Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 5303–5309

Synthesis of 2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones by the domino Michael addition retro-ene reaction of 2-alkoxyiminoimidazolidines and acetylene carboxylates

Jarosław Sączewski,[a,*] Zdzisław Brzozowski[a] and Maria Gdaniec[b]

[a]*Department of Chemical Technology of Drugs, Medical University of Gdańsk, Poland*
[b]*Department of Crystallography, A. Mickiewicz University, 60-780 Poznań, Poland*

Received 11 January 2005; revised 2 March 2005; accepted 18 March 2005

Available online 12 April 2005

Abstract—2-Alkoxyiminoimidazolidines **2**–**3** react with acetylene dicarboxylates and ethyl phenylpropiolate to give 8-alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones **C**, which subsequently undergo a sterically induced multihetero-retro-ene fragmentation to give imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones **4**–**7** together with formaldehyde or benzaldehyde. On the other hand, a similar reaction of **2**–**3** with ethyl propiolate gives corresponding 8-alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones **8**–**10**. The unsubstituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-one **11** can be prepared by retro-ene reaction of **9** upon prolonged heating in refluxing ethanol. A direct synthetic approach to 1-formyl-7-phenyl-imidazo[1,2-*a*]pyrimidine-5(1*H*)-one **14** is reported using DMF/sulfonyl chloride as a new Vilsmeier-type *N*-formylating reagent.

1. Introduction

Imidazo[1,2-*a*]pyrimidine-5-ones possess diverse biological activities and this structural motif is present in analgesics and inflammation inhibitors[1,2] benzodiazepine receptor ligands[3] as well as insecticidal, acaricidal and nematocidal agents.[4] The structural feature of imidazo[1,2-*a*]pyrimidine nucleus is related to the purine ring system, and therefore, we were interested in the synthesis of various substituted compounds of type **A** and **B** (Fig. 1) in anticipation of their anticancer activity.

The existing methods for building up the imidazo[1,2-*a*] pyrimidine core, which include the elaboration of 2-aminopyrimidines[5] or reaction of 2-aminoimidazoline with acetylene carboxylates,[1] are either multistep procedures or require ion exchange chromatography to obtain the free base of 2-aminoimidazoline. Moreover, the above methods are not general and the parent compound **B** (R, R^1=H) was not obtained.

Herein we report a new strategy for preparation of the compounds of type **A** and **B** based on two consecutive reactions: the well-established reaction of 2-aminoimidazolines with acetylene carboxylates[1], which leads to 2,8-dihydroimidazo[1,2-*a*]pyrimidin-5(3*H*)-ones (**A**, R= alkoxyl), and the retro-ene fragmentation associated with N^1-alkoxyamidine[6,7] giving rise to the formation of 2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones (**B**).

2. Results and discussion

The domino reactions have been defined as a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and where the subsequent reaction results as a consequence of the functional group formed in the previous step.[8,9]

In developing a new strategy for the synthesis of

2,8- dihydroimidazo[1,2-*a*] pyrimidin-5(3*H*)-ones

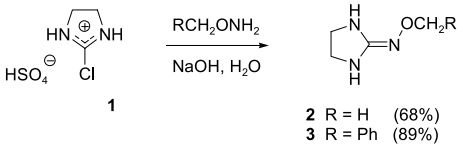
2,3- dihydroimidazo[1,2-*a*] pyrimidin-5(1*H*)-ones

Figure 1. Structures of imidazo[1,2-*a*]pyrimidin-5-ones.

Keywords: 2,3-Dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-ones; 8-Alkoxy-imidazo[1,2-*a*]pyrimidin-5(3*H*)-ones; Domono Michael addition retro-ene reacion; N-alkylation; N-acylation; N-formylation; X-ray crystal structure analysis.
* Corresponding author. Tel.: +48 58 3493250; fax: +48 58 3493257; e-mail: js@amg.gda.pl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.063

imidazo[1,2-*a*]pyrimidin-5-ones, we first focused on the ability to synthesize a bis-nucleophilic 2-alkoxyiminoimidazolidine that could undergo cyclocondensation upon treatment with acetylene carboxylates. As illustrated in Scheme 1, the desired 2-alkoxyiminoimidazolidines **2** and **3** were obtained in 68–89% yield from 2-chloro-4,5-dihydroimidazole (**1**) and commercially available *O*-methyl- and *O*-benzyl-hydroxylamines. The molecular structure of these compounds was confirmed by X-ray crystal structure analysis of **3** [CCDC 259437].



Scheme 1. Preparation of 2-alkoxyiminoimidazolidines **2** and **3**.

Novel reagents **2** and **3** thus developed were first utilized for the preparation of known[1] imidazo[1,2-*a*]pyrimidin-5-ones **4** and **7** as well as novel derivatives **5** and **6** as shown in Scheme 2. The two reagents were each reacted with acetylene dicarboxylates, ethyl phenylpropiolate or ethyl butynoate in suitable alcohol at reflux. The reaction sequence involves as the key intermediate, 8-alkoxyimidazopyrimidine **C**, which eludes isolation under the reaction conditions, and undergoes subsequent retro-ene fragmentation with simultaneous extrusion of aldehyde. Formaldehyde was trapped by dimedone, while the presence of benzaldehyde was confirmed by isolation of its 2,4-dinitrophenyl-hydrazone derivative.

It should be noted that the reaction of **2** and **3** with less reactive ethyl butynoate required 10 h to reach completion. The end products **4** and **7** were found to be identical in all respects (mp, IR, NMR and MS) with authentic samples synthesized independently.[1]

The fact that compounds **4**–**7** could be obtained without contamination by alternative products of type **D** (Scheme 2) underlines regiospecificity of the reaction. In order to identify nucleophilic sites in 2-iminoimidazolidine and 2-methoxyiminoimidazolidine (**2**) atomic charges were calculated.[15] As shown in Figure 2, introduction of an alkoxy group into 2-iminoimidazolidine evidently lowers the

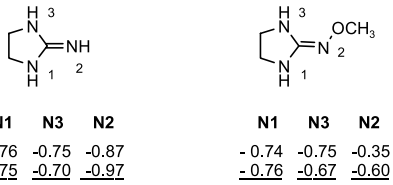


Figure 2. Calculated[15] atomic charges and charges derived from the electrostatic potential (underlined) of the nitrogen atoms of 2-iminoimidazolidine and 2-methoxyiminoimidazolidine (**2**).

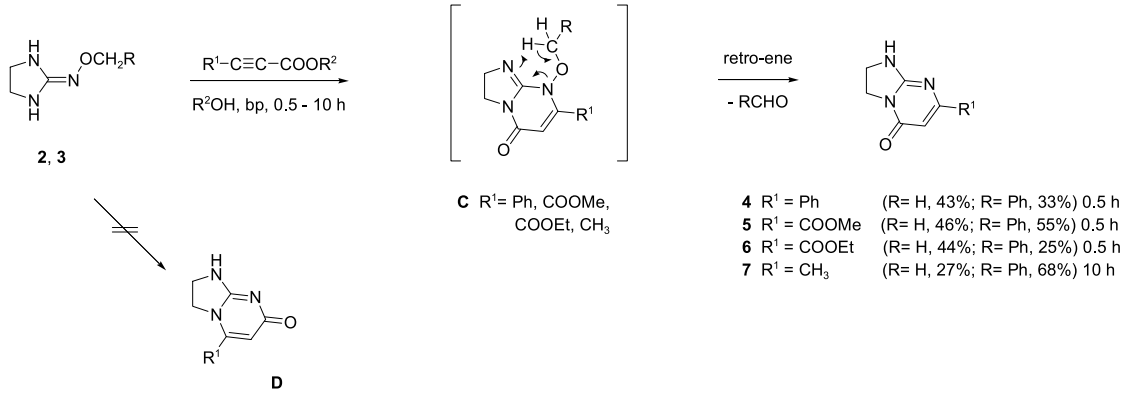
nucleophilicity of the exocyclic nitrogen atom sufficiently to prevent reaction with carboxylate.

Having established that the domino reaction takes place with both **2** and **3**, our attention was turned to its primary purpose: its ability to provide parent 2,3-dihydroimidazo[1,2-*a*]pyrimidine-5(1*H*)-one (**11**).

The reaction of **2** and **3** with ethyl propiolate in boiling ethanol for 0.5 h led to the formation of 8-alkoxyimidazo[1,2-*a*]pyrimidin-5-ones **8** and **9** (Scheme 3), the molecular structure of which was confirmed by X-ray crystal structure analysis [CCDC 259433 (**8**); CCDC 259436 (**9**)]. A similar reaction of 2-methoxyiminoimidazolidine (**2**) with ethyl butynoate gave 8-methoxyimidazo[1,2-*a*]pyrimidin-5-one (**10**) in 60% yield.

Apparently, the 8-alkoxy derivatives **8**, **9** and **10** are less reactive than **C** under identical conditions and can be separated from the reaction mixture in 81, 40 and 60% yield, respectively. It is well known that rates of retro-ene reactions may be enhanced[10–12] or diminished[13,14] by steric effects. The difference in reactivity between the **C** and **8**–**9** is presumably the result of the steric augmentation, i.e. the retro-ene process is induced by steric hindrance caused by bulky substituents at position 7 of **C**. The steric hindrance between the 7-phenyl or 7-alkoxycarbonyl and 8-alkoxy groups in **C** inhibits free rotation of the latter, which results in a fixed conformation that is conductive to a retro-ene mechanism.

We examined several reaction parameters including solvent, temperature, reaction time and type of bis-nucleophilic reagent **2** and **3**. At room temperature or shorter reaction time, the imidazopyrimidine **9** formation was incomplete. However, at higher temperature and reaction time greater



Scheme 2. Preparation of imidazo[1,2-*a*]pyrimidin-5-ones **4**–**7**.