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Chinese Chemical Letters 21 (2010) 1–4
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

7-Deazapurines: Synthesis of new pyrrolo[2,3-d]pyrimidin-4-ones catalyzed by a Brønsted-acidic ionic liquid as a green and reusable catalyst

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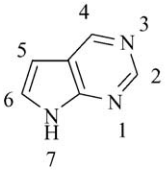
Received 2 July 2009

Abstract

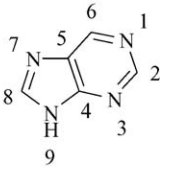
Some new 2-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones have been prepared through cyclocondensation of 2-amino-1*H*-pyrrole-3-carboxamides with aromatic aldehydes followed by air oxidation in the presence of 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate $[(CH_2)_4SO_3HMIM][HSO_4]$, a Brønsted-acidic ionic liquid, as a green and reusable catalyst in solvent-free conditions.

Keywords: Pyrrolo[2,3-d]pyrimidin-4-ones; 7-Deazapurines; Aromatic aldehydes; Brønsted-acidic ionic liquids

Pyrrolo[2,3-d]pyrimidine (**I**) may be regarded as an analogue of purine (**II**) in which its N-7 has been replaced by a CH group and therefore can be named as 7-deazapurine. Literature reports had already established pyrrolo[2,3-d]pyrimidins as antitumor [1], antimicrobial [2], antiangiogenic [3] agents with potential application as enzyme inhibitors [4]. 7-Deazapurine moiety is also found in some important antibiotics [5–7]. Moreover, these compounds have been shown to induce neurogenesis in murine embryonic stem cells [8]. On the other hand, 7-deazapurines have been synthesized as analogues of potent A_1- and A_2-adenosine receptor antagonists [9]. Some of 2-phenyl-4-substituted aminopyrrolo[2,3-d]pyrimidin derivatives have been identified as selective A_1-adenosine receptor antagonists [10]. The later compounds are generally prepared from pyrrolo[2,3-d]pyrimidin-4-ones as precursors [10].



(I)



(II)

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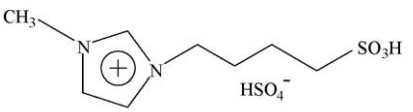
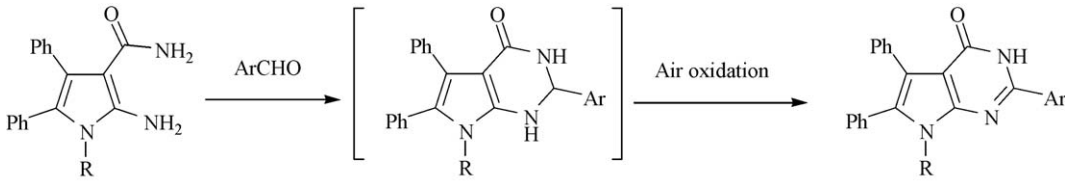
doi:10.1016/j.cclet.2009.09.002



[$(CH_2)_4SO_3HMIM][HSO_4$]

Fig. 1. Brønsted-acidic IL structure.



1a-b **2a-i** **3a-i**

1a: R = CH_2Ph
1b: R = C_6H_{11}

3a: R = CH_2Ph, Ar = 3-ClC_6H_4
3b: R = CH_2Ph, Ar = 4-ClC_6H_4
3c: R = CH_2Ph, Ar = 3-MeC_6H_4
3d: R = CH_2Ph, Ar = 4-MeC_6H_4
3e: R = CH_2Ph, Ar = 4-$MeOC_6H_4$

3f: R = C_6H_{11}, Ar = 4-ClC_6H_4
3g: R = C_6H_{11}, Ar = 3-MeC_6H_4
3h: R = C_6H_{11}, Ar = 4-MeC_6H_4
3i: R = C_6H_{11}, Ar = 4-$MeOC_6H_4$

Scheme 1.

Prompted by these findings and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities [11–16], in this paper we wish to report an efficient approach to the synthesis of new 2-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones **3a–i** (7-deazapurines) using 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate [$(CH_2)_4SO_3HMIM][HSO_4$] (Fig. 1), a Brønsted-acidic ionic liquid (IL), as a green and reusable catalyst through cyclocondensation of 2-amino-1*H*-pyrrole-3-carboxamides **1a–b** with aromatic aldehydes followed by air oxidation (Scheme 1).

Ionic liquids (ILs), being recognized as environmentally benign media, have been widely applied in many reactions as catalysts or dual catalyst–solvent due to their low vapor pressure, reusability and high thermal and chemical stability [17,18]. The introduction of Brønsted-acidic functional groups into cations or anions of the ILs, especially the SO_3H-functional groups, obviously enhanced their acidities and water solubilities [19–21]. Therefore, Brønsted-acidic ILs can be used as highly efficient acidic catalysts. 3-Methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate [$(CH_2)_4SO_3HMIM][HSO_4$] is one of Brønsted-acidic ILs that can be easily prepared from the inexpensive available reagents [22]. There are many reports in the literature for the application of this catalyst in organic synthesis [22–24].

Treatment of 2-amino-1*H*-pyrrole-3-carboxamides **1a–b** [25] with aromatic aldehydes in the presence of [$(CH_2)_4SO_3HMIM][HSO_4$] as catalyst (Method A) in solvent-free conditions gave products identified as 2-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones **3a–i**. In the absence of the catalyst, the products were obtained in low yields, while good results were obtained in the presence of [$(CH_2)_4SO_3HMIM][HSO_4$]. The optimal amount of [$(CH_2)_4SO_3HMIM][HSO_4$] was 20 mol%, the higher amount of the catalyst did not increase the yields noticeably. The yields increased as the reaction temperature was raised and at 85 °C the products **3a–i** were obtained in good yields. Under these conditions, attempts to isolate the intermediates 2-aryl-1,2,3,7-tetrahydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones **2a–i** failed when we carefully monitored the reactions. The formation of the products **3a–i** was assumed to proceed *via* a cyclocondensation reaction followed by air oxidation of the intermediates **2a–i** (Scheme 1). The structural assignments of new compounds **3a–i** were based upon the spectral data (Section 1).

The preparation of the compounds **3a–i** in boiling glacial acetic acid and in the absence of the catalyst (Method B) was also investigated. Therefore, compounds **1a–b** were refluxed with various aromatic aldehydes in glacial acetic acid for the indicated time (Table 1). From the data in Table 1, it is obvious that in the presence of [$(CH_2)_4SO_3HMIM][HSO_4$], the reaction times are shorter and the yields are higher which is a good indication of the catalytic effect of the Brønsted-acidic IL.