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Useful approach for *O*-functionalization of trifluoromethyl-substituted spirotetracyclic isoxazolines, and their application in the synthesis of 1,2,3-triazole derivatives

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ABSTRACT

The present paper describes first an efficient methodology for an easy *O*-functionalization (alkylation) of tetracyclic hydroxyisoxazolines **1** applied to the synthesis of eight examples of new 3-(alkoxy)-3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno [4,3-*c*]isoxazole-4,1′-cycloalkanes] (**6-9**) at 61–84% yields, in which the alkoxy substituents were methoxy, benzyloxy, allyloxy, or prop-2-yn-1-yloxy; while the cycloalkanes were 5-, 6-, and 7-membered carbocycles, as well as 4′-methyl- and 4′-*t*-butyl-cyclohexane. The reaction medium used **1**, four alkyl halides (**2-5**), K_2CO_3, and KI in DMF at room temperature. The selected 3-(prop-2-yn-1-yloxy)-substituted isoxazolines **6** were successfully used as a *CC*-fragment in the construction of another series of five examples of 3-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)-3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazole-4,1′-cycloalkanes] (**10**), at 36–84% yields, through a regioselective 1,3 dipolar cycloaddition reaction catalyzed by copper iodide (CuAAC), using benzyl azide as an *NNN*-building block (Click Chemistry).

1. Introduction

Over the years, the synthesis of complex heterocyclic molecules has attracted the interest of many researchers. The reason for this is the vast potential uses for these compounds. Many heterocycles—which are extracted from nature, from plants, bacteria, and fungi —have complex structures and well-defined biological properties [1–3].

Among the biologically active classes of compounds, heterocycles like isoxazoles and triazoles are notable, because many molecules of interest include these heterocyclic moieties in their structures [4–6]. Considering the synthesis of isoxazole systems, different synthetic strategies can be used. The synthesis of 2-isoxazoles is commonly done by using nitrile oxides and olefins in a [CNO] + [CC] cycloaddition reaction[4,7,8], or by the use of α,β-unsaturated ketones or 1,3-diketones and hydroxylamine [CCC] + [NO] cycloaddition [9,10]. Despite the use of nitrile oxides and alkenes being the most common approach for synthesizing these systems, it lacks the possibility of forming isoxazoles fused with other carbocyclic or heterocyclic rings, due to the nature of the two building blocks.

Like isoxazoles, another equally important heterocyclic scaffold is the 1,2,3-triazole ring system. This moiety is interesting due to both its pharmacological significance and it being widely used recently as a linking agent through Sharpless's Cu (I) catalyzed cycloaddition (Click Chemistry) [11–14].

Due to the fact that around 20–30% of all drug molecules contain at least one fluorine atom, many different fluorinated molecules with biological properties (e.g., cardioprotection, antirheumatism, and anticonvulsiveness) have been described in the literature as (Fig. 1) [15–19].

Seeking the synthesis of more complex heterocyclic structures, over the years our research group has explored the use of cyclic trifluoromethylated α,β-unsaturated ketones, which have proven to be very versatile synthons in the regioselective synthesis of heterocycles [5,20]. These ketones have been used as a [CCC] block for an efficient and regioselective synthesis of 3-hydroxy-3-trifluoromethyl-isoxazolines[21]. It is important to mention that hydroxy-2-isoxazolines —which do not have electron-withdrawing groups (like halomethyl groups) bonded to any position of the ring—are generally not stable and undergo spontaneous aromatization [22–24]. Moreover, a review of the literature shows very few derivatization reactions for the selected hydroxy-isoxazolines—there are only reports of acylation of the hydroxyl group [25,26]. Thus, the large potential of alkyl derivatization remains unexplored.

Considering the importance of the use of fluorinated precursors in the synthesis of trifluoromethylated hydroxy-2-isoxazolines—which

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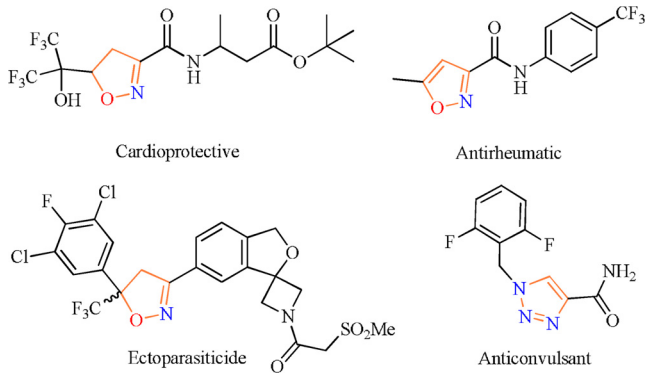


Fig. 1. Biologically active molecules containing isoxazole and triazole moieties.

can undergo further derivatization reactions scarcely found in the literature—and in order to study the chemical stability of hydroxy-2-isoxazolines with the aim of avoiding the *O*-elimination reactions that usually occur during the *O*-alkylation processes, we decided to develop a useful alkylation method for: the synthesis of 3-(alkoxy)-3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazole-4,1′-cyclalkanes] (**6–9**) from the respective hydroxy-2-isoxazoline precursors **1** and the alkylating agents of interest (**2–5**)—see Scheme 1; and further application of the specific *O*-propargylated isoxazolines (**6**) through a copper catalyzed cycloaddition using benzyl azide (CuAAC) to obtain the 1,2,3-triazole derivatives **10** (Scheme 2).

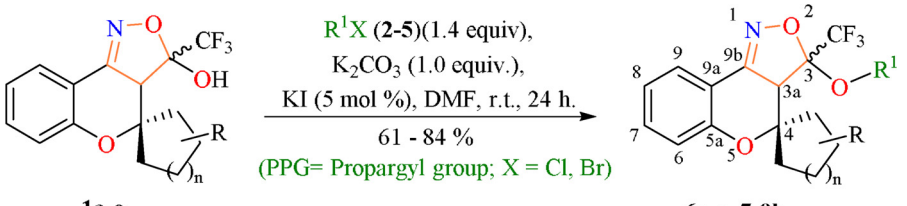
2. Results and discussion

Firstly, the precursors 3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazole-4,1′-cycloalkane]-3-ols (**1a–e**) were produced as a pair of enantiomers—at good yields, from a cyclocondensation reaction using 2,2,2-trifluoro-1-(4-methoxyspiro[chromene-2,1′-cycloalkan]-3-yl)ethan-1-ones and hydroxylamine, in accordance with a methodology previously described by our research group [21]—and these were then properly characterized by melting point, NMR spectroscopy, and GC−MS spectrometry. In the next step—for obtaining the novel series of 3-(alkoxy)-3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazole-4,1′-cycloalkanes] (**6a–e** and **7b–9b**)—we selected the following alkylating agents: iodomethane (**2**), benzyl chloride (**3**), allyl bromide (**4**), and propargyl bromide (**5**). Also, in order to construct a specific *O*-alkylation protocol for the isoxazolines **1a–e**, we based our methodology on the work of Reddy et al. [13], who developed an *O*-alkylation methodology for 2-hydroxy-2-trifluoromethyl chromene-3-carboxylate ethyl esters—using propargyl bromide—and further transformed the terminal alkynes into triazole and isoxazole derivatives. Consequently, we selected the 3-hydroxy-2-isoxazoline **1b** and propargyl bromide (**5**) to perform an optimization of the reaction conditions for the *O*-alkylation reaction. To obtain the 3-(prop-2-yn-1-yloxy)-substituted isoxazoline **6b**, the molar ratio between the reagents (**1b**:**5**:base:KI), as well as the amount of the solvents and reaction temperature, were varied, and the progress of all reactions was monitored via TLC (Table 1 – entries 1–11). The full optimization data can be found in the supplementary material. This optimization let us find that the best reaction condition involved a magnetically stirred solution of **1b** (1 mmol), the respective alkylating agent **5** (1.4 equiv), the base K_2CO_3 (1.0 equiv), and KI (5 mol%) in *N*,*N*-dimethylformamide (2.5 mL) as solvent, at room temperature (25 °C) for 24 h, — see Table 1 (entry 9). With the successful *O*-alkylation procedure in hand, this methodology was extended to produce a series of eight 3-(alkoxy)-3-(trifluoromethyl)-3,3a-dihydrospiro[chromeno[4,3-*c*]isoxazole-4,1′-cyclalkanes] (**6a–e**, **7b**, **8b**, and **9b**) at good yields of 61–84%—see Scheme 1.

Despite our efforts, we were unable to synthesize the alkylated *O*-*i*-propyl and *O*-*t*-butyl isoxazolines, which was probably due to the absence of an adjacent methylene unit and the presence of a secondary or a tertiary carbon bonded to the halogen in the alkylating agents, which generated greater steric hindrance during the *O*-alkylation reaction.

The alkylated products were characterized by ^{1}H and ^{13}C NMR spectroscopy and GC−MS spectrometry, and their purity was confirmed by elemental analysis. The MS fragmentation spectra for the compounds **6–9** showed similar fragmentation for all the compounds of this series. For elucidation, **6b** was used as a model to demonstrate the fragmentation pattern. For this compound, a signal with *m/z* 309 (15%) [$C_{16}H_{14}F_3NO_2$] identified the loss of a prop-2-yn-1-olate group followed by aromatization of the isoxazoline. The fragment with *m/z* 240 (84%) [$C_{15}H_{14}NO_2$] signaled the loss of both a prop-2-yn-1-olate and trifluoromethyl groups. Lastly, a fragment with *m/z* 212 (100%) [$C_{14}H_{14}NO$] showed the isoxazoline cleavage with formation of an azirine as the most stable fragment.

Observing the ^{1}H NMR spectra, which was recorded in $CDCl_3$ for the propargyl derivatives **6a–e**, it can be seen that there is very little difference in the chemical shifts in the signals for either the molecules **6a–e** or the precursors **1a–e**. For this reason, only the new signals from the propargyl portion of the molecule will be addressed. In all five molecules, the methylenic hydrogen atoms form two doublet of doublets on average at 4.63 and 4.45 ppm, and the terminal alkyne hydrogen atom appears as a triplet on average at 2.44 ppm. The ^{13}C NMR, which was recorded in $CDCl_3$ for the propargyl derivatives **6a–e**, follows the same trend observed for the ^{1}H NMR data. Similarly, only the propargyl group's signals will be addressed, given that they are new. For all the molecules of this series, the methylene unit appears at 53.3 ppm, and the carbon atoms from the triple bond appear on average at 78.3 and 75.1 ppm for the internal and terminal carbon atoms, respectively. From the NMR spectra of compounds **7b–9b**, the alkylation reaction was also easily identified from the characteristic signals of the alkyl substituents. The ^{1}H NMR spectrum of 3-(methoxy)-isoxazoline (**7b**) in $CDCl_3$ showed the methoxyl group as a multiplet, ranging from 3.63–3.60 ppm due to the asymmetric carbons at C-3 and C-3a. The ^{13}C



1a-e **6a-e, 7-9b**

nr.	1,6a	1,6b	1,6c	1,6d	1,6e	7b	8b	9b
R	H	H	H	4'-Me	4'-Bu^t	H	H	H
R^1	PPG	PPG	PPG	PPG	PPG	Me	Bn	Allyl
n	1	2	3	2	2	2	2	2

Scheme 1. Synthetic route for the *O*-alkylation reaction of hydroxylisoxazolines **1a–e, 7–9b**.