Journal of Fluorine Chemistry 158 (2014) 16–20

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Efficient synthesis of new biheterocyclic 1-(5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-3-(6-trifluoro methylpyrimidin-4-yl)-propan-1-ones

Juliana L. Malavolta [a], Alynne A. Souto [a], Debora L. de Mello [a], Darlene C. Flores [b], Alex F.C. Flores [b,*]

[a] Departamento de Química, Universidade Federal de Santa Maria, 97105 900 Santa Maria, RS, Brazil
[b] Escola de Química e Alimentos, Universidade Federal de Rio Grande, 96203 900 Rio Grande, RS, Brazil

ARTICLE INFO

Article history:
Received 21 October 2013
Received in revised form 18 November 2013
Accepted 22 November 2013
Available online 1 December 2013

Keywords:
Heterocycles
Pyrimidines
Pyrazoles
Levulinic acid

ABSTRACT

Several new 1-(5-hydroxy-5-trifluoromethyl-1*H*-pyrazol-1-yl)-3-(6-trifluoromethyl pyrimidin-4-yl)-propan-1-ones were prepared by cyclocondensation between two different 3-[6-trifluoromethyl-2-(substituted)pyrimidin-4-yl]propanoylhydrazides derived from levulinic acid and versatile 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones. The structure of new propionyl-spaced bis trifluoromethylated biheterocycles was characterized based on ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy and mass spectrometry data.

© 2013 Elsevier B.V. All rights reserved.

1. Introduction

The ever-increasing interest in fluorine-containing heterocyclic compounds is largely due to the fact that they exhibit enhanced biological activity and can be used as medicinal or agricultural chemicals, in addition to their role in the development of new technological materials. The presence of fluorinated groups in organic substances modifies the physicochemical profile, increasing lipophilicity and metabolic stability [1]. Among these groups, pyrimidine and pyrazole rings have shown important bioactivities [2], including analgesic, anti-inflammatory, and antinociceptive activities [3]; cytotoxicity against cancer cell lines [4]; and inhibitory activities against monoamine oxidase, a crucial feature of anticonvulsant and antimicrobial agents as well as compounds used for treating Parkinson's and Alzheimer's diseases [5]. Pyrazole derivatives are used in insecticides [6] and can be used as analytical reagents for complexation of transition metal ions [7] and as ultraviolet stabilizers in the dyeing industry [8]. Owing to their versatile chemotherapeutic importance, a great deal of research has been focused on these nuclei.

On the other hand, heteroarylpropanoates have been demonstrated to exhibit diverse biological activities, in particular in the central nervous system. Their importance is exemplified by their role as agonist/antagonist mediators of neuronal signals. (*S*)-a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is a classic AMPA receptor agonist, and a large number of heterocyclic Glu analogs are potent and selective agonists at AMPA receptors [9]. The 3-heteroaryl-propanoates are important targets for the development of potent and selective AMPA antagonists and represent potential drugs for cerebral ischemia or epilepsy. In particular, ethyl 3-(2-ethoxycarbonyl-1*H*-imidazol-4-yl) propenoate and its saturated derivative at micromolar concentrations have been shown to be effective, and phenyl-substituted semicarbazones from LA have been shown to have very good anticonvulsant activity with low neurotoxicity [10]. The synthesis of new drugs targeting glutamatergic or GABAergic systems is also important for the treatment of mood disorders [11].

We recently reported the synthesis of methyl 1,1,1-trihalo-4-methoxy-6-oxo-4-heptenoates, derived from renewable levulinic acid [12], as building blocks for the production of promising trihalomethyl-containing heterocyclic systems [13]. In the present work, we report an efficient procedure for synthesizing new heterocyclic systems with a propionyl spacer between heterocyclic pyrimidine and pyrazole nuclei, 1-(5-hydroxy-5-trifluoromethyl-4,5-dihydro pyrazol-1-yl)-3-(6-trifluoromethylpyrimidin-4-yl)-propan-1-ones. We also investigated the behavior of 3-(6-trifluoromethylpyrimidin-4-yl)propanoylhydrazides **3** and **4** toward some 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones as potential

* Corresponding author. Tel.: +55 5332336964.
E-mail addresses: alexflores@furg.br, alex.fcf@ufsm.br (Alex F.C. Flores).

0022-1139/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2013.11.014

precursors of interesting biologically active biheterocyclic systems.

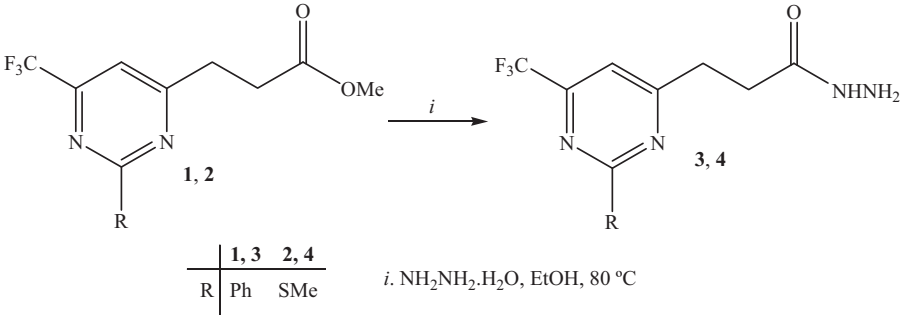
2. Results and discussion

The 3-(4-trifluoromethyl-2-phenylpyrimidin-4-yl)propanoylhydrazide (**3**) and 3-(4-trifluoromethyl-2-thiomethylpyrimidin-4-yl)propanoylhydrazide (**4**) were obtained from methyl 3-(6-trifluoromethylpyrimidin-4-yl)propanoates **1** and **2**, respectively, as described previously (Scheme 1) [13b].

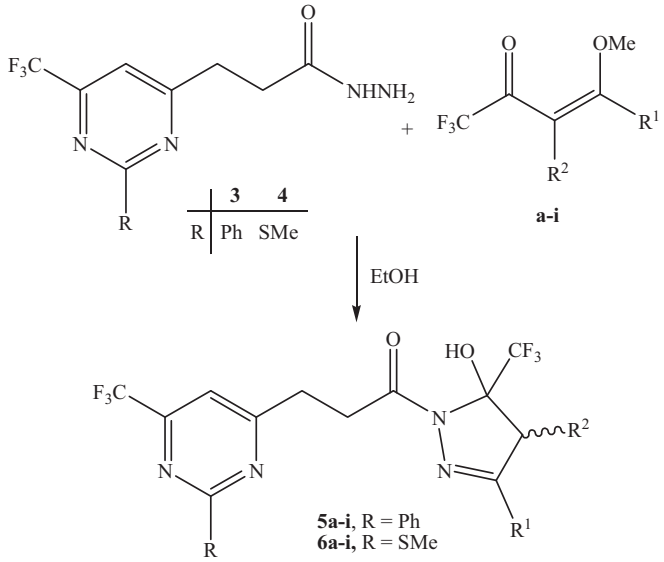
The 1,1,1-trifluoro-4-methoxy-3-alken-2-ones **a**–**h** were obtained by reacting the respective enol ether or acetal with trifluoroacetic anhydride [14]. Of these, 1,1,1-trifluoro-4-methoxy-8-methylnona-3,7-dien-2-one (**c**) and 1,1,1-trifluoro-4-methoxy-6-phenylhex-3-en-2-one (**d**) are new, and the nuclear magnetic resonance (NMR) data are presented in Supplementary material.

The condensation of 3-heteroarylpropanoylhydrazide **3** with 1,1,1-trifluoro-4-methoxy-3-penten-2-one (**b**) was carried out in MeOH at 25 °C for 24 h and the reactant was not consumed (see Supplementary material). The reaction occurred only at 50 °C, and the reactants were completely consumed after 16 h, leading to biheterocyclic derivative **5b** at 71% yield. Refluxing with MeOH at 65 °C resulted in the same product and took the same amount of reaction time, but showed a slight improvement in yield (75%). The same reaction conducted with EtOH led to product **5b** at 69% yield; however, due to its lower toxicity (to humans and the environment) we chose it as the solvent for the cyclocondensations. These conditions were extended for the entire series of 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones cyclocondensations with the hydrazide **4** (Scheme 2). No evidence of the formation of other regioisomers of pyrazole derivatives was observed [15]. After cyclocondensation, the products were isolated and purified by recrystallization or column chromatography and identified based on NMR spectroscopy and gas chromatography mass spectrometry (GC–MS) or liquid chromatography MS (LC–MS). The purity of the products was assessed by elemental analysis.

Our attempts to dehydrate the dihydropyrazole derivatives **5b** and **6d** to obtain the respective aromatic biheterocyclic derivatives even using mild conditions reported in literature (HCl, AcOH or $SOCl_2$) [15] has led to a mixture of products. These mixtures contain the corresponding aromatic 3(5)-substituted-5(3)-trifluoromethyl-1H-pyrazole, however, the portion with 3-(pyrimidyl)propanoate was not identified.



Scheme 1. Synthesis of (6-trifluoromethylpyrimidin-4-yl)propanoyllhydrazides.



	a	b	c	d	e	f	g	h	i
R^1	H	Me	$-(CH_2)_2CHCMe_2$	$-(CH_2)_2Ph$	$-(CH_2)_2CO_2Me$	Ph	$4\text{-}MeC_6H_4$	OEt	$-(CH_2)_5-$
R^2	H	H	H	H	H	H	H	H	

Scheme 2. Synthesis of 1-(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pirazol-yl)-3-(6-trifluoromethylpyrimidin-4-yl)propan-1-ones.

Download English Version:

https://daneshyari.com/en/article/1314366

Download Persian Version:

https://daneshyari.com/article/1314366

Daneshyari.com