Journal of Fluorine Chemistry 182 (2016) 28–33

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

A new synthesis of 4- or/and 6-CF_3-containing hexahydro- and 1,2,3,4-tetrahydropyrimidin-2-ones

Pavel A. Solovyev, Anastasia A. Fesenko, Anatoly D. Shutalev *

Department of Organic Chemistry, Moscow State University of Fine Chemical Technologies, 86 Vernadsky Avenue, 119571 Moscow, Russian Federation

ARTICLE INFO

Article history:
Received 20 October 2015
Received in revised form 23 November 2015
Accepted 27 November 2015
Available online 2 December 2015

Keywords:
Amidoalkylation
Hexahydropyrimidin-2-ones
Tetrahydropyrimidin-2-ones
Trifluoromethyl-substituted heterocycles

ABSTRACT

A novel simple approach to 4- or/and 6-trifluoromethyl-substituted 5-acylhexahydro- and 5-acyl-1,2,3,4-tetrahydropyrimidin-2-ones has been developed. The method is based on an amidoalkylation reaction using CF_3-containing building blocks, namely, Na-enolates of 1,3-dicarbonyl compounds and *N*-(1-tosylalkyl)- or *N*-(1-acetoxyalkyl)ureas. The obtained products, 4-hydroxyhexahydropyrimidin-2-ones or their acyclic isomers were dehydrated under the action of TsOH to give corresponding tetrahydropyrimidin-2-ones.

1. Introduction

The multifunctionalized tetrahydro- and hexahydropyrimidine scaffolds (e.g., **1** and **2**, Fig. 1), particularly 5-acyl-substituted ones are of considerable interest in medicinal chemistry. These compounds have emerged as orally active antihypertensive agents, mitotic kinesin Eg5 inhibitors, α_{1a} adrenoceptor-selective antagonists, etc. [1].

Some efforts have been attempted to develop simple approaches to trifluoromethyl-substituted pyrimidines, since the unique features of this group, such as its lipophilicity, strong electron-withdrawing properties, and metabolic stability could give rise to new useful pharmacological activities for pyrimidines **1** and **2** [2]. Most of the described methods involve the Biginelli-like condensation of aromatic aldehyde, urea or thiourea and fluorinated 1,3-dicarbonyl compound to give 6-aryl-4-hydroxy-hexahydropyrimidin-2-ones(thiones) and differ only in the catalysts applied [3]. None of them allows to obtain pyrimidines by using aliphatic aldehydes. Another particular method based on addition of acetone to 4-(trifluoromethyl)-1,2-dihydropyrimidin-2-ones in the presence of secondary amines gives access only to *N*-alkyl-substituted tetrahydropyrimidines [4].

Previously, we developed a general and flexible approach to various 5-functionalized 4-hydroxyhexahydro- **4** and 1,2,3,4-tetrahydropyrimidin-2-ones(thiones, imines) **5**, particularly to 5-acyl-substituted ones, based on amidoalkylation of ketone enolates with substituted ureas, thioureas, and guanidines **3** bearing a good leaving group at the α-position to the nitrogen (Scheme 1) [5]. We hypothesized that this method could be also applied to the synthesis of CF_3-substituted pyrimidines using corresponding fluoro-containing building blocks.

Herein we describe the preparation of two amidoalkylating reagents, *N*-(1-tosylethyl)urea and *N*-[(1-acetoxy-2,2,2-trifluoro)ethyl]urea, their reaction with sodium enolates of acetylacetone, ethyl acetoacetate and ethyl trifluoroacetoacetate, and dehydration of the obtained products affording 4- or 6-trifluoromethyl- and 4,6-bis(trifluoromethyl)-substituted tetrahydropyrimidin-2-ones.

2. Results and discussion

According to our strategy, the first step of the pyrimidine synthesis was the preparation of amidoalkylating reagents. Two reagents with *N*-ethylurea skeleton were obtained using urea and acetaldehyde or fluoral.

Tosylethylurea **8** was obtained by three-component condensation of acetaldehyde, *p*-toluenesulfinic acid (**7**) and urea in H_2O at room temperature (Scheme 2). Sulfone **8** precipitated from the solution formed after the addition of all reagents and was isolated by filtration.

This reaction is accompanied by the formation of corresponding *N*,*N*′-bis-substituted urea **9**. The amount of the latter is notably greater than that of analogous products in reactions of urea with other aldehydes [5 m]. This can be explained by a higher solubility

* Corresponding author. Tel.: +7 495 246 0555x908; fax: +7 495 246 0555x909.
E-mail addresses: anatshu@gmail.com, shutalev@orc.ru (A.D. Shutalev).

http://dx.doi.org/10.1016/j.jfluchem.2015.11.008
0022-1139/

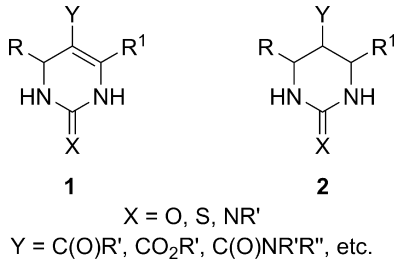


Fig. 1. Structures of multifunctionalized tetrahydro- and hexahydropyrimidines.

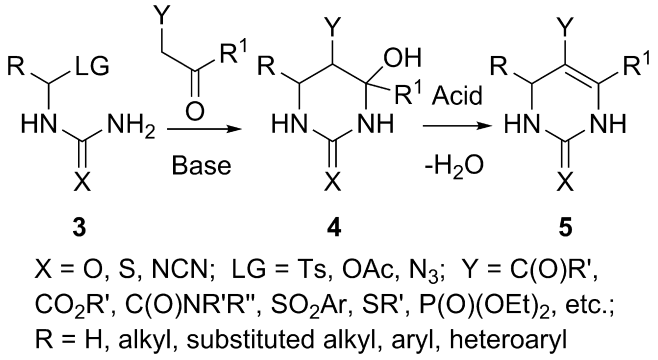
of *N*-substituted urea **8** in water. We studied the dependence of purity of tosylethylurea **8** on reagents ratio (Table 1, entries 1, 2, and 6, entries 4 and 7), reaction time (entries 2 and 3, entries 4 and 5), and the order of addition of reagents (entries 6 and 7).

We found that excess of urea completely suppressed the formation of by-product **9**. Under optimal conditions, sulfone **8** was obtained using fivefold excess of urea (rt, 2 h) in high yields and 98% purity (entries 6 and 7) and was used in the next step without further purification.

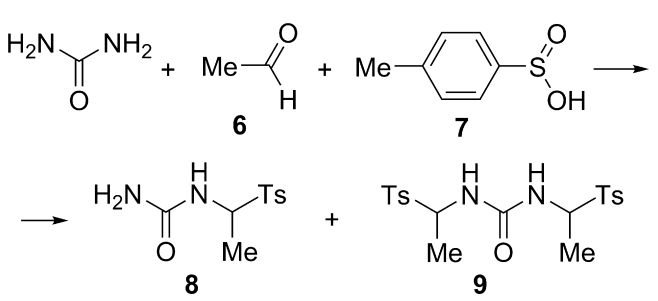
CF_3-containing amidoalkylating reagent was synthesized starting from urea **11**. Compound **11** was prepared by the reaction of urea and aqueous solution of fluoral hydrate (**10**) (Scheme 3) according to a modified method of Ingrassia et al. [6]. Prolonged cooling of the reaction mixture increased the yield of **11**, compared with that described (55%), up to 75%.

The reaction between compound **11** and sulfinic acid **7** affording sulfone **12** did not proceed under conditions used for the preparation of sulfone **8**. Sulfinic acid was recovered after the filtration of the reaction mixture. Previously we demonstrated that *N*-(1-acetoxyalkyl)ureas can serve as effective amidoalkylating reagents [5g,h]. Thus, we prepared acetoxyethylurea **13** by the reaction of urea **11** with acetic anhydride in pyridine at room temperature for 4 h in 73% yield.

Next, we used compounds **8** and **13** in the reaction with sodium enolates of acetylacetone (**14a**), ethylacetoacetate (**14b**), and ethyl



Scheme 1. A general approach to pyrimidine scaffolds via amidoalkylation.



Scheme 2. Synthesis of *N*-(1-tosylethyl)urea (**8**).

Table 1
Reaction of urea with ethanal (**6**) and *p*-toluenesulfinic acid (**7**) in water at rt.

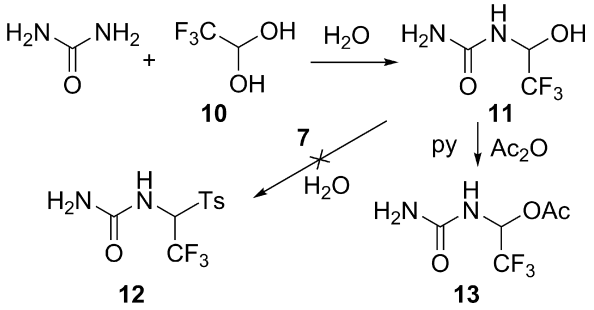
Entry	Method[a]	Urea/**6**/**7** molar ratio	Time (h)	**8**/**9** Molar ratio[b]	Yield (%)[c]
1	A	1.05:1:1	2	56:44	84
2	A	3.00:1:1	2	93:7	89
3	A	3.00:1:1	4	93:7	89
4	B	3.00:1:1	2	93:7	78
5	B	3.00:1:1	6.33	92:8	78
6	A	5.00:1:1	2	98:2	89
7	B	5.00:1:1	2	98:2	79

[a] Method A: to an aqueous solution of **6** was successively added urea and acid **7**; Method B: to an aqueous solution of **6** was added acid **7**, and after 15 min was added urea.
[b] ^{1}H NMR spectroscopic data for crude isolated material.
[c] Isolated yields.

trifluoroacetoacetate (**14c**), generated by treatment of the corresponding CH-acids with NaH in dry MeCN. The reactions smoothly proceeded at room temperature for 6–8 h affording the corresponding products of acetoxy- or tosyl-group substitution in 76–81% yields (Scheme 4).

The initially formed products of the reaction of **8** and **13** with the Na-enolate of ethyl trifluoroacetoacetate (**14c**), (3-oxoalkyl)ureas **15c,d**, cyclized spontaneously into the corresponding 4-hydroxypyrimidines **16c,d** due to high electrofilicity of the trifluoroacetyl-group. Pyrimidines **16c,d** were isolated as a single diastereomer with equatorial orientation of the CF_3- and COOEt-groups in DMSO-d_6 solution ($^3J_{5\text{-H},6\text{-H}}$ = 11.2–11.3 Hz). In contrast, NMR and IR spectroscopic data of the products obtained by the reaction of acetate **13** with enolates of **14a,b** indicate that these compounds exist in the acyclic form **15a** and **15b** (two diastereomers, 58:42) both in solid state and in DMSO-d_6 solution. It should be noted that according to the literature data [5j,k,l,7] and our experience, only 4-hydroxypyrimidin-2-ones(thiones) formed in analogous reactions between the same nucleophiles and *N*-(1-tosylalkyl)(thio)ureas bearing alkyl- or aryl-groups at the α-position to the nitrogen. We suppose that the formation of **15a,b** proceeded under kinetic control and their subsequent cyclization into pyrimidines **16a,b** could be complicated by dipole-dipole interactions with participation of the CF_3-group. Indeed, the crystallization of compound **15b** from hot water resulted in its partial cyclization to give a 95:5 mixture of urea **15b** (two diastereomers, 58:42) and hydroxypyrimidine **16b** (a single isomer). Compound **16b** adopts conformation with equatorial orientation of the CF_3- and COOEt-groups in DMSO-d_6 solution ($^3J_{5\text{-H},6\text{-H}}$ = 10.9 Hz).

Oxoalkylureas **15a,b** readily underwent heterocyclization-dehydration under the action of TsOH (0.3 equiv.) in refluxing MeCN for 0.75–1.5 h to give 4-trifluoromethyl-substituted pyrimidines **17a,b** in 76 and 80% yields, respectively. For dehydration of pyrimidines **16c,d** more drastic conditions were employed, since formation of the corresponding intermediate carbocations at the C4 was considerably hampered by the neighboring CF_3-group. First, with compound **16d** we used refluxing toluene in the



Scheme 3. Synthesis of *N*-[(1-acetoxy-2,2,2-trifluoro)ethyl]urea (**13**).