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Synthesis of 2*H*-benzimidazole 1,3-dioxides, separase inhibitors, by reaction of *o*-benzoquinone dioximes with ketones

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ABSTRACT

The synthesis of novel 2*H*-benzimidazole 1,3-dioxides on the basis of *o*-benzoquinone dioximes interaction with ketones in the presence of acids is described. Nitration of these compounds by nitric acid in acetic acid yields the 5-nitro derivatives of 2*H*-benzimidazole 1,3-dioxide.

1. Introduction

2*H*-Benzimidazole 1,3-dioxides exhibit high biological activity and can be used as drugs against parasites *Tripanosoma cruzi* and *Leishmania* spp.[1] Approximately 30 million people are infected by these parasites, and more than 400 million are constantly under threat of infection according to the World Health Organization.[2] Recently, it was reported that 2*H*-benzimidazole 1,3-dioxides are inhibitors of separase - cysteine protease has playing an important role in cell division.[3] An appropriate patent has been published.[4] The most potent inhibitor according to the authors is 2,2-dimethyl-5-nitro-2*H*-benzimidazole 1,3-dioxide, that was first synthesized and described by us.[5] It was named Sepin-1. It was found that Sepin-1 inhibits the growth of malignant tumors by inhibiting separase in cancer cells.[6] The introduction of substituents other than methyl in the second position of the benzimidazole cycle, according to these authors, could increase the inhibitory activity of 2*H*-benzimidazole 1,3-dioxides against separase.

The search for biologically active compounds in the series of 2*H*-benzimidazole 1,3-dioxides as drugs, both against *Trypanosoma cruzi* and as separase inhibitor, involves the synthesis and biological testing of new compounds. Fig. 1 shows the possible locations of Sepin-1 molecule modification.

In this paper, we have considered significant changes in the structure of Sepin-1:

Modification 1 - the introduction of a nitro- and other groups in various positions of the benzene ring.

Modification 2 - introduction of various substituents other than methyl in the 2-position.

Modification 3 - removal one oxygen atom to afford monoxides of 2*H*-benzimidazole.

There are two methods of synthesis of 2*H*-benzimidazole 1,3-dioxides (Scheme 1): a) the reaction of benzofuroxans with secondary nitroalkane in the presence of bases,[7] b) the condensation of benzofuroxans with alcohols in the presence of acids.[8] Unfortunately, both methods have their limitations and provide the

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