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Alternative method for the synthesis of imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one—a substrate for the preparation of phosphodiesterase (5) inhibitors

Teresa Olszewska, Ewa P. Gajewska, Maria J. Milewska *

Department of Organic Chemistry, Gdańsk University of Technology, 80-233 Gdańsk, Poland

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ABSTRACT

Imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones, as isosteres of purine, are of interest for pharmaceutical research as potential substrates for the synthesis of cGMP-PDE5 inhibitors. We present a novel, alternative method for the synthesis of imidazotriazinones, that differs from the previously reported ones with respect to the method of construction of the triazinone ring in the molecule. The key step in our approach is condensation of an appropriate α-keto-ester with amidrazones, leading to the triazinone heterocycle. Several different substituted imidazolotriazinones have been synthesized in this manner.

1. Introduction

Phosphodiesterases (PDEs) are a large family of enzymes, which are responsible for breaking the phosphodiester bonds in biological molecules and some of them are involved in regulation of physiological functions.[1,2] Some of the PDEs are drug targets for the treatment of various diseases, including: heart failure, depression, asthma, inflammation, and erectile dysfunction.[3–5] In particular, phosphodiesterase 5 (PDE5), which is involved in the hydrolysis of a secondary messenger, cyclic guanosine monophosphate (cGMP), present in the corpus cavernosum tissue, plays an important role in mediating the sexual response.[6–8] Inhibition of PDE5 increases the cGMP level, triggering erection via relaxation of the penile arterioles.[9] Selective inhibitors of PDE5 have a great clinical significance in treatments of the erectile dysfunction disease and their other therapeutic applications are being proposed and investigated.[10,11] There are three commercially available drugs acting as PDE5 inhibitors, namely: sildenafil citrate (the active ingredient in Viagra), vardenafil (Levitra) and tadalafil.[12] A core structure in vardenafil **2**, which has been approved by the FDA and launched in 2003, is imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one—general structure **1** (Fig. 1).

Several method for the synthesis of imidazotriazinones have been reported so far.[13–17] They can be divided into two major groups depending on the sequence of steps of ring construction. These in which the triazinone ring is built at the beginning are generally based on the method described by Charles et al.,[17] where the ring is formed by condensation of an acyloamino-α-keto-ester **3a** or enol ester **3b** with a benzamidrazone **4** or generally amidrazone, as shown in Scheme 1.

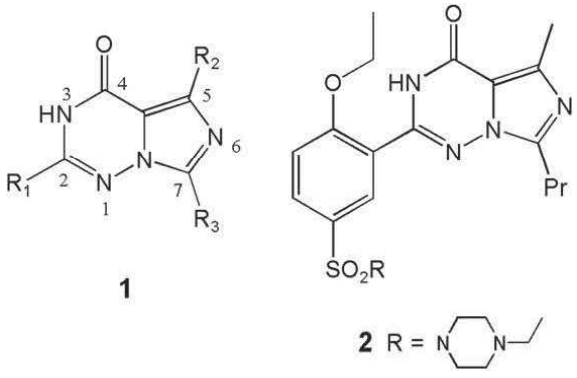

Fig. 1. Chemical structure of imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one **1** and vardenafil **2**.

The main drawback in this approach is the availability of the active intermediate **3a** or **3b**, both of which are obtained from α-amino acids and ethyl oxalate via the Dakin–West reaction.[18,19] It is well known that these compounds are very capricious and cannot be obtained with purity greater than 50%. This limitation led us to investigate a novel route for the construction of the imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one core, which does not require the reactive intermediate **3a** or **3b** and gives rise to the possibility of synthesis of different substituted imidazotriazinones.

* Corresponding author. E-mail address: marmilew@pg.gda.pl (M.J. Milewska).

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