COMMUNICATION

ChemComm
www.rsc.org/chemcomm

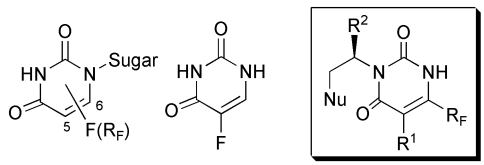
An efficient synthesis of new fluorinated uracil derivatives†

Santos Fustero,* Esther Salavert, Juan F. Sanz-Cervera, Julio Piera and Amparo Asensio
Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain.
E-mail: Santos.Fustero@uv.es; Fax: +34 963 544 339; Tel: +34 963 544 279

Received (in Cambridge, UK) 20th January 2003, Accepted 12th February 2003
First published as an Advance Article on the web 27th February 2003

A series of potentially biologically active fluorinated uracil derivatives has been prepared in three steps from oxazolines and fluorinated nitriles with good chemical yields.

Because of the essential role that nucleic acids play in metabolic processes, much emphasis has been placed on the design of antimetabolites with a similar structure. For instance, analogs of nucleosides have been successfully used as antineoplasic and antiviral agents.[1] The structures can be modified to affect the base ring, the sugar, or both. Thus far, most research in this area has focused on the preparation of nucleosides or their derivatives with pyrimidinic bases, and particularly uracils with fluorinated groups in position 5 or 6 of the ring (see structure **1** below). While compounds in which the substituent appears on C-5 have found applications as antitumoral agents,[2] those in which it appears on C-6 act mostly as herbicides, insecticides, and acaricides.[3] An important example of the former is 5-fluorouracil **2**, which displays potent anticarcinogenic activity.[1]



1 **2** **3**

In this paper, we describe a convenient and efficient synthetic strategy for the preparation of new C-6 fluoroalkylated N-3 alkylated pyrimidin-2,4-diones **3** from 2-alquil-Δ²-oxazolines **4** and fluorinated nitriles **5**.

In our synthesis we used two commercial oxazolines, namely 2-methyl-Δ²-oxazoline (**4a**) and 2-ethyl-Δ²-oxazoline (**4b**), as well as (*R*)-2-methyl-4-phenyl-Δ²-oxazoline (**4c**) (Scheme 1). This last compound, although not yet commercially available, can be easily prepared following methods described in the literature.[4] In addition, both aromatic and aliphatic fluorinated nitriles **5** were also used as starting materials. While all the aromatic fluorinated nitriles were commercially available, only one of the aliphatic nitriles (**5d**, perfluorooctanenitrile) could be purchased. For that reason, **5a**,[5] **5b**,[5,6] and **5c**[6] were prepared with previously described procedures.

First, 2-alkyl-Δ²-oxazolines **4** were treated with 1 equiv. of LDA at −78 °C to afford their enolates. These were then condensed with different fluorinated nitriles **5**, which after hydrolysis† gave a variety of chiral and achiral oxazolin-protected β-enamino acids **6** in yields ranging from 60 to 93% (Scheme 1 and Table 1).‡§

Next, the condensation of the protected, fluorinated β-enamino acids **6** with either phosgene or triphosgene[7]¶ yielded a mixture of isomeric oxazolopyrimidinones **7** and **8** in yields ranging from 70 to 95% (Scheme 1 and Table 2). In all cases, the pyrimidinone derivatives **8** were the predominant products of the condensation reaction. In more than half of the cases, both oxazolopyrimidinones **7**§ and **8**§ were isolated and purified, but in some instances only **8** was isolated (entries 2, 3, 5, 6, and 9).The results of an assay with a non-fluorinated compound (entry 11, Table 2) seem to indicate that the outcome of this reaction is not dependent on whether the starting oxazoline β-enamino acid is fluorinated or not.

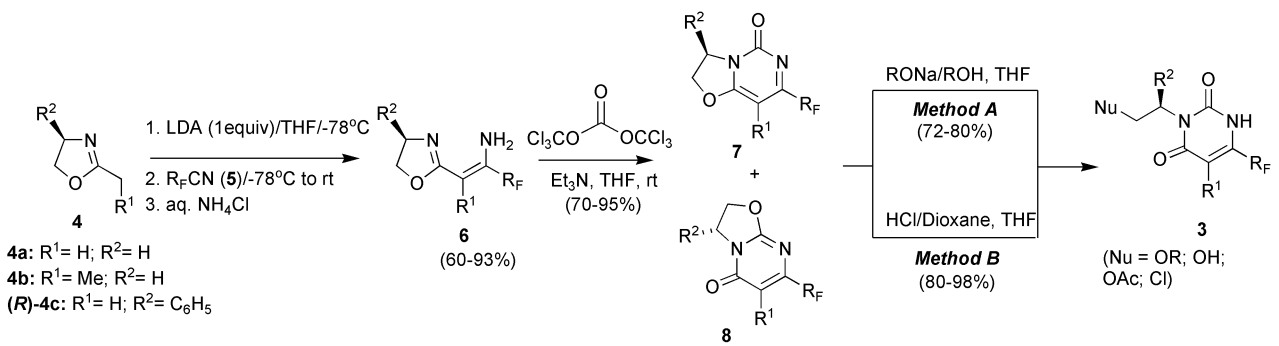
Because of the structural similarities between isomeric compounds **7** and **8**, their structural elucidation was only possible through X-ray diffraction analysis. The results for

Table 1 Results for the reaction between oxazolines **4** and nitriles **5**

Entry	4	5	R^1	R^2	R_F[a]	Product	Yield (%)[b]
1	**4a**	**5a**	H	H	CF_2(β-$C_{10}H_7$)	**6a**	84
2	**4a**	**5b**	H	H	CF_2(α-$C_{10}H_7$)	**6b**	80
3	**4a**	**5c**	H	H	$CF_2C_6H_5$	**6c**	70
4	**4a**	**5d**	H	H	$(CF_2)_6CF_3$	**6d**	60
5	**4b**	**5a**	Me	H	CF_2(β-$C_{10}H_7$)	**6e**	76
6	**4c**	**5a**	H	C_6H_5	CF_2(β-$C_{10}H_7$)	**6f**	74
7	**4c**	**5b**	H	C_6H_5	CF_2(α-$C_{10}H_7$)	**6g**	65
8	**4a**	**5e**	H	H	2,4-$F_2C_6H_3$	**6h**	70
9	**4a**	**5f**	H	H	*p*-$CF_3C_6H_4$	**6i**	93
10	**4a**	**5g**	H	H	*p*-FC_6H_4	**6j**	70
11	**4c**	**5g**	H	C_6H_5	*p*-FC_6H_4	**6k**	72

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

† Electronic supplementary information (ESI) available: general procedures for the preparation of compounds **3**, **6**, **7**, **8** and **9**. See http://www.rsc.org/suppdata/cc/b3/b300796k/



Scheme 1 Synthetic sequence for the preparation of fluorinated uracil derivatives **3**.

DOI: 10.1039/b300796k

compounds **7h** and **8k** indicated that, whereas compound **7h** displayed a fluorinated oxazolo[3,2-c]pyrimidone structure, **8k** was an oxazolo[3,2-a]pyrimidone.‖

Finally, **7** and **8** underwent an oxazoline ring-opening reaction with several nucleophiles under either basic (Method A) or acidic (Method B) conditions, to give compounds **3**§ (Scheme 1 and Table 3) in good to excellent yields.[8,9].**

It is worth noting that uracil **3** was obtained as the only reaction product regardless of whether compound **7**, **8** or a mixture thereof were used. In all examples, the ring-opening reaction in acidic medium was faster (0.5–2 h) and produced better yields (80–98%) than the corresponding reactions under basic conditions (5–7 h; 72–80%).

To confirm the validity of our approach as a general method of introducing a nucleophile into these systems, we attempted the incorporation of the cyclic amine *t*-butyl 1-piperazinecarboxylate†† (Scheme 2). Thus, **7g** and **8g** reacted with of *N*-BOC-piperazine at 100 °C for 24 h, to yield the desired compound **9** § in 80% yield, proving the validity of our approach.

Table 2 Results for the reaction of compounds **6** with triphosgene

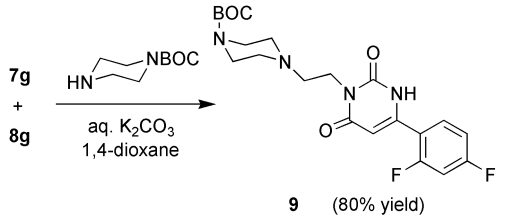
Entry[a]	R^2	R_F[b]	Yield (%)[c]	**7**/**8**[d]	Isolated products
1	H	$CF_2(\beta\text{-}C_{10}H_7)$	80	30/70	**7a**, **8a**
2	H	$CF_2(\alpha\text{-}C_{10}H_7)$	82	10/90	**8b**
3	H	$CF_2C_6H_5$	72	5/95	**8c**
4	H	$(CF_2)_6CF_3$	70	10/90	**7d** + **8d**[e]
5	H	$CF_2(\beta\text{-}C_{10}H_7)$	85	20/80	**8e**
6	(*R*)-Ph	$CF_2(\beta\text{-}C_{10}H_7)$	90	10/90	**8f**
7	H	$2,4\text{-}F_2C_6H_3$	95	35/65	**7g**, **8g**
8	H	$p\text{-}CF_3C_6H_4$	89	30/70	**7h**, **8h**
9	H	$p\text{-}FC_6H_4$	82	35/65	**8i**
10	(*R*)-Ph	$p\text{-}FC_6H_4$	87	30/70	**7j**, **8j**
11[f]	H	$p\text{-}CH_3C_6H_4$	79	30/70	**7k**, **8k**

[a] In all cases, R^1 = H, except in entry 5, where R^1 = CH_3. [b] $\beta\text{-}C_{10}H_7$ = β-naphtyl; $\alpha\text{-}C_{10}H_7$ = α-naphtyl. [c] Yield of **7** + **8** crude mixture. [d] Proportion **7**/**8** in the crude reaction mixture, as determined through ^1H and/or ^{19}F NMR analysis. [e] The separation of this mixture was not possible. [f] Non-fluorinated derivative.

Table 3 Results for the ring-opening reaction of pyrimidinones **7** and/or **8** with nucleophiles. Synthesis of uracils **3**

Entry[a]	R^2	R_F	Nu	Method[b]	Yield (%)[c]	**3**
1	H	$CF_2(\beta\text{-}C_{10}H_7)$	Cl	B	98	**3a**
2	H	$CF_2(\alpha\text{-}C_{10}H_7)$	OMe	A	80	**3b**
3	H	$CF_2C_6H_5$	Cl	B	96	**3c**
4	H	$(CF_2)_6CF_3$	OH	A	72	**3d**
5	H	$CF_2(\beta\text{-}C_{10}H_7)$	Cl	B	95	**3e**
6	(*R*)-Ph	$CF_2(\alpha\text{-}C_{10}H_7)$	Cl	B[d]	92	**3f**
7	H	$2,4\text{-}F_2C_6H_3$	OH	A	75	**3g**
8	H	$2,4\text{-}F_2C_6H_3$	Cl	B	91	**3h**
9	H	$p\text{-}CF_3C_6H_4$	OMe	A	78	**3i**
10	H	$p\text{-}CF_3C_6H_4$	OH	A	72	**3j**
11	H	$p\text{-}FC_6H_4$	OEt	A	78	**3k**
12	(*R*)-Ph	$p\text{-}FC_6H_4$	Cl	B[d]	92	**3m**
13	H	$p\text{-}CH_3C_6H_4$	OAc	A	75	**3n**
14	H	$p\text{-}CH_3C_6H_4$	Cl	B	80	**3o**

[a] In all cases, R^1 = H, except in entry 5, where R^1 = CH_3. [b] Method A: RONa/ROH, THF, reflux. Method B: HCl/dioxane, THF, rt. [c] Yield of purified product. [d] At 50 °C.



Scheme 2 Preparation of compound **9**.

In summary, we have developed a straightforward synthesis of new fluorinated uracil derivatives **3** from oxazolines **4** and fluorinated nitriles **5** in only three steps and with good chemical yields. The ring-opening reaction of intermediate oxazolopyrimidinones **7** and **8** by a number of different nucleophiles allows the preparation of a variety of interesting analogues with potential biological activity.

We thank the Ministerio de Ciencia y Tecnología of Spain for financial support (PPQ2000–0824). E.S. and J.P. thank the Generalitat Valenciana and the Ministerio de Educación y Cultura of Spain, respectively, for predoctoral fellowships.

Notes and references

‡ These compounds appeared exclusively in the enamino form.

§ Compounds **3**, **6**, **7**, **8** and **9** showed spectroscopic (^1H, ^{19}F, ^{13}C-NMR) and HRMS data in agreement with their structures.

¶ In our synthesis, substituting phosgene for triphosgene did not affect the yields; thus, since triphosgene is easier to handle, we used one molar equivalent of triphosgene in each reaction. An excess of triphosgene did not influence the yields and proportion of the products.

‖ Full details of the X-ray structures of **7h** and **8k** will be published in a full account of this work.

** It is noteworthy that when treated with a base (*e.g.* aq. K_2CO_3/dioxane), those compounds **3** in which Nu = Cl revert to a mixture **7** + **8** in proportions similar to those when they were obtained from **8**.

†† We chose this compound not only because it would allow for introduction of other groups after *N*-BOC deprotection, but also because analogous systems are present in several pharmaceutically significant compounds, for example Ketanserine (see ref. 9), a $5\text{-}HT_2$ serotonin antagonist drug, and Zopiclone, a recently discovered ansiolytic drug which acts as a benzodiazepine receptor agonist (see ref. 10).

1 *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, ed. C. K. Chu and D. C.Baker, Plenum Press, New York, 1993.
2 S. Ozaki, *Med. Res. Rev.*, 1996, **16**, 51–86.
3 As examples, see: T. Yoshimoto and S. Yuzuru, Eur. Pat. Appl. N° 1122244 A1, 2001; G. Theodoridis and S. Crawford (FMC Corporation, USA) N° 6277847 B1, 2001; V. Kamesweran, (American Cyanamid Co. USA) N° 6191275 B1, 2001; K. Yagi, K. Akimoto, N. Mimori, T. Miyake, M. Kudo, K. Arai and S. Ishii, *Pest Manag. Sci.*, 2000, **56**, 65–73.
4 K. Kamata, I. Agata and A. I. Meyers, *J. Org. Chem.*, 1998, **63**, 3113–3116.
5 C. C. Kotoris, M.-J. Chen and S. Taylor, *J. Org. Chem.*, 1998, **63**, 8052–8057.
6 W. J. Middleton and E. M. Bingham, *J. Org. Chem.*, 1980, **45**, 2883–2887.
7 For a review see: L. Cotarca, P. Delogu, A. Nardelli and V. Sunji, *Synthesis*, 1996, 553–576.
8 R. Lis, T. K. Morgan, A. J. Marisca, R. P. Gómez, J. M. Lind, D. D. Davey and G. B. Philips and M.E. Sullivan, *J. Med. Chem.*, 1990, **33**, 2883–2891; C. Agami, L. Dechoux, L. Hamon and M. Melaimi, *J. Org. Chem.*, 2000, **65**, 6666–6669 and references cited therein.
9 J. L. Herndon, A. Ismaiel, P. Ingher, M. Teitle and R. A. Glennon, *J. Med. Chem.*, 1992, **35**, 4903–4910.
10 S. Noble, H. Langtry and H. M. Lamb, *Drugs*, 1998, **55**, 277–302.