Synthesis of CF_3-substituted 5-functionalized hexahydro- and tetrahydropyrimidin-2-ones

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Abstract

5-Functionalized hexahydro- and 1,2,3,4-tetrahydropyrimidin-2-ones are currently the focus of considerable interest due to their multifaceted pharmacological profiles. During the last two decades, remarkable progress has been achieved in the development of synthetic approaches to these heterocycles. However, some of them particularly those containing pharmacophoric trifluoromethyl group remained practically unknown. Here we report a general and convenient synthesis of CF_3-substituted 5-functionalized hexahydro- and tetrahydropyrimidin-2-ones. The synthesis started with preparation of readily available *N*-(1-tosylethyl)urea and *N*-[(1-acetoxy-2,2,2-trifluoro)ethyl]urea. The prepared ureidoalkylating reagents were treated with sodium enolates of such CH-acids as acetyl acetone, ethyl acetoacetate, and ethyl trifluoroacetoacetate to give either the products of substitution of the tosyl or acetoxy groups, CF_3-containing oxoalkylureas, or their cyclic isomers, 4-hydroxyhexahydropyrimidin-2-ones in high yields and diastereoselectivity. The obtained products were converted into the corresponding CF_3-substituted 5-acyl-1,2,3,4-tetrahydropyrimidin-2-ones using acid-catalyzed dehydration.

Keywords

Ureidoalkylation, Trifluoromethyl-substituted heterocycles, Hexahydropyrimidin-2-ones, 1,2,3,4-Tetrahydropyrimidin-2-ones

Introduction

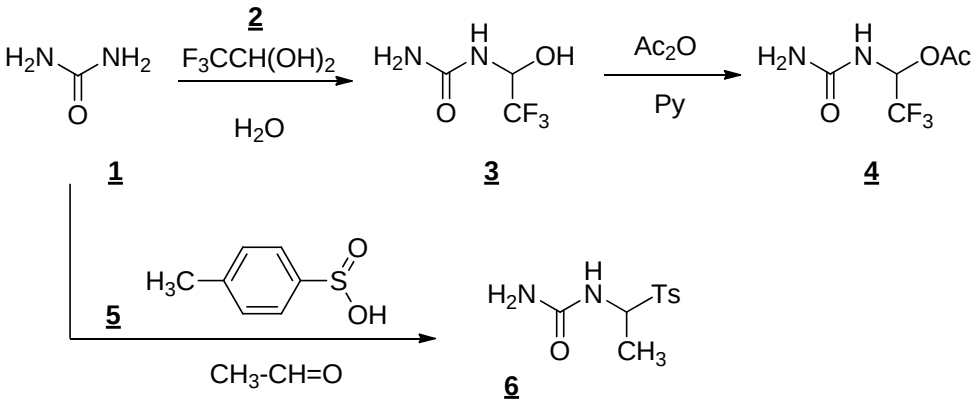
In the past two decades 5-functionalized hexahydro- and 1,2,3,4-tetrahydropyrimidin-2-ones have attracted considerable interest due to their diverse spectrum of biological and pharmacological properties. These compounds have emerged as orally active antihypertensive agents, mitotic kinesin Eg5 inhibitors, α_{1a} adrenoceptor-selective antagonists, etc.[1-4] Significant progress has been achieved in the development of synthetic approaches to these heterocycles.

The approaches include the Biginelli three-component condensation,[5,6] Atwal procedure,[7] ureidoalkylation of ketone enolates,[8] etc.

It is well documented that the introduction of pharmacophoric trifluoromethyl group into various compounds is quite beneficial for drug design.[9,10] Synthesis of CF_3-substituted 5-functionalized pyrimidin-2-ones has been reported.[11] However, the methods used were based mainly on the Biginelli reaction which strongly limited structural variability of the target compounds. Herein, we report a straightforward synthesis of trifluoromethyl substituted 5-functionalized hexahydro- and tetrahydropyrimidin-2-ones using ureidoalkylation as a key step.

Results and discussion

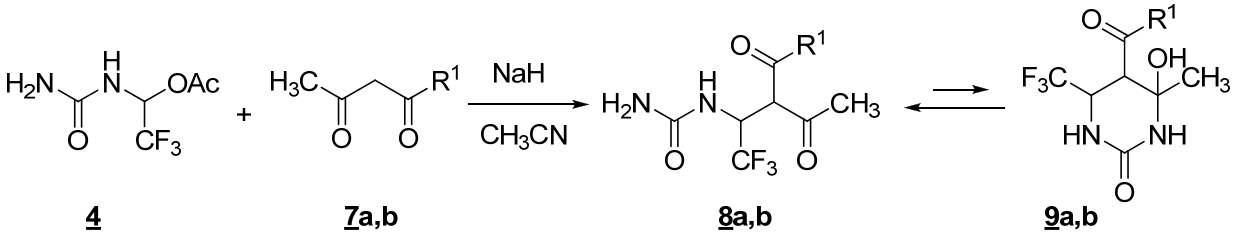
The synthesis was started from *N*-alkylureas **4** and **6** bearing a leaving group at the α-position to nitrogen (*Scheme 1*). *N*-[(1-Acetoxy-2,2,2-trifluoro)ethyl]urea (**4**) was readily prepared by acylation of the corresponding trifluoromethyl-substituted methylol urea **3** with acetic anhydride in pyridine. Methylol urea **3** was synthesized by reaction of urea (**1**) with fluoral hydrate (**2**) in water.[12] *N*-(1-Tosylethyl)urea (**6**) was obtained by three-component condensation of ethanal, urea and *p*-toluenesulfinic acid (**5**) in water at room temperature for a few hours.



Scheme 1

The obtained electrophilic ureidoalkylating reagents **4** and **6** were subjected to reactions with the sodium enolates of acetyl acetone, ethyl acetoacetate, and ethyl trifluoroacetoacetate generated *in situ* by treatment of the corresponding CH-acids with sodium hydride in anhydrous acetonitrile. The reactions proceeded smoothly at room temperature for 7-9 hours, and the structure of the products obtained differed depending on the starting electrophilic reagent and CH-acid. When **4** was treated with the sodium enolates of acetyl acetone and ethyl acetoacetate

7a,b, the products of nucleophilic substitution of the acetoxy group, oxolalkyl ureas **8a,b**, were isolated (*Scheme 2*).



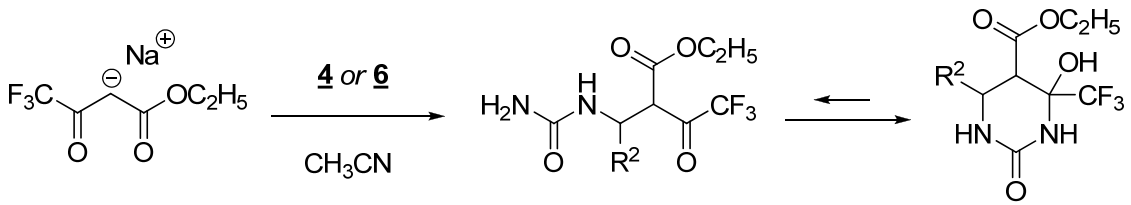
4 **7a,b** **8a,b** **9a,b**

8, 9 a $R^1 = CH_3$, **b** $R^1 = OC_2H_5$

Scheme 2

According to the NMR and IR spectroscopic data, compounds **8a,b** have been shown to exist both in solutions and crystalline form exclusively as oxoalkyl ureas **8**. Compound **8b** possessing two chiral centers was obtained as a mixture of two diastereomers with one slightly predominant.

In contrast to the above reactions, the reactions of ureas **4** and **6** with the sodium enolate of ethyl trifluoroacetoacetate (**7c**) in anhydrous acetonitrile gave 4-hydroxyhexahydropyrimidin-2-ones **9c,d** (*Scheme 3*).



7c **8c,d** **9c,d**

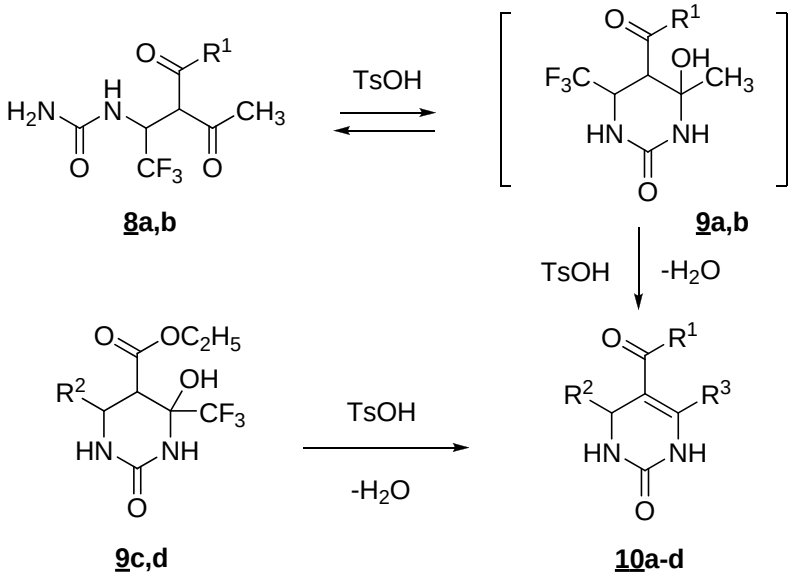
8, 9c $R^2 = CF_3$, **d** $R^2 = CH_3$

Scheme 3

According to the NMR and IR spectroscopic data, compounds **9c,d** exist in cyclic form; no traces of the isomeric acyclic forms **8c,d** were observed. Notably, pyrimidines **9c,d** possessing three chiral centers formed as a single diastereomer. Relative configuration of the chiral centers was determined on the basis of the values of the spin-spin coupling constants in the ^{1}H NMR

spectra of **9c,d** in DMSO-d_6. Thus, pyrimidines **9c,d** had *trans*-position of the substituents at C(5) and C(6) which were equatorially orientated.

The final step of the CF_3-substituted pyrimidine synthesis was acid-catalyzed cyclization-dehydration of oxoalkyl ureas **8a,b** and dehydration of hydroxypyrimidines **9c,d**. Thus, refluxing **8a,b** for 1-1.5 hours with a catalytic amount of *p*-toluenesulfonic acid in ethanol or acetonitrile gave the corresponding 1,2,3,4-tetrahydropyrimidin-2-ones **10a,b** (*Scheme* 4).



10 a $R^1 = R^3 = CH_3$, $R^2 = CF_3$; **b** $R^1 = OC_2H_5$, $R^2 = CF_3$, $R^3 = CH_3$;
c $R^1 = OC_2H_5$, $R^2 = R^3 = CF_3$; **d** $R^1 = OC_2H_5$, $R^2 = CH_3$, $R^3 = CF_3$

Scheme 4

In the case of dehydration of compounds **9c,d**, more drastic conditions were required due to the presence of electron-withdrawing trifluoromethyl group adjacent to the hydroxyl group. We found that refluxing **9c,d** in *p*-xylene in the presence of 60 mol% of TsOH for 7-8 hours with separation of water furnished the corresponding tetrahydropyrimidin-2-ones **10c,d** in high yields and purity.

Conclusions

In summary, we have developed an efficient protocol for preparation of CF_3-substituted 5-functionalized hexahydro- and 1,2,3,4-tetrahydropyrimidin-2-ones. This protocol is based on the reaction of α-functionalized ketone enolates with ureidoalkylating reagents. Compared with the literature methods, advantages of our procedure include its high synthetic flexibility.

Acknowledgements

This research was supported by the Presidential grant for young scientists No. MK-4400.2011.3.

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