Journal of Fluorine Chemistry 201 (2017) 19–23

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Carbamoyl imines of methyl trifluoropyruvate in cyclocondensation and cycloaddition reactions

Alexey Yu. Aksinenko*, Tatyana V. Goreva, Tatyana A. Epishina, Sergey V. Trepalin, Vladimir B. Sokolov

Institute of Physiologically Active Compounds of Russian Academy of Sciences, Severnyi pr. 1, Chernogolovka, Moscow region, 142432, Russia

ARTICLE INFO

Keywords:
Fluorinated heterocycles
Cyclocondensation
Cycloaddition

ABSTRACT

Dimethyl and morpholinyl carbamoyl imines of trifluoropyruvate **1a,b** were synthesized and studied in cyclocondensation and cycloaddition reactions. Cyclocondensation of carbamoyl imines **1a,b** with benzyl urea, benzamidine, 3-aminocrotonitryl, 6-aminouracil, and acetylacetone led to 5-membered trifluoromethylated heterocycles with an ureido substituent. The [2 + 4]-cycloaddition reactions of carbamoyl imines **1a,b** were performed with dialkylcyan amines and cyclopentadiene. Formerly unknown carbamoyl imines **1a,b** and their derivatives were characterized by NMR spectroscopy (^{1}H, ^{13}C, ^{19}F) and elemental analysis.

1. Introduction

Nitrogen and oxygen heterocycles represent an important class of compounds which are found in natural products as well as known drugs. These moieties are widely prevalent in pharmaceuticals, agrochemicals, and functional materials. For this reason, an introduction of heterocyclic skeleton to a known molecule or formation of a different heterocyclic skeleton of a known molecule became a continuous task for organic and medicinal chemistry.

Within the scope of this common approach of combining two or more pharmacophore fragments in one molecule aimed at discovery of new drugs, it was proposed to modify known biologically active amines and amides to obtain reactive imines of polyfluoroketones and construct fluorinated heterocycles with biologically active residue of these amines [1–9]. In the case of dialkyl amines, it is necessary to form an intermediate structure with primary amino- or amido-group. One way of doing this is the transformation of amine into correspondent urea. The structural fragment of urea is present in many of a vital meaningful compounds and drugs. Examples of acyclic and cyclic ureas such as Phenacetamide [10], Phenytoin [11], Diethylcarbamazine [12], 5-Fluorouracil [13], Ritonavir [14], Lizuride [15], Sertindole [16] are shown in Fig. 1.

The appearance of the ureido-fragment allows the formation of polyfluoroketone imines and consequent cyclocondensation and cycloaddition reactions with appropriate compounds (see Fig. 2).

Before applying this approach it is important to estimate its efficiency using simple and available dialkylamines such as dimethyl amine and morpholine. In this paper, we describe synthesis of new trifluoromethylated heterocycles derived from *N*-carbamoyl imines of trifluoropyruvate using an early developed cyclocondensation and cycloaddition methods. It should be noted that only a few methods for the synthesis of carbamoyl imines of polyfluororoketones have been described in the literature such as thermal decomposition of dioxazines – adducts of polyfluororoketones with cyanamides [17,18] or 5-dimethylamino-2-oxo-3,3-bis(trifluoromethyl)-3*H*-1,2,4-oxathiazole [19], and isomerization of 2- dimethylamino-2-isocyanatoperfluoropropane [20]. At the same time, there are no data on the synthesis of carbamoyl imines of trifluoropyruvates.

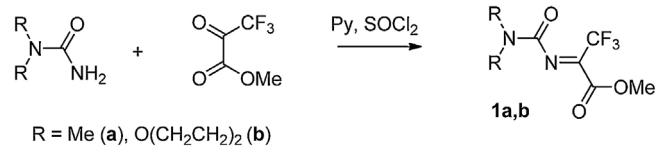
2. Results and discussion

Dimethyl- and morpholinyl carbamoyl imines of trifluoropyruvate were obtained by the sequential addition of methyl trifluoropyruvate and $SOCl_2$ to a suspension of dimethyl or morpholinyl urea in benzene solution of pyridine to a suspension of dimethyl or morpholinyl urea and pyridine in benzene. After removing Pyto a suspension of dimethyl or morpholinyl urea and pyridine in benzene·HCl from the reaction mixture by filtration, the desired imines were isolated by distillation (Scheme 1).

Cyclocondensation of imines **1a,b** was performed with 1,3-binucleophiles such as benzyl urea and benzamidine (*N,N*-binucleophiles), 3-aminocrotonitryl and 6-aminouracil (*C,N*-binucleophiles), and acetylacetone as *C,O*-binucleophile. In all cases, these reactions resulted in the formation of corresponding CF_3-heterocycles **2-6** bearing an ureido

* Corresponding author.
E-mail address: alaks@ipac.ac.ru (A.Y. Aksinenko).

http://dx.doi.org/10.1016/j.jfluchem.2017.07.015
Received 3 February 2017; Received in revised form 5 May 2017; Accepted 27 July 2017
Available online 05 August 2017
0022-1139/



Scheme 1. Condensation of carbamoyl imines with trifluoropyruvate.

moiety (Scheme 2).

In the reactions of [2 + 4]-cycloaddition carbamoyl imines **1** react easily and exothermically as heterodienes with dialkylcyan amines. However, the reactivity of imines **1** as dienophiles in the reaction with cyclopentadiene was low and required a prolonged heating in a sealed ampoule (20 h at 80–90 °C) (Scheme 3).

The spectral and analytical data of synthesized compounds **1-8** are in agreement with the proposed structures. The signals of substituents in ^{1}H NMR spectra are in conformity with their usual appearance. In the ^{19}F NMR spectra, the observed signals of the trifluoromethyl groups appear in the region of −71 to −79 ppm that is characteristic range for such groups. ^{13}C NMR spectra of **1** and **8** showed characteristic quartets at 118 ppm with the constant of spin–spin coupling (CSSC) $^{1}J_{CF}$ = 278 Hz (**1a,b**) and at 124 ppm with $^{1}J_{CF}$ = 283 Hz (**8a,b**) for the CF_3-atom and quartets at 150 ppm with $^{2}J_{CF}$ = 38 Hz for the C=N-atom (**1a,b**) and at 67 ppm with $^{2}J_{CF}$ = 28 Hz for the $CF_3\underline{C}$-atom (**8a,b**). The signals of other **8a,b** skeleton's carbon atoms were assigned as follows: the signals at 32 ppm undoubtedly belong to a nodal (apical) $\underline{C}HCCF_3$ carbon atom because the middle-distance CSSC $^{3}J_{CF}$ = 2.2 Hz, while another nodal $\underline{C}HN$ carbon atom has a signal at 82.8 ppm; the bridge methylene carbon atoms showed signals in the range of 36–40 ppm, and finally, the signals of carbon atoms at double bond of the cycle were assigned to $NC\underline{C}H$ = 128.9 ppm and $CC\underline{C}H$ = 139.9 ppm.

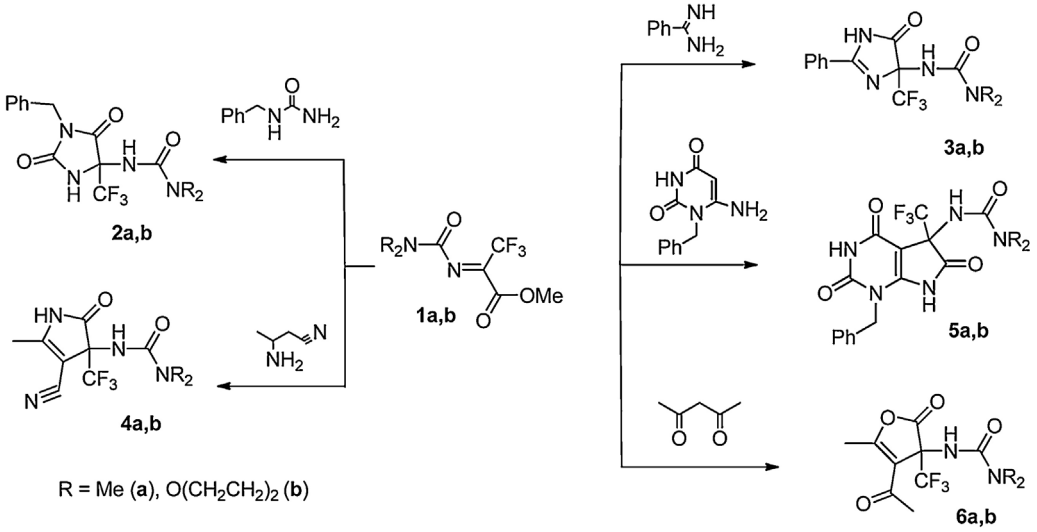
3. Conclusion

In the present work, first representatives of carbamoylimines of methyltrifluoropyruvate were synthesized and studied in cyclocondensation reactions with 1,3-binucleophiles and [2 + 4]-cycloaddition reactions with dienes and dienophiles. The elaborated approach represents a convenient route to exo- and endocyclic modification of ureas with 5- and 6-membered trifluoromethylated heterocycles and can find broad applications in medicinal chemistry.

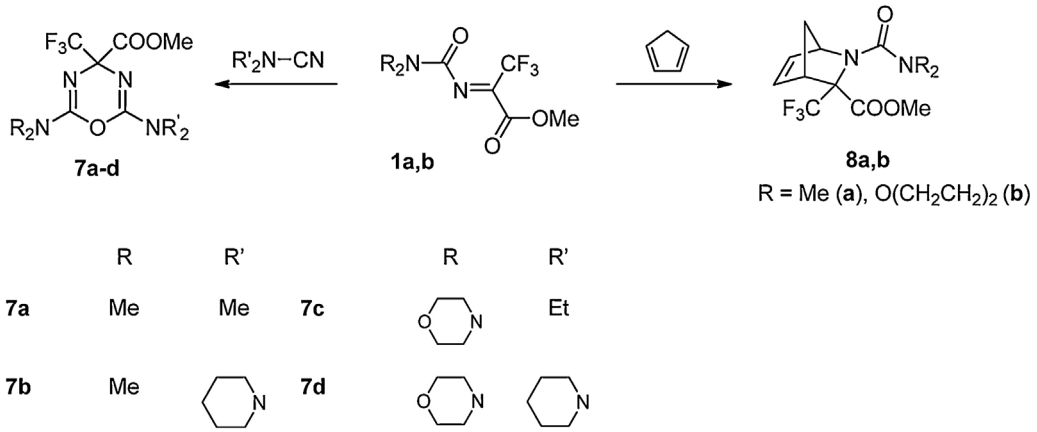
4. Experimental

4.1. General

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker DXP at 200, 50, and 188 MHz, respectively, in $CDCl_3$ and Me_2SO-d_6 using tetramethylsilane as an internal standard and CCl_3F as an external standard. Chemical shifts are reported in ppm units with the use of δ scale. Melting points were measured in open capillary tubes and are uncorrected.



Scheme 2. Cyclocondensation of imines **1a,b** with 1,3-binucleophiles.



Scheme 3. [2 + 4]-Cycloaddition reactions of carbamoyl imines **1.**