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Functionalization of 2-(*S*)-isopropyl-5-iodo-pyrimidin-4-ones through Cu(I)-mediated 1,3-dipolar azide–alkyne cycloadditions

Hélio A. Stefani [a,*], Mônica F.Z.J. Amaral [a], Flávia Manarin [a], Rômulo A. Ando [b], Nathália C.S. Silva [a], Eusebio Juaristi [c]

[a] Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, SP, CEP 05508-000, Brazil
[b] Instituto de Química, Universidade de São Paulo, São Paulo, SP, Brazil
[c] Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D.F., Mexico

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ABSTRACT

A series of 2-(*S*)-isopropyl-pyrimidinones functionalized at C5 with triazole rings, in which the substituents are found at N-1′ of the triazole ring, were synthesized. Through the azide–acetylene cycloaddition reaction, using CuI as a copper source and ultrasonic waves as an energy source it was possible to obtain products with yields ranging from 79% to 89% within 5 min or less. A preliminary study to gain further insight into the reaction was performed using in situ ReactIR technology.

Introduction

Heterocyclic compounds comprise the largest and one of the most important groups in organic chemistry. A vast majority of molecules that present physiological and therapeutic activities on the pharmaceutical market have at least one heterocyclic nucleus.[1] Among these, the pyrimidinones and triazoles have attracted particular interest since they are present in several drugs (Fig. 1), such as antiretrovirals (**1**, **2**), antifungals (**3**), antivirals (**4**), anti-allergic (**5**), barbiturates (**6**, **7**), and β-lactamase inhibitors (**8**), among many others.[2,3]

In recent years, a growing number of research groups have become interested in the derivatization of different types of pyrimidinones. Juaristi, recently published a Letter on the synthesis of 5-iodopyrimidinone with further functionalization through the Sonogashira coupling reaction and subsequent synthesis of α-substituted β-aminoacids.[4,5]

Similarly, interest in the 1,2,3-triazole nucleus has increased due to recent findings on its generation, biological activities, and applications, particularly by the pharmaceutical industry which uses these compounds as imidazoles, 1,2,4-triazoles, and tetrazoles bioisosteres.[6]

Regarding synthesis of triazoles, experiments by the Sharpless group accelerated the 1,3-dipolar cycloaddition reaction, while maintaining regioselectivity, generating the 1,4-disubstituted triazole only.[7a] This reaction is acknowledged as the most striking example of click chemistry, defined as an approach to the synthesis of various compounds based on 'almost perfect' carbon-heteroatom bonds formation.[7b]

It is well-known that organic reactions are accelerated by ultrasonic waves. Compared with traditional methodologies, this approach is very convenient, since it allows energy conservation and minimizes residue production.[8] In recent years, our group has developed reactions for the synthesis of derivatives of several classes of compounds using sonochemistry, such as imines,[9] arylacetylenes,[10] symmetric 1,3-diines,[11] 1,3-enynes,[12] symmetric biaryls,[13] and heterocycles.[14] Beyond this, sonochemistry was used to accelerate Suzuki–Miyaura cross-coupling reactions.[15]

As part of our ongoing research interests in sonochemistry[16] and focusing on the derivatization of 2-(*S*)-isopropyl-5-alkynyl-pyrimidin-4-ones into 2-(*S*)-isopropyl-5(1,2,3-triazoles)-pyrimidin-4-ones through Cu(I)-catalyzed alkyne–azide Huisgen [3+2] cycloaddition reaction mediated by ultrasonic waves, a set of these 1,2,3-triazole compounds was synthesized.

2-(*S*)-Isopropyl-perhydropyrimidinone-6-carboxylic acid (2*S*,6*S*)-**10** was prepared via a condensation reaction of (*S*)-asparagine **9** with isobutyraldehyde, followed by in situ N-benzoylation (Scheme 1).[17] In the next step, after the recrystallization of the

* Corresponding author.
E-mail address: hstefani@usp.br (H.A. Stefani).

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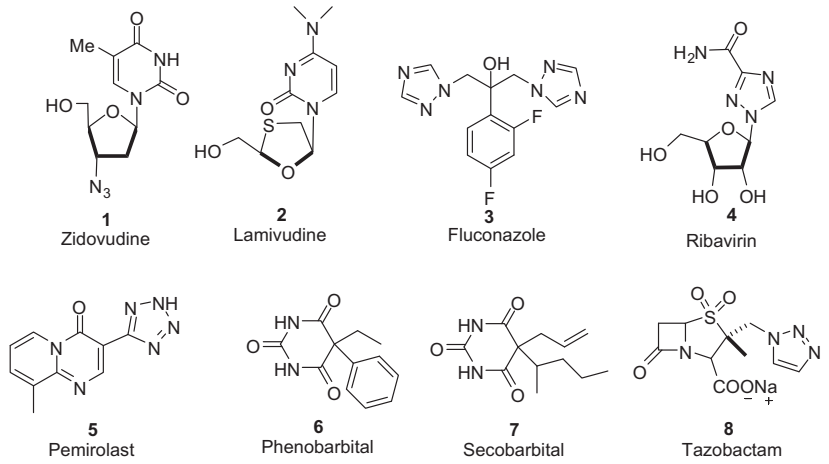
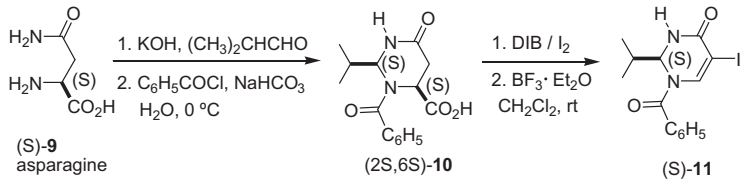
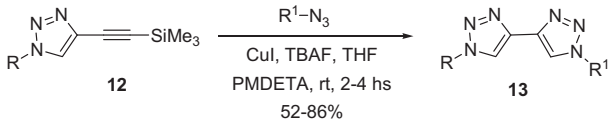


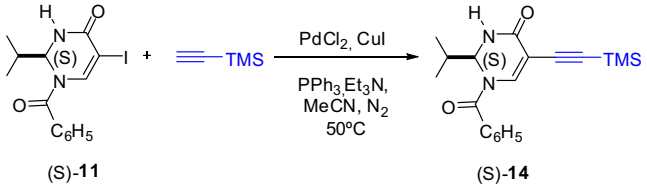
Figure 1. Biologically active triazoles and pyrimidinones.



Scheme 1. Synthesis of 2-(*S*)-isopropyl-5-iodopyrimidinone (*S*)-**11**.



Scheme 2. Synthesis of asymmetric 4,4′-bitriazoles.



Scheme 3. Synthesis of 2-(*S*)-isopropyl-5-ethynyl (trimethylsilyl)-pyrimidinone (*S*)-**14**.

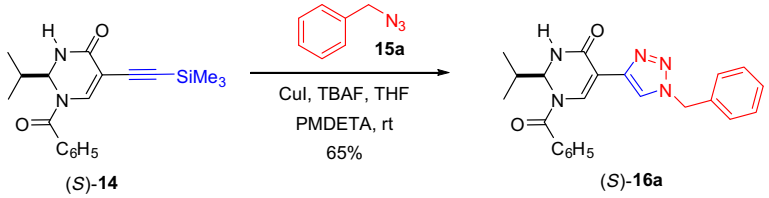
carboxylic acid **10** with methanol and hexane, $BF_3{\cdot}Et_2O$ was added (2 equiv) to the reaction mixture previously treated with the acid DIB/I_2 in the presence of $BF_3{\cdot}Et_2O$, leading to rapid conversion of (*S*)-pyrimidinone into the corresponding 2-(*S*)-isopropyl-5-iodo-pyrimidinone (*S*)-**11**,[5] with 78% yield (Scheme 1).

Based on the methodology described by Fiandanese,[18] in which they performed deprotection with TBAF and the azide–alkyne cycloaddition reaction in one step in order to synthesize asymmetric 4,4′-bitriazoles **13** (Scheme 2), we could react the compound (*S*)-**11** with trimethylsilyl acetylene via a Sonogashira coupling reaction.[5] In this way, 2-(*S*)-isopropyl-5-ethynyl (trimethylsilyl)-pyrimidinone (*S*)-**14** was obtained in 85% yield (Scheme 3).

A test with (*S*)-**14** and benzyl azide **15a** was made in order to visualize the reproducibility of the reaction with other derivatives (Scheme 4). Therefore, using TBAF as the desilylation agent and CuI as the copper source in the presence of 1,1,4,7,7-pentamethyldiethylenetriamine (PMDETA), the reaction took place with THF as the solvent at room temperature. The desired pyrimidinone functionalized at the C5 with the 1,2,3-triazole ring (S)-**16a** was obtained in 65% yield within 90 min.

Despite the good performance, the reaction was repeated to improve yield and reduce time, running it with ultrasonic waves as a source of energy, a process that is called cavitation.[16] Thus, the reaction time was reduced from 90 min to less than 5 min, and the yield increased from 65% to 87%. It was observed that the reaction occurred almost instantaneously with ultrasound.

Still, in order to improve the conditions even further, through reducing the unnecessary use of reagents, a second test was performed. This time, the experiment was performed without the addition of PMDETA, as TBAF should have the same role as the base



Scheme 4. Synthesis of 1,2,3-triazole ring (*S*)-**16a**.