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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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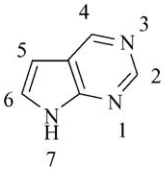
Abstract

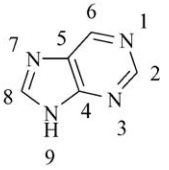
Some new 2-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones have been prepared through cyclocondensation of 2-amino-1*H*-pyrrole-3-carboxamides with aromatic aldehydes followed by air oxidation in the presence of 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate $[(CH_2)_4SO_3HMIM][HSO_4]$, 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Pyrrolo[2,3-d]pyrimidine (**I**) may be regarded as an analogue of purine (**II**) in which its N-7 has been replaced by a CH group and therefore can be named as 7-deazapurine.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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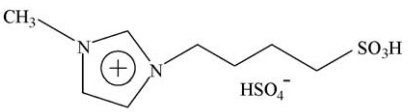
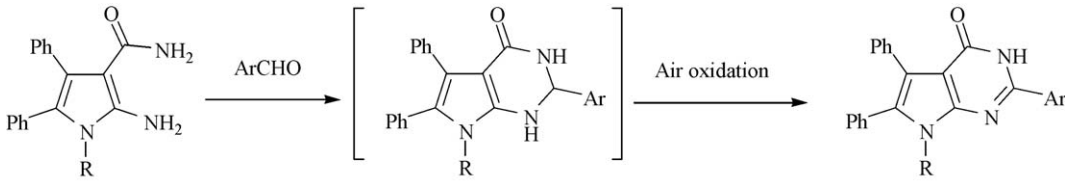


[$(CH_2)_4SO_3HMIM][HSO_4$]

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.

Table 1
Effect of the catalyst on the synthesis of compounds **3a–i**[a].

Entry	R	Ar	Method A		Method B		m.p. (°C)
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]	
3a	CH_2Ph	3-ClC_6H_4	90	81	420	71	285–287
3b	CH_2Ph	4-ClC_6H_4	60	82	270	73	296–298
3c	CH_2Ph	3-MeC_6H_4	70	84	360	73	248–250
3d	CH_2Ph	4-MeC_6H_4	60	86	300	75	287–289
3e	CH_2Ph	4-$MeOC_6H_4$	60	79	300	70	268–270
3f	C_6H_{11}	4-ClC_6H_4	50	85	210	76	367–369
3g	C_6H_{11}	3-MeC_6H_4	60	88	300	78	338–340
3h	C_6H_{11}	4-MeC_6H_4	50	90	240	80	318–320
3i	C_6H_{11}	4-$MeOC_6H_4$	50	88	240	76	352–354

[a] Method A: carboxamides **1a–b** (1 mmol), aromatic aldehyde (1.3 mmol) in the presence of $[(CH_2)_4SO_3HMIM][HSO_4]$ (20 mol%) at 85 °C in solvent-free conditions. Method B: carboxamides **1a–b** (1 mmol), aromatic aldehyde (1.3 mmol) in boiling glacial acetic acid (15 mL).
[b] Isolated yields.

In conclusion, we have reported the synthesis of some new 2-aryl-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-ones **3a–i** (7-deazapurines) through cyclocondensation of 2-amino-1*H*-pyrrole-3-carboxamides **1a–b** with aromatic aldehydes followed by air oxidation in the presence and absence of $[(CH_2)_4SO_3HMIM][HSO_4]$, a Brønsted-acidic IL. In the presence of $[(CH_2)_4SO_3HMIM][HSO_4]$, the reaction times are shorter and the yields are higher. It is also noteworthy to mention that the catalyst can be recovered and reused without loss of its structure and activity.

1. Experimental

All chemicals were commercially available and used without further purification. The Brønsted-acidic ionic liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ was synthesized according to the literature. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument.

*1.1. Preparation of 2-aryl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-ones **3a–i**: general procedure*

1.1.1. Method A

A mixture of 2-amino-1*H*-pyrrole-3-carboxamides **1a–b** (1 mmol), the appropriate aromatic aldehyde (1.3 mmol) and $[(CH_2)_4SO_3HMIM][HSO_4]$ (0.2 mmol, 20 mol%) was heated on the oil bath at 85 °C for 50–90 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and then water was added. The precipitate was filtered off and recrystallized from EtOH/$CHCl_3$ to give compounds **3a–i** in good yields. The catalyst is soluble in water and therefore could be recycled of the filtrate by evaporation of the water in vacuo. The recovered catalyst was washed with diethyl ether, dried at 50 °C under vacuum for 1 h and reused in another reaction without appreciable reduction in the catalytic activity. Such procedure applied for **3d** in a second run resulted in 84% yield.

1.1.2. Method B

To a solution of 2-amino-1*H*-pyrrole-3-carboxamides **1a–b** (1 mmol) in boiling glacial acetic acid (15 mL), the appropriate aromatic aldehyde (1.3 mmol) was added. The reaction mixture was heated under reflux for 3.5–7 h. After the completion of the reaction (monitored by TLC, n-hexane:ethylacetate, 80:20), the mixture was cooled to room temperature and allowed to stand at room temperature overnight. The precipitate was then collected and recrystallized from EtOH/$CHCl_3$ to give compounds **3a–i** in good yields.

*7-Benzyl-2-(3-chlorophenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one **3a***. ^{1}H NMR ($CDCl_3$): δ 5.45 (s, 2H, CH_2), 6.90–8.10 (m, 19H, arom-H), 11.32 (br s, 1H, NH); IR (KBr disc): υ 1665 (C=O), 3448 cm^{-1} (NH); MS, *m/z*: 489 (M^++2), 487 (M^+).

7-Benzyl-2-(4-chlorophenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3b***. ^{1}H NMR ($CDCl_3$): δ 5.47 (s, 2H, CH_2), 6.90–8.30 (m, 19H, arom-H), 11.90 (br, 1H, NH); IR (KBr disc): υ 1667 (C=O), 3409 cm^{-1} (NH); MS, *m/z*: 489 (M^++2), 487 (M^+).

7-Benzyl-2-(3-methylphenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3c***. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 6.85–8.10 (m, 19H, arom-H), 11.30 (br s, 1H, NH); IR (KBr disc): υ 1666 (C=O), 3393 cm^{-1} (NH); MS, *m/z*: 467 (M^+).

7-Benzyl-2-(4-methylphenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3d***. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 6.80–8.10 (m, 19H, arom-H), 12.05 (br s, 1H, NH); IR (KBr disc): υ 1667 (C=O), 3378 cm^{-1} (NH); MS, *m/z*: 467 (M^+).

7-Benzyl-2-(4-methoxyphenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3e***. ^{1}H NMR ($CDCl_3$): δ 3.71 (s, 3H, CH_3O), 5.37 (s, 2H, CH_2), 6.50–8.40 (m, 19H, arom-H), 12.50 (br s, 1H, NH); IR (KBr disc): υ 1656 (C=O), 3395 cm^{-1} (NH); MS, *m/z*: 483 (M^+).

2-(4-Chlorophenyl)-7-cyclohexyl-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3f***. ^{1}H NMR ($CDCl_3$): δ 1.10–2.20 (m, 8H, cyclohexyl), 2.50–3.05 (m, 2H, cyclohexyl), 3.80–4.30 (m, 1H, CH-N), 6.90–8.25 (m, 14H, arom-H), 12.52 (br s, 1H, NH); IR (KBr disc): υ 1673 (C=O), 3386 cm^{-1} (NH); MS, *m/z*: 481 (M^++2), 479 (M^+).

7-Cyclohexyl-2-(3-methylphenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3g***. ^{1}H NMR ($CDCl_3$): δ 1.05–2.20 (m, 8H, cyclohexyl), 2.32 (s, 3H, CH_3), 2.55–3.10 (m, 2H, cyclohexyl), 3.80–4.30 (m, 1H, CH-N), 7.00–8.20 (m, 14H, arom-H), 11.65 (br s, 1H, NH); IR (KBr disc): υ 1649 (C=O), 3380 cm^{-1} (NH); MS, *m/z*: 459 (M^+).

7-Cyclohexyl-2-(4-methylphenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3h***. ^{1}H NMR ($CDCl_3$): δ 0.90–2.10 (m, 8H, cyclohexyl), 2.28 (s, 3H, CH_3), 2.45–3.00 (m, 2H, cyclohexyl), 3.70–4.15 (m, 1H, CH-N), 6.75–8.20 (m, 14H, arom-H), 12.09 (br s, 1H, NH); IR (KBr disc): υ 1672 (C=O), 3348 cm^{-1} (NH); MS, *m/z*: 459 (M^+).

7-Cyclohexyl-2-(4-methoxyphenyl)-5,6-diphenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one ***3i***. ^{1}H NMR ($CDCl_3$): δ 0.90–2.20 (m, 8H, cyclohexyl), 2.40–3.00 (m, 2H, cyclohexyl), 3.55–4.15 (m, 4H, CH_3O and CH-N), 6.40–8.30 (m, 14H, arom-H), 12.26 (br s, 1H, NH); IR (KBr disc): υ 1648 (C=O), 3395 cm^{-1} (NH); MS, *m/z*: 475 (M^+).

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