	5	yield (%)[a]
1	$CF_2C_6H_5$	H	*p*-F−C_6H_4	O	**5a**	90
2	$CF_2C_6H_5$	H	*p*-CH_3O−C_6H_4	O	**5b**	84
3	$CF_2C_6H_5$	H	*m*-CF_3−C_6H_4	O	**5c**	76
4	$CF_2C_6H_5$	H	C_6H_5	O	**5d**	86
5	$CF_2C_6H_5$	H	*sec*-C_4H_9	O	**5e**	71
6	$CF_2C_6H_5$	H	C_2H_5	O	**5f**	78
7	$CF_2C_6H_5$	H	(*S*)-C_6H_5(Me)CH	O	**5g**	90
8	$CF_2C_6H_5$	H	*p*-(COOEt)−C_6H_4	O	**5h**	75
9	$CF_2C_6H_5$	H	CH_2COOEt	O	**5i**	73
10	$CF_2C_6H_5$	H	*p*-F−C_6H_4	S	**5j**	64
11	$CF_2C_6H_5$	H	*p*-CH_3−C_6H_4	S	**5k**	68
12	$CF_2C_6H_5$	H	*p*-NO_2−C_6H_4	S	**5l**	70
13	$CF_2C_6H_5$	H	C_2H_5	S	**5m**	66
14	$CF_2C_6H_5$	CH_3	*p*-F−C_6H_4	O	**5n**	82
15	$CF_2C_6H_5$	CH_3	*m*-CF_3−C_6H_4	O	**5o**	79
16	$CF_2C_6H_5$	C_6H_5	*p*-F−C_6H_4	O	**5p**	85
17	$CF_2C_6H_5$	Br	*p*-F−C_6H_4	O	**5q**	78
18	CF_2(α-$C_{10}H_7$)	H	*p*-F−C_6H_4	O	**5r**	64
19	$CF_3(CF_2)_6$	H	*p*-F−C_6H_4	O	**5s**	82
20	$CF_3(CF_2)_6$	H	C_6H_5	O	**5t**	84

[a] Yields of purified products.

synthesis of uracils in the solid phase, but in that case the diversity introduced was minimal and only mixtures of isomeric nonfluorinated uracils were obtained.[14] Furthermore,

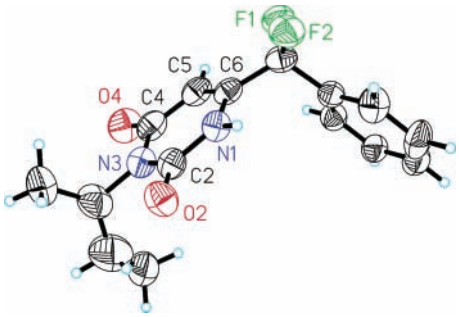
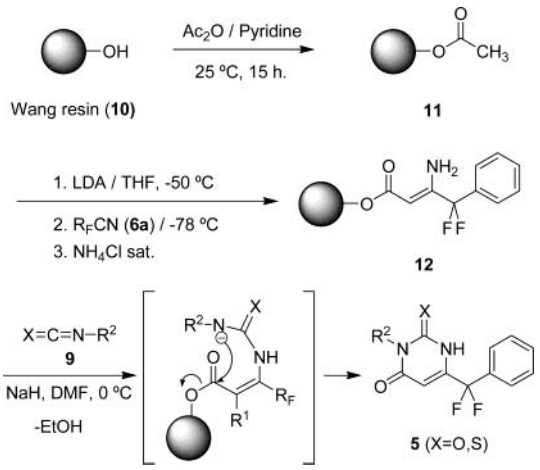


Figure 1. Ellipsoid plot of compound **5e** (50% probability level).

the literature contains very few examples of solid-phase parallel syntheses of fluorinated compounds,[15] a fact that makes the search for new solid-phase syntheses for organofluorinated compounds even more appealing.

Our solid-phase synthesis of fluorinated uracils as outlined in Scheme 2 is parallel to that described above. First, Wang

Scheme 2



resin **10** (0.83 mmol/g loading) was loaded with acetic anhydride in the presence of pyridine at room temperature for 15 h, followed by washings with DMF, CH_2Cl_2, and MeOH to afford the acetylated Wang resin **11** (0.80 mmol/g loading, Scheme 2). Next, resin **11** was reacted with an excess (3 equiv) of LDA in THF at −50 °C for 1.5 h to generate the enolate, which was then treated with difluorophenylacetonitrile **6a** (3 equiv) at −78 °C for 3 h.

After hydrolysis with aqueous NH_4Cl solution and washings, the coupling was confirmed by means of FT-IR spectroscopy of the resin, which showed the appearance of two new characteristic N−H tension bands, which correspond to the new amino group at 3523 and 3417 cm^{-1}, as well as bands for the carboxyl (C═O tension, 1731 cm^{-1}) and enamino groups (C═C tension, 1679 cm^{-1}). These bands confirmed the presence of a *β*-enamino ester bound to the resin in **12**.

Resin **12** was then treated with 3.6 equiv of NaH in DMF at 0 °C for 30 min, followed by addition of 2.4 equiv of several different iso(thio)cyanates **9** and orbital stirring for 15 h. This caused not only the formation of the uracils but also their cleavage from the resin, which precluded the need for a specific cleavage step. This cyclization−cleavage strategy thus combines linker cleavage and ring formation in a single reaction step.[16] After extraction of the uracil with EtOAc and removal of the solvents in a vacuum, the C-6-difluorobenzylated uracils **5** (X = O) were obtained in satisfactory yields (67−89%) and with high purity (65−99%) (Figure 2). In contrast, the corresponding C-6-difluorobenzylated thiouracils **5** (X = S) prepared with thioisocyanates instead of isocyanates were obtained in lower yields (55−63%) and with lower purity (61−73%). This result was not surprising, as our solution synthesis of the thiouracils had

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(15) See, for instance: (a) Vidal, A.; Nefzi, A.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8268−8272. (b) Volonterio, A.; Chiva, G.; Fustero, S.; Piera, J.; Sánchez Roselló, M.; Sani, M.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 7019−7022.

(16) Bräse, S.; Dahmen, S. In *Handbook of Combinatorial Chemistry*; Nicolau, K. C., Hanko, R., Hartwig, W., Eds; Wiley-VCH: Weinheim, 2002; Vol. 1, pp 59−169.

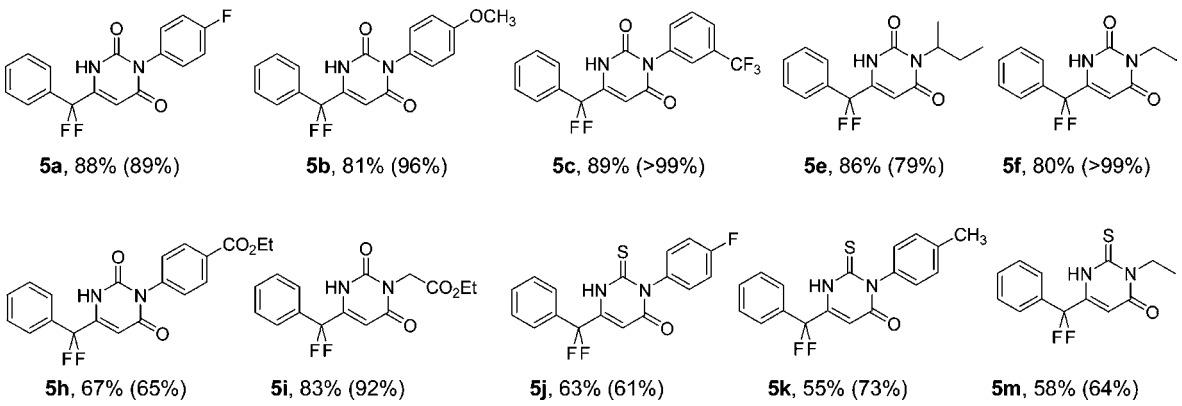

Figure 2. Uracils and thiouracils **5** prepared with solid-phase methodology. Shown are yields and, in parentheses, purities of the crude products after cyclative cleavage before purification.

already shown clearly lower yields than for the uracils. In any event, a variety of (thio)uracils were prepared through solid-phase synthesis (Scheme 2 and Figure 2). Although in our example only one ester and one nitrile were used, the utilization of different esters and nitriles would allow for easy preparation of ample libraries of (thio)uracils.

In conclusion, we have described a simple and efficient synthesis of fluorinated (thio)uracils that starts with an ester and a fluorinated nitrile to furnish the corresponding fluorinated β-enamino esters, which in turn react with iso-(thio)cyanates to yield the desired products. The solution method has been successfully adapted to solid-phase methodology with high diversity, which allows for the first time the creation of extensive fluorinated uracil and thiouracil libraries in a straightforward manner.

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Supporting Information Available: Spectroscopic data, experimental details for compounds **5a**−**t**, **8a**−**e**, **11**, and **12**, and crystal data for compound **5e** in CIF format (11 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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