Journal of Fluorine Chemistry 154 (2013) 73–79

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of fluorinated pyrimidinones

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ARTICLE INFO

Article history:
Received 22 May 2013
Received in revised form 25 June 2013
Accepted 30 June 2013
Available online 10 July 2013

Keywords:
Heterocycles
Isocyanates
Cyclization
Pyrimidinones
Coupling reaction

ABSTRACT

A method for the construction of fluorinated pyrimidinones based on the reaction of cyanodifluoromethyl-substituted amines with isocyanates is described. The use of *ortho*-iodophenylisocyanate in this reaction followed by copper catalyzed intramolecular amination affords fluorinated fused heterocycles – 4-fluoropyrimido[1,6-*a*]benzimidazol-1(2*H*)-ones.

1. Introduction

The ability of fluorine to modify biological properties of organic compounds has sparked the interest to partially fluorinated molecules [1]. Since heterocycles are ubiquitous in pharmaceuticals, compounds containing one or two fluorine atoms in the ring have gained significant attention in medicinal chemistry [2]. Among diverse classes of fluorinated heterocycles, derivatives of pyrimidinones and pyrimidinediones have become particularly important exhibiting anti-cancer, antiviral, and antifungal activity [1b,2b,3,4]. Fluorinated uracil and cytosine were the first examples of successful drugs of this type followed by numerous analogs (Fig. 1). The conventional synthetic approach toward mono- and difluorinated pyrimidinones involves fluorination of parent heterocycles using elemental fluorine or O–F and N–F reagents [5,6]. An alternative method for the preparation of difluoro-substituted pyrimidinediones (dihydrouracils) based on building-block strategy was suggested, but the method has a limited scope [7].

Herein we describe a general approach for making fluorinated six-membered heterocycles based on coupling of three components – imines, difluoroacetonitrile carbanion, and a reagent with electrophilic multiple bond (Scheme 1). Thus, we have recently described that imines react with difluoro(trimethylsilyl)acetonitrile leading to products **1** [8]. The latter compounds possess a nucleophilic amine and an electrophilic nitrile group, and reaction of this 1,4-bipolar system with an appropriate double or triple bond is expected to afford heterocyclic molecule. In this work we demonstrate this concept by using isocyanates as the AB component [9]. The process affords pyrimidinones (A = CO, B = NR^3) bearing *N*-unsubstituted imino-function, which can be further exploited for constructing more complex heterocyles.

2. Results and discussion

First, the reactions of amines **1** with isocyanates were investigated (Table 1). Due to the presence of fluorine atoms

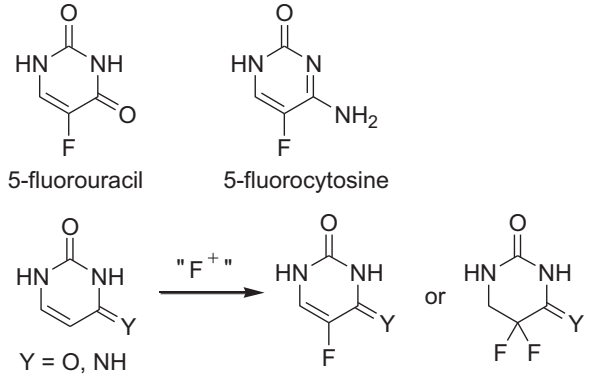

Fig. 1. Fluorinated pyrimidinones.

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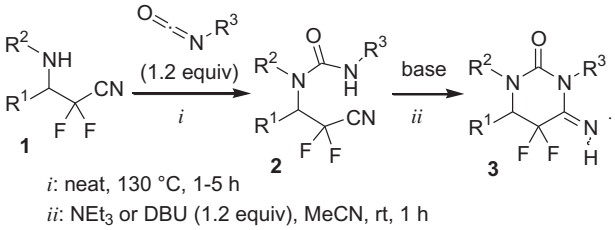
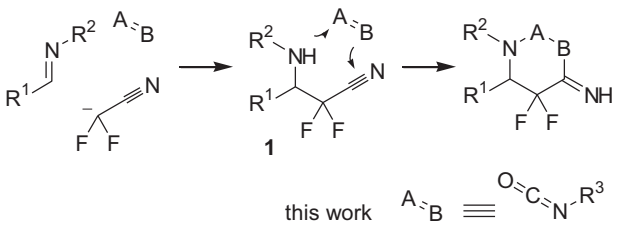
http://dx.doi.org/10.1016/j.jfluchem.2013.06.018

Table 1
Reaction of 3-amino-2,2-difluoropropanenitriles with isocyanates.

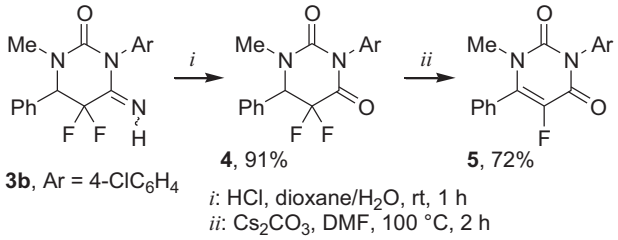


R^1	R^2	R^3	1	2	Time for **1**→**2**, h	Yield of **2**,[a] %	3	Base	Yield of **3**,[a] %
Ph	Me	Ph	**1a**	**2a**	3	95	**3a**	NEt_3	95
Ph	Me	4-ClC_6H_4	**1a**	**2b**	1	95	**3b**	NEt_3	97
	Bn	Ph	**1b**	**2c**	3	83	**3c**	NEt_3	98
	Bn	4-ClC_6H_4	**1b**	**2d**	3	80[b]	**3d**	NEt_3	99
Ph	Me	Pr	**1a**	**2e**[c]	5	93	**3e**	DBU	78

[a] Isolated yield.
[b] Additionally, *ca.* 10% of heterocycle **3d** was formed.
[c] Performed using 3 equiv. of PrNCO.



Scheme 1. Approach to six-membered heterocycles.



Scheme 2. Synthesis of fluorouracil **5**.

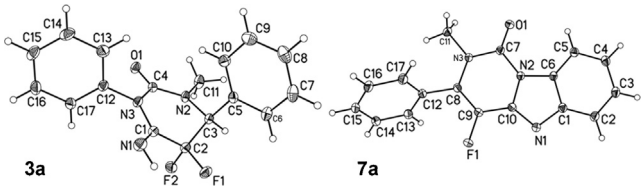
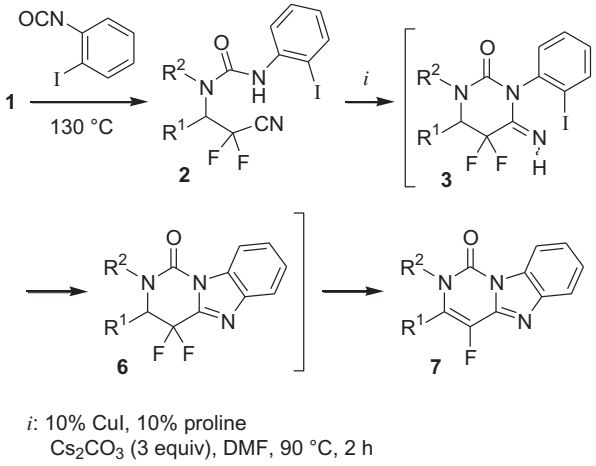


Fig. 2. The molecular structures of compounds 3a (left) and 7a (right). Non-hydrogen atoms are presented by thermal ellipsoids at 50% probability.

Table 2
Synthesis of fused heterocycles **7**.



R^1	R^2	1	2	Time for **1**→**2**, h	Yield of **2**,[a] %	7	Yield of **7**,[a] %
Ph	Me	**1a**	**2f**	2	94	**7a**	81
	Bn	**1b**	**2g**	5	67	**7b**	80
	Me	**1c**	**2h**	2	96	**7c**	77
1-Naphthyl	Me	**1d**	**2i**	2	95	**7d**	79
4-$MeOC_6H_4$	Et	**1e**	**2j**	3	92	**7e**[b]	75

[a] Isolated yield.
[b] Reaction time 5 h.