General Synthetic Approach to 2-Phenolic Adenine Derivatives

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Abstract: A simple and general 'one-pot' procedure for the synthesis of 2,9-diarylpurines with one or multiple hydroxyl groups in the 2-aryl unit is described, from the reaction of 5-amino-4-amidinoimidazoles with phenolic aldehydes.

Key words: nucleobases, phenols, condensations, aldehydes, ring closure

Purines have attracted attention of the scientific community mainly due to their biological activity.[1] During the last decade, purine derivatives were identified as a promising new class of antitubercular agents. The research was focused on the synthesis of nucleoside analogues as siderophore biosynthesis inhibitors[2] and on non-nucleosides.[3] In the non-nucleoside series, purines having an aryl, a small alkyl, or a proton on N-9 were essentially inactive, whereas 9-benzyl-6-(2-furyl)purines,[3b,h,j] 9-sulfonyl-6-mercaptopurines, or 6-alkylthiopurines[3e,k] were highly potent. In addition, we recently described the first example of 2,9-diarylpurines (Figure 1) active against *Mycobacterium tuberculosis*.[4] The results from biological evaluation showed that the potency of the compounds depends on the substituents in N-9, C-2, and C-6 of the purine core. The presence of a 4-tolyl group in N-9 and a 3-hydroxyphenyl or a 4-hydroxyphenyl substituent in C-2 combined with a secondary amine in C-6 proved to be important features for activity (Figure 1) but a clear structure–activity correlation pattern could not be identified.[4]

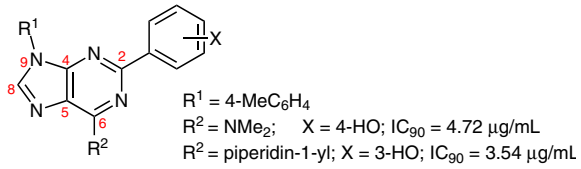

Figure 1 Hit compounds active on *Mycobacterium tuberculosis*

A number of synthetic methods were developed to incorporate functional groups in the purine core, but costly reagents are usually required.[5a,b] In our research group purine derivatives have been obtained by a simple and inexpensive synthetic approach that uses the versatile reactivity of a substituted imidazole.[4,5c–l]

The 6-amino-2,9-diarylpurines (Figure 1) are a new promising scaffold active against *Mycobacterium tuberculosis* and the presence of hydroxyl groups in the aryl subunit in C-2 was considered an important feature for activity. The microorganism needs iron for the biochemical processes, and multiple hydroxyl groups in the phenolic subunit could enhance the complexation with the metal. This perception prompted us to develop a new synthetic approach that would allow the efficient synthesis of purines **6** (Table 1) having a phenolic subunit in C-2 with two and three hydroxyl substituents. The previous method only allowed the introduction of phenolic units with one hydroxyl group as the reaction with polyphenolic aldehydes, performed in basic medium, was very slow (8–54 d) and extensive degradation occurred.[4]

Herein we describe a new and general synthetic approach for 6-amino-9-aryl-2-hydroxy or 2-(polyhydroxyphenyl)purines **6** using imidazole **1**, phenolic aldehydes **2**, and a cascade of acid and base catalysis.

When compound **1a** (Scheme 1) was combined with 3,4,5-trihydroxybenzaldehyde (**2a**) in ethanol at 0 °C, using trifluoroacetic acid as catalyst, the starting materials were dissolved and a new white solid precipitated after five minutes. This compound was identified as the trifluoroacetate salt of starting material **3**. When the reaction was repeated using 2.0 equivalents of the acid, a yellow solid precipitated after four hours and was identified as **4a**[6] (Scheme 1).

When imidazole **1b** was reacted with monohydroxy or dihydroxyphenylaldehydes **2b** or **2c**, at 6 °C, no solid precipitated from the initial yellow solutions. When the TLC showed the absence of imines **4**, off-white solids were isolated and identified as dihydropurines **5a**,**b**[7a] (Scheme 1, method i). Dihydropurine **5c**[7a] was also isolated in the reaction of imidazole **1a** with 3,4,5-trihydroxyphenylaldehyde (**2a**) when the reaction was carried out at room temperature (Scheme 1, method i). The imine **4a** also evolved to the dihydropurine **5c**[7b] after ten days in ethanolic solution at 8 °C (Scheme 1, method ii).

The pure imine **4a** showed a single spot on TLC, however, by ^{1}H NMR spectroscopy the spectrum obtained in DMSO solution showed signals consistent with the presence of two compounds in a 7:3 molar ratio. The major compound was identified as **4a** (70%) and the minor compound as the dihydropurine **5c** (30%). These results suggested that, in DMSO solution, the imine **4a** was cyclizing to the dihydropurine **5c**. In order to confirm this result a new ^{1}H NMR spectrum was registered after two hours. The spectrum showed once again a mixture of **4a** and **5c** but in a 1:9 molar ratio, and this ratio did not change after one week at room temperature.

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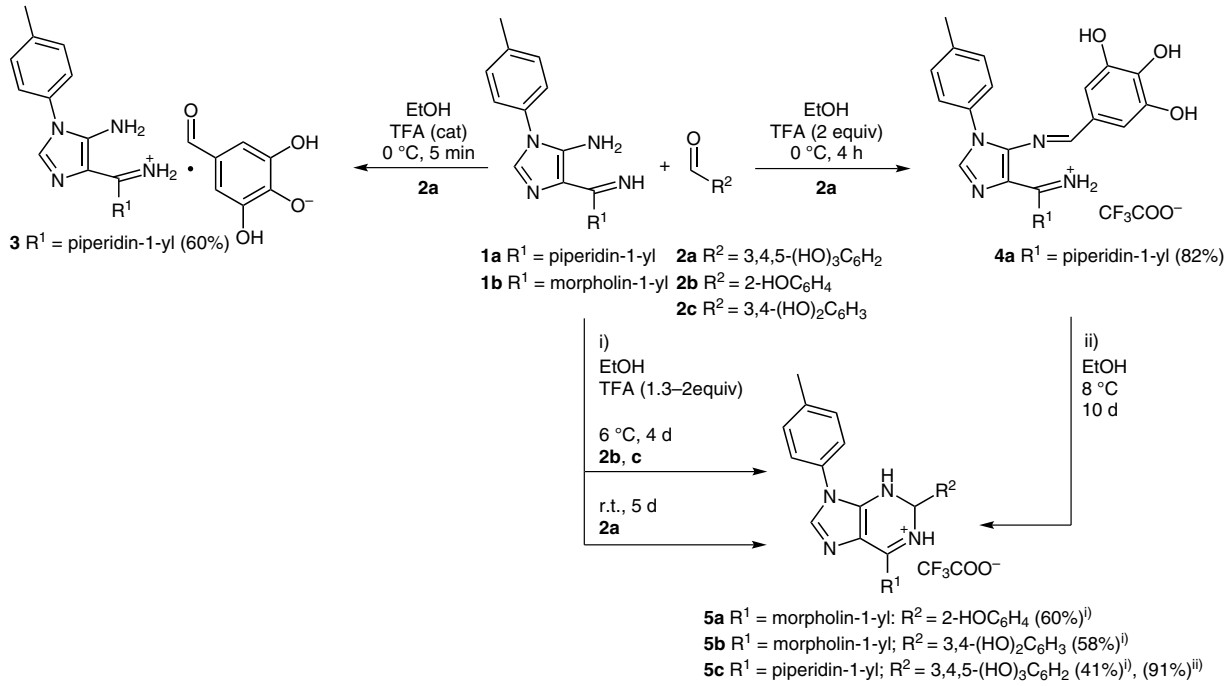

Scheme 1 Reactions of imidazoles **1** with phenolic aldehydes **2** in acidic medium

When the solution was heated in the NMR tube at 60 °C during ten minutes a mixture of **4a** and **5c** was still present, however, new signals were observed in the spectrum, assigned to purine **6i** and to the imidazole **1a** and aldehyde **2a**, the starting reagents. The hydrolysis of the imine **4a** was also observed by ^{1}H NMR spectroscopy in an acidified solution of **4a** in DMSO-d_6. These results indicate that in DMSO solution at room temperature the imine **4a** evolves rapidly to the dihydropurine **5c** leading to an equilibrium mixture. Under heating, compound **5c** evolves to generate the purine **6i**. However, in acid solution hydrolysis of the imine regenerates the starting materials **1a** and **2a**.

The dihydropurine **5c** was also solubilized in DMSO-d_6 and the ^{1}H NMR spectrum, acquired after five minutes, showed that **5c** was the only product present in solution. However, after the addition of triethylamine and heating at 80 °C for 20 hours only purine **6i** was present in solution.

Considering that (1) the reaction of imidazoles **1** with aldehydes **2** led to imines **4** and dihydropurines **5** (in EtOH in the presence of 1.3–2 equiv of TFA), and (2) compounds **4** and **5** with triethylamine in DMSO solution under heating generated the desired purine **6**, a new 'one pot' synthetic procedure starting from imidazoles **1** and aldehydes **2** leading to purines **6**[8] has been designed. The reaction was initially carried out in ethanol and acid (1.3–2 equiv) until total consumption of the starting materials (by TLC). The solvent was then removed in the rotary evaporator, and the reactions proceeded in DMSO and base under heating.

These experimental conditions were applied to the reaction of imidazoles **1a**–**c** with aldehydes **2a**–**g**, having one, two, or three hydroxyl groups. The purines **6a**–**k** were obtained directly from the reaction mixture after 2–10 days (Table 1). When degradation was observed, the pure products were isolated in lower yields after dry flash chromatography (compounds **6e**–**h**).

In summary this work describes a new versatile and simple 'one-pot' method to synthesize 6-amino-9-substituted 2-hydroxy or 2-(polyhydroxyphenyl)purines **6** starting from imidazoles **1** and phenolic aldehydes **2**. The formation of the imine intermediate is favored in ethanol using acid catalysis, however, the cyclization and oxidation, to generate the purine core, is favored in dimethylsulfoxide under heating using base catalysis.

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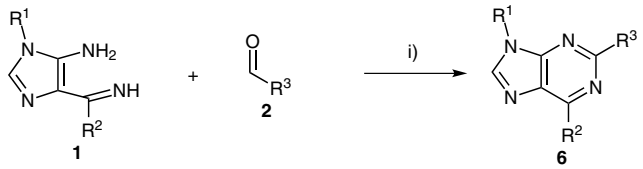
Table 1 Synthesis of Purines **6**



Imidazole			Aldehyde		Reaction conditions	Product	Yield
1	R^1	R^2	**2**	R^3		**6**	(%)
1b	4-MeC_6H_4	morpholin-1-yl	**2b**	2-HOC_6H_4	i) a) **1b** (0.12 g), **2b** (1.1 equiv), EtOH, TFA (1.3 equiv), 11 °C, 1 d b) DMSO (0.2 mL), Et_3N (10 equiv), 40 °C, 2 d	**6a**	73
1b	4-MeC_6H_4	morpholin-1-yl	**2d**	3-HOC_6H_4	i) a) **1b** (0.12 g), **2d** (1.1 equiv), EtOH, TFA (1.3 equiv), 11 °C, 7 d b) DMSO (0.2 mL), Et_3N (10 equiv), 40 °C, 2 d	**6b**	79
1b	4-MeC_6H_4	morpholin-1-yl	**2e**	4-HOC_6H_4	i) a) **1b** (0.13 g), **2e** (1.1 equiv), EtOH, TFA (1.3 equiv), 11 °C, 1 d b) DMSO (0.2 mL), Et_3N (10 equiv), 40 °C, 2 d	**6c**	78
1b	4-MeC_6H_4	morpholin-1-yl	**2f**	2,3-$(HO)_2C_6H_3$	i) a) **1b** (0.17 g), **2f** (1.1 equiv), EtOH, TFA (2.0 equiv), r.t., 30 min b) DMSO, EtOH, Et_3N(10 equiv), 40 °C, 6 d	**6d**	88
1b	4-MeC_6H_4	morpholin-1-yl	**2c**	3,4-$(HO)_2C_6H_3$	i) a) **1b** (0.12 g), **2c** (1.1 equiv), EtOH, TFA (1.3 equiv), 11 °C, 1 d b) DMSO, Et_3N (10 equiv), 40 °C, 4 d	**6e**	58
1b	4-MeC_6H_4	morpholin-1-yl	**2g**	2,3,4-$(HO)_3C_6H_2$	i) a) **1b** (0.30 g), **2g** (1.1 equiv), EtOH, TFA (1.3 equiv), r.t., 1 d b) DMSO, Et_3N (10 equiv), 40 °C, 6 d	**6f**	59
1b	4-MeC_6H_4	morpholin-1-yl	**2a**	3,4,5-$(HO)_3C_6H_2$	i) a) **1b** (0.28 g), **2a** (1.1 equiv), EtOH, TFA (1.3 equiv), r.t., 6 d b) DMSO, Et_3N (10 equiv), 40 °C, 1 d	**6g**	50
1a	4-MeC_6H_4	piperidin-1-yl	**2c**	3,4-$(HO)_2C_6H_3$	i) a) **1a** (0.21 g), **2c** (1.1 equiv), EtOH, TFA (1.5 equiv), r.t., 6 d b) DMSO, Et_3N (10 equiv), 40 °C, 4 d	**6h**	57
1a	4-MeC_6H_4	piperidin-1-yl	**2a**	3,4,5-$(HO)_3C_6H_2$	i) a) **1a** (0.21 g), **2a** (1.1 equiv), EtOH, TFA (1.5 equiv), r.t., 10 d b) DMSO, Et_3N (10 equiv), 80 °C, 1 d	**6i**	57
1c	4-MeC_6H_4	thiomorpholin-4-yl	**2a**	3,4,5-$(HO)_3C_6H_2$	i) a) **1c** (0.16 g), **2a** (1.1 equiv), EtOH, TFA (1.3 equiv), r.t., 5 d b) DMSO, Et_3N (10 equiv), 80 °C, 1 d	**6j**	67
1c	4-MeC_6H_4	thiomorpholin-4-yl	**2g**	2,3,4-$(HO)_3C_6H_2$	i) a) **1c** (0.11 g), **2g** (1.1 equiv), EtOH, TFA (1.3 equiv), r.t., 4 d b) DMSO, Et_3N (10 equiv), 40 °C, 5 d	**6k**	60

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(6) **Procedure for the Synthesis of Imine 4a (Scheme 1)**
To a stirred suspension of imidazole **1a** (0.14 g, 0.49 mmol) in EtOH (0.4 mL), aldehyde **2a** (0.09 g, 1.1 equiv) and TFA (75 µL, 2 equiv) were added at 0 °C. A yellow solution developed, and a yellow solid started to precipitate after 25 min. When the TLC indicated the absence of starting material (4 h), EtOH was added (0.8 mL), and the yellow solid was filtered. The solid was washed with EtOH and Et_2O and identified as compound **4a** (0.22 g, 0.40 mmol, 82%); mp 124–126 °C. IR (mull): 3498, 3352, 3210, 1665, 1626, 1604, 1586, 1521 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.62 (s, 6 H, CH_2), 2.37 (s, 3 H, CH_3), 3.58 (br s, 4 H, CH_2), 6.82 (s, 2 H, ArH), 7.30–7.45 (m, 4 H, ArH), 8.17 (s, 2 H, 2-H, N=CH), 8.80–9.60 (m, 5 H, NH, HO, D_2O exchangeable). Anal. Calcd for $C_{23}H_{25}N_5O_3 \cdot TFA \cdot H_2O$: C, 54.44; H, 5.08; N, 12.70. Found: C, 54.68; H, 5.41; N, 12.45.

(7) **Procedure for the Synthesis of Dihydropurine 5c (Scheme 1)**
(a) **Method i**
Aldehyde **2a** (0.07 g, 1.0 equiv) and TFA (40 µL,1.3 equiv) were added to a stirred suspension of imidazole **1a** (0.11 g, 0.40 mmol) in EtOH (2.0 mL) at r.t. The yellow solution became light yellow, and when TLC showed the absence of imine **4** (5 d), the solution was concentrated in the rotary evaporator. The off-white solid was filtered, washed with EtOH and Et_2O and identified as compound **5c** (0.09 g, 0.16 mmol, 41%).
(b) **Method ii**
A yellow ethanolic solution of **4a** (0.09 g, 0.16 mmol) was stirred at 8 °C until TLC showed the absence of starting material (10 d). The solution was concentrated in the rotary evaporator leading to an off-white solid that was filtered and washed with Et_2O and identified as compound **5c** (0.08 g, 0.15 mmol, 91%); mp 218–220 °C. IR (mull): 3535, 3202, 1679, 1613, 1530 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.69 (s, 6 H, CH_2), 2.39 (s, 3 H, CH_3), 3.70 (m, 4 H, CH_2), 5.71 (t, 1 H, *J* = 4.8 Hz, 2-H), 6.28 (s, 2 H, ArH), 7.40–7.46 (m, 4 H, ArH), 7.88 (s, 1 H, 8-H), 8.07 (d, 1 H, *J* = 4.8 Hz, NH, D_2O exchangeable), 8.23 (br s, 1 H, HO, D_2O exchangeable), 8.88 (d, 1 H, *J* = 4.8 Hz, NH, D_2O exchangeable), 8.99 (s, 2 H, HO, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.62 (CH_3), 23.32, 25.80, 48.82, 64.77 (2-C), 105.12, 110.60, 124.14, 129.16, 130.32, 130.88, 133.39, 135.14 (8-C), 138.65, 145.73, 145.84, 150.00. Anal. Calcd for $C_{23}H_{25}N_5O_3 \cdot TFA \cdot 2.1H_2O$: C, 52.56; H, 5.29; N, 12.26. Found: C, 52.55; H, 5.10; N, 12.07.

(8) **Procedure for the Synthesis of Purine 6f (Table 1)**
Aldehyde **2g** (0.18 g, 1.1 equiv) and TFA (166 µL, 1.3 equiv) were added to a stirred suspension of imidazole **1b** (0.30 g, 1.08 mmol) in EtOH (0.3 mL) at r.t. during 1 d. Then, the solvent was removed in the rotary evaporator, and DMSO (0.3 mL) was added to the crude solid followed by Et_3N (1.35 mL, 10 equiv), and the reaction was stirred at 40 °C during 6 d. Addition of H_2O and cooling for 10 min led to a brown solid that was filtered and washed with H_2O and Et_2O (0.42 g). The brown solid was purified by dry flash chromatography on silica gel using 500 mL of Et_2O as eluent to give an off-white solid identified as **6f** (0.25 g, 0.60 mmol, 59%); mp >300 °C. IR (mull): 3550, 3465, 3337, 3101, 1637, 1624, 1581, 1528 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 2.41 (s, 3 H, CH_3), 3.85 (s, 4 H, CH_2), 4.30 (br s, 4 H, CH_2), 6.36 (d, 1 H, *J* = 9.0 Hz, ArH), 7.43 (d, 2 H, *J* = 8.4 Hz, ArH), 7.64 (d, 2 H, *J* = 8.7 Hz, ArH), 7.68 (d, 1 H, *J* = 9.0 Hz, ArH), 8.24 (br s, 1 H, HO, D_2O exchangeable), 8.45 (s, 1 H, 8-H), 9.16 (br s, 1 H, HO, D_2O exchangeable), 13.45 (s, 1 H, HO, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.64 (CH_3), 45.52, 66.13, 107.05, 111.53, 117.57, 119.45, 123.82, 130.17, 131.99, 132.69, 137.77, 139.18 (8-C), 148.54, 148.93, 149.36, 152.66, 158.86 (2-C). Anal. Calcd for $C_{22}H_{21}N_5O_4 \cdot 0.5H_2O$: C, 61.68; H, 5.14; N, 16.36. Found: C, 61.75; H, 5.06; N, 16.20.

