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Synthesis, antibacterial and antifungal activities of new chiral 5-alkyl-3-(1′-benzenesulfonylpyrrolidin-2′-yl)-4,5-dihydro-1,2,4-oxadiazin-6-ones

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ABSTRACT

Chiral α-bromoacid chlorides can be easily prepared from amino acids. Their condensation with new 1-benzenesulfonylpyrrolidin-2-carboxamidoxime derived from proline lead to the corresponding *O*-(bromoacyl) amidoximes. The latter afforded new chiral 5-alkyl-3-(1′-benzenesulfonylpyrrolidin-2′-yl)-4,5-dihydro-1,2,4oxadiazin-6-ones in good chemical yields via intramolecular cyclization in the presence of one equivalent of NaH. These new compounds were evaluated for their antibacterial and antifungal activities using micro-dilution tests against some strains of bacteria and fungi. Our compounds showed an excellent antibacterial activity, which is better than the drug levofloxacin.

RÉSUMÉ

Des chlorures de α-bromoacides chiraux préparés facilement au départ d'acides aminés sont condensés avec le 1-benzènesulfonylpyrrolidin-2-carboxamidoxime dérivant de la proline et conduisent aux *O*-(bromoacyl) amidoximes correspondantes. Ces derniers composés conduisent aux nouvelles 5-alkyl-3-(1′-benzènesulfonylpyrrolidin-2′-yl)-4,5-dihydro-1,2,4-oxadiazin-6-ones chirales avec de bons rendements chimiques via une cyclisation intramoléculaire en présence d'un équivalent de NaH. Ces nouveaux produits ont été évalués pour leurs activités antibactérienne et antifongique en utilisant des tests de microdilution contre quelques souches de bactéries et de champignons. L'un de nos produits a montré une excellente activité antibactérienne meilleure que celle du médicament lévofloxacin.

1. Introduction

Oxadiazinones are quite important biologically-active compounds which have gained more interest thanks to their utility as central nervous system stimulants [1,2] and as oxidase B (MAO-B) inhibitor [3]. As far as we know, no works reporting the antibacterial or antifungal activities of this class of heterocycles have been reported.

The high synthetic value of oxadiazinones has been demonstrated specially in Diels–Alder cycloaddition [4,5] and Favorski ring contraction [6]. Recently, fluorinated oxadiazinones have been proposed as a rare example of low molecular weight (LMW) hydrogelators [7].

On the other hand, the synthesis of optically-active oxadiazinones has recently attracted considerable interest in the asymmetric organic synthesis. Optically-active 1,3,4-oxadiazin-2-ones have been successfully investigated by Hitchcock et al. and Vaughn and Hitchcock [8,9] as chiral auxiliaries in the aldol reaction. Moreover, these compounds have been utilised by

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Husson et al. as chiral auxiliaries to perform diastereoselective alkylations [10].

Among oxadiazinones, 1,2,4-oxadiazin-6-ones are not very broadly explored and little is known about these compounds which were prepared only once by Hussein et al. [11]. Hussein et al.'s method was not general and gave 1,2,4-oxadiazin-6-ones with moderate yields ranging from 12 to 73% and with no indication of the product's optical purity. Therefore, there is further scope to explore more efficient synthetic methods. Herein, chemically speaking, we report a simple and practical method to achieve the synthesis of new optically pure 5-alkyl-3-(1′-benzenesulfonylpyrrolidin-2′-yl)-4,5-dihydro-1,2,4-oxadiazin-6-ones by the condensation of chiral 1-benzenesulfonylpyrrolidin-2-carboxamidoxime with chiral 2-(S)-2-bromoacid chlorides, followed by cyclization in the presence of one equivalent of sodium hydride. Some tests have been conducted in order to evaluate the antibacterial and antifungal activities of our new 1,2,4-oxadiazin-6-ones.

2. Results and discussion

2.1. Chemistry

The synthetic route to the target compounds **4a–f** is outlined in Scheme 1. We have successfully converted commercially available (L)-proline to the corresponding optically pure (2*S*)-1-benzenesulfonylpyrrolidine-2-carbonitrile **1** [12]. The treatment of this compound with hydroxylamine hydrochloride and two equivalents of triethylamine overnight at room temperature led to the corresponding chiral (2*S*)-1-benzenesulfonylpyrrolidine-2-carboxamidoxime **2**. The condensation of amidoxime **2** with different α-bromoacid chlorides, easily prepared from the corresponding α-aminoacids following a known procedure [13], gave the chiral (*O*-bromoacyl) (2*S*)-1-benzenesulfonylpyrrolidine-2-carboxamidoximes **3a–f** with chemical yields ranging from 79 to 87%. The final step of this sequence is the intramolecular cyclization of **3a–f** in the presence of one equivalent of NaH affording the corresponding 5-alkyl-3-(1′-benzenesulfonylpyrrolidin-2′-yl)-4,5-dihydro-1,2,4-oxadiazin-6-ones **4a–f** with good chemical yields and excellent diastereomeric excesses.

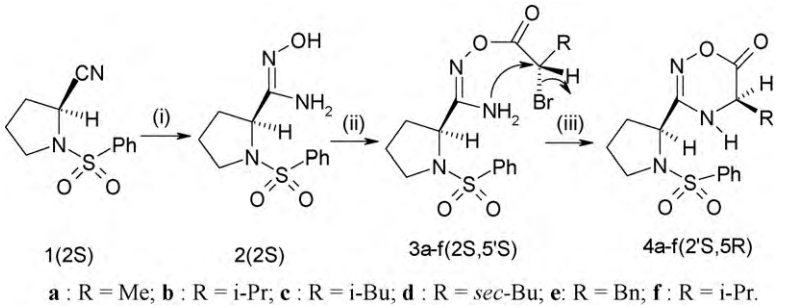
The addition reaction of amidoxime to the activated carboxylic acid derivatives has always been described as an easy method for the synthesis of 1,2,4-oxadiazoles [14,15]. As part of our work, directed towards the synthesis of new heterocyclic compounds from amino acids [16,17], we investigate chiral new (2*S*)-1-benzenesulfonylpyrrolidine-2-carboxamidoxime to cyclise with α-bromoacid chlorides yielding new 1,2,4-oxadiazin-6-ones.

The synthesis of the amidoxime group, mostly involve the preparation of the cyano group, followed by the conversion into an amidoxime group. During this study, we describe the first synthesis of chiral (2*S*)-1-benzenesulfonylpyrrolidine-2-carboxamidoxime **2**. This compound was easy prepared by treatment of (2*S*)-1-benzenesulfonylpyrrolidine-2-carbonitrile **1** with a hydroxylamine alkaline solution. However, unfortunately, the treatment of α-aminonitriles derived from other amino acids did not provide the corresponding amidoxime with good yields even after heating and prolonging the reaction time.

Work on condensation of amidoximes with acid chlorides has been described before. It is well known that acid chloride reacts with the O-part of the amidoxime [18,19]. The desired esterification products **3a–f** were afforded with use of one equivalent of α-bromoacid chloride and 1.2 equivalent of triethylamine. Reaction was performed in an ice bath with short reaction times (45–60 min). In the event of longer reaction times, the reaction leads to a complex mixture.

Finally, the intermediates **3a–f** undergo an intermolecular cyclization in the presence of one equivalent of NaH to yield compounds **4a–f** within 3 h at −25 °C with good yields. Only one equivalent of NaH has been used in order to avoid the racemisation of the initial stereocenter of the proline by a possible elimination of the proton. We have found that compounds **4a–f** were formed without a significant racemization of the asymmetric carbon 5 of the oxadiazinone ring. This result is proved by NMR and by HPLC studies.

According to ^{1}H NMR spectra of compound **4f** prepared from optically pure (2′*S*)-1-benzenesulfonylpyrrolidine-2′-carboxamidoxime **2** and (D,L) valine, the signal relative to the proton linked to the asymmetric carbon of oxadiazinone ring resonates in different positions for each pair of diasteromers. As shown in Fig. 1, the signal of the C*-H proton of the mixture of the two diastereomers (2′*S*,5*R*) and (2′*S*,5*S*) **4f** appeared as two doublets. A first doublet at 3.95 ppm (*J* = 5.7 Hz) corresponding to the diastereomer (2′*S*,5*S*) and a second doublet at 3.99 ppm (*J* = 5.1 Hz)



Scheme 1. Synthesis of (2′S, 5R), 5-alkyl-3-(1'-benzenesulfonyl-pyrrolidin-2′-yl)-4,5-dihydro-1,2,4-oxadiazin-6-ones **4a–f**. Reaction conditions: (i) $NH_2OH.HCl/Et_3N/CHCl_3$; (ii) 2-(S)-2-bromo-acid chlorides/Et_3N/CH_2Cl_2, 0 °C ; (iii) NaH/THF, 3 h, −25 °C.