One-Pot Regioselective Synthesis of 2,6,9-Trisubstituted Adenines

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Abstract: A series of 2,6,9-substituted adenines were obtained from the easily accessible 5-amino-4-cyanoformimidoyl imidazoles, acetic and benzoic anhydrides, and primary alkyl amines in a three-step sequence. Acylation of 5-amino-4-cyanoformimidoyl imidazoles followed by addition of the amine led to the intermediates 5-amino-4-(*N*-acyl)formamidino imidazoles under mild conditions. Cyclization of 5-amino-4-(*N*-acyl)formamidino imidazoles under reflux in ethanol led to the desired substituted adenine. A preliminary stepwise study led to the development of three general and efficient one-pot methods for the synthesis of adenine derivatives. The one-pot, three-step reaction in the presence of DMAP was the most convenient synthetic approach.

Key words: heterocycles, cyclization, ring closure, ring opening, imidazole, purine

Adenine is one of the most important naturally occurring nitrogen heterocycles. This purine nucleobase plays a fundamental role in the nucleic acid chemistry and cellular biochemistry.[1] In fact, the function of a remarkable number of proteins is governed by adenine nucleotides as cofactors or co-substrates.[1,2] Moreover, the increasing number of reports describing new biological activities of synthetic adenine derivatives reveals the great potential of these compounds as new chemical-biological tools and therapeutic target as enzyme inhibitors or receptor agonists/antagonists.[2,3] For instance, adenines, adenine nucleosides, and their analogues have found potential therapeutic application against cancer,[4] autoimmune disease,[5] viral infections,[6] and microbial infections.[7] The natural catalytic role and supramolecular assembly capacity of adenine inspired intense research on the field of organocatalysis and other applications ranging from coordination chemistry to the synthesis of new materials.[1,8]

The most common synthetic method to prepare 2- and 6-substitued adenines involves nucleophilic substitution of a suitable leaving group from commercially available 2-halo and 6-chloro, 6-amino or 6-sulfonyl purines with amines or carbon nucleophiles and metal-catalyzed couplings.[2–7] To introduce functionality at the 9-position, *N*-alkylation(arylation) of adenine or 6-chloropurine has been accessed by treatment with alkyl halides, by a Mitsunobu reaction with an appropriate alcohol, or the coupling of purine bases with aryl boronic acids.[2,9] These methods suffer from several drawbacks including the use of toxic, expensive, and explosive reagents. An alternative route is amination of the 5-amino-4,6-dihalopyrimidine, followed by a ring-closing reaction with triethyl orthoformate or acid derivatives.[2,4b,9c]

To the best of our knowledge, there are few reports on the synthesis of adenines from 5-amino-4-carboxamidino imidazoles, prepared from ring opening of *N*1-alkoxyadenines or from 5-amino-4-cyano imidazoles, mostly involving multistep, low-yield processes.[10]

In our research group, 5-amino-4-cyanoformimidoyl imidazoles **1** have been used as versatile precursors for substituted purines.[11] In previous work, imidazoles **1** were easily reacted with ethyl chloroformate at the imine carbon atom. The obtained ethoxycarbonyl derivatives promptly reacted with methyl and benzylamine under mild conditions to give mixtures of *N*1- and *N*6-substituted isoguanines.[12a] The acylation of imidazoles **1** with acetic and benzoic anhydrides also occurred under mild experimental conditions, and the corresponding acetyl and benzoyl imidazoles **2** and **3** were obtained in good yield (Table 1). The reaction of **2** and **3** with hydrazine led to imidazolyl 1,2,4-triazoles.[12b]

In the present work, an efficient synthetic method was developed for the preparation of 2,6,9-substituted adenines **6/7** from imidazoles **2/3** and primary aliphatic amines (Table 1).

When benzylamine was added to a suspension of **2** in ethanol, the resulting solution was concentrated in the rotary evaporator using a hot bath to accelerate the process. Addition of acetone to the residue gave a first crop of a white solid identified as adenine **6a**. The second crop, isolated by the same method, proved to be a mixture of two components in a 2:1 ratio. The major component was identified as the desired product **4a** and, according to ^{1}H NMR data, imidazole **8a** was the most plausible structure for the second component (Scheme 1). Attempts to reproduce this procedure evidenced that this is an instantaneous reaction even at 0 °C, nevertheless the product **4a** always remained in solution. Maintaining the reaction mixture for ca. 24 hours, at room temperature, led to a mixture of **8a** and adenine **6a** as a minor contaminant. Heating the reaction mixture for several hours, at 40–80 °C, selectively led to adenine **6a**.

The same reaction was carried out in dichloromethane at room temperature, and the bright yellow solid disappeared instantly also leading to a homogeneous solution. The pure imidazole **4a** could be isolated as an off-white solid, in 71% yield, but a careful workup was required to avoid evolution of this compound in solution.

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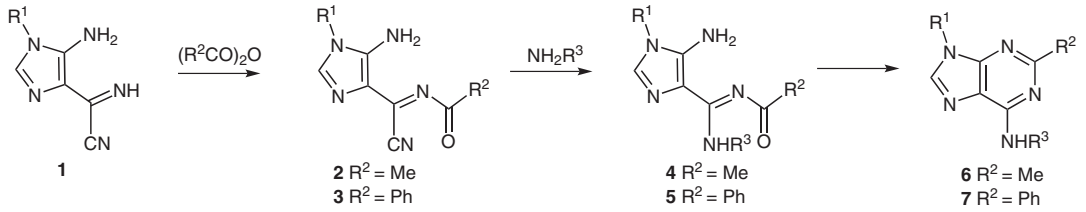
In a final attempt, the same synthesis was performed using acetonitrile at 0 °C. The imidazole **4a** precipitated from solution after 20 minutes and was isolated in 63% yield. Evolution to side products was never detected. Thus, acetonitrile was selected for the preparation of **4b–d** and the products were isolated in 44–63% yield (Table 1).[13]

Attempts to prepare imidazoles **4/5** with other primary amines demonstrated that, in general, these products are not easy to isolate.

Table 1 Synthesis of Compounds **4–7**



Compd	R^1	R^3	Method[a]	Reaction conditions[a]	Yield (%)
4a	Ph	Bn		MeCN, 20 min, 0 °C	63
4b	Me	Bn		MeCN, 10 min, 0 °C	47
4c	Me	Me		MeCN, 5 min, 0 °C	44
4d	Me	*i*-Pr		MeCN, 10 min, r.t.	56
5b	Me	Bn		MeCN, 90 min, r.t.	59
6a	Ph	Bn	D	1. MeCN, DMAP, 5 min, r.t. 2. EtOH, 1 h, reflux	76
6b	Me	Bn	C	1. MeCN, 1 h, r.t. 2. EtOH, 6.5 h, reflux	80
6c	Me	Me	A	EtOH, 2.5 h, reflux	90
6d	Me	*i*-Pr	A A	EtOH, 35 min, reflux MeCN, 2.5 h, reflux	96 94
6e	Ph	Me	A	EtOH, 5 min, reflux	92
6f	4-MeC_6H_4	Bn	C	1. MeCN, 3 h, r.t. 2. EtOH, 6 h, reflux	55
6g	4-FC_6H_4	Bn	C	1. MeCN, 3 h, r.t. 2. EtOH, 7 h, reflux	67
6h	4-FC_6H_4	$(CH_2)_2OMe$	B	1. EtOH, 5 min, r.t. 2. MeCN, 3 h, reflux	36
6i	$(CH_2)_2OH$	$(CH_2)_2OMe$	D	1. MeCN, DMAP, 5 min, r.t. 2. EtOH, 2 h, reflux	52
6j	4-FC_6H_5	Me	D	1. MeCN, DMAP, 5 min, r.t. 2. EtOH, 1 h, reflux	88
7b	Me	Bn	A	EtOH, 1.5 h, reflux	75
7f	4-MeC_6H_4	Bn	B	1. MeCN, 2 h, r.t. 2. MeCN,7 h, reflux	50
			C	1. MeCN, 5 h, r.t. 2. EtOH, 5 h, reflux	63
7g	4-FC_6H_4	Bn	C	1. MeCN, 3 h, r.t. 2. EtOH, 7.5 h, reflux	67

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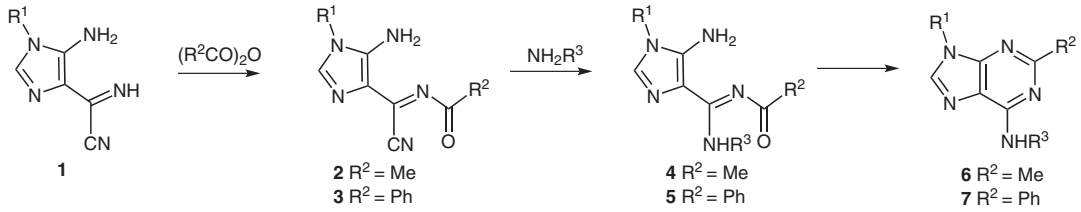
Table 1 Synthesis of Compounds **4–7** (continued)



Compd	R^1	R^3	Method[a]	Reaction conditions[a]	Yield (%)
7j	4-FC_6H_4	Me	C	1. MeCN, 5 h, r.t. 2. EtOH, 9 h, reflux	40
			D	1. MeCN, 5 h, r.t. 2. EtOH, 5 h, reflux	53
7l	$(CH_2)_2OH$	Bn	C	1. MeCN, 6 h, r.t. 2. EtOH, 9 h, reflux	62
7m	Bn	$(CH_2)_2OMe$	B	1. MeCN, 30 min, r.t. 2. EtOH, 7 h, reflux	49

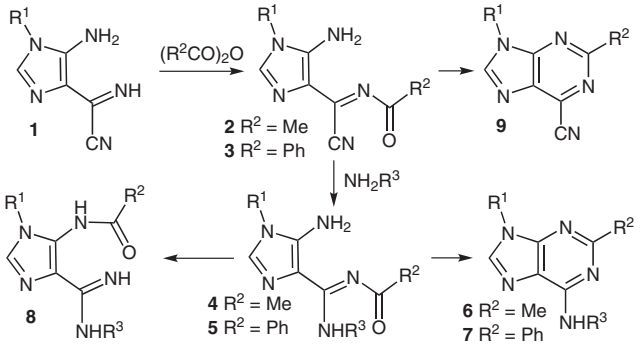
[a] Method A (from **4** or **5**): MeCN or EtOH, reflux. Method B (from **2** or **3**): 1. RNH_2 (1.2 equiv), MeCN, r.t. or 0 °C; 2. MeCN or EtOH, reflux. Method C (from **1**): 1. (a) Ac_2O or Bz_2O (2 equiv), MeCN, r.t. or 0 °C; (b) RNH_2 (1.2 equiv), r.t. or 0 °C; 2. EtOH, reflux. Method D (from **1**): 1. (a) Ac_2O or Bz_2O (1.2 equiv), DMAP (1.5 equiv), MeCN, 0 °C; (b) RNH_2 (1.2 equiv); 2. EtOH, reflux.

To generate adenines **6/7**,[14] different experimental methods were investigated.

In method A, imidazoles **4/5** were isolated after a stepwise process and refluxed as a suspension in ethanol. Intramolecular cyclization led to adenines **6c–e** and **7b**, isolated in very good to excellent yield (75–96%) after 5 minutes to 2.5 hours reflux. Two parallel experiments were carried out to generate purine **6d** in ethanol and in acetonitrile. This product was isolated in a similar yield (96% and 94% yield, respectively) although a slower reaction was observed in acetonitrile. A 52% global yield was achieved from **2/3** and a further reduction to 30–40% yield could be estimated if the first step of the sequence (synthesis of **2/3**) was included.

Method B involves the reaction of imidazoles **2/3** with the amine, at room temperature, followed by reflux. This method would allow to overcome the experimental problems associated with the isolation of imidazoles **4/5**. Acetonitrile was also the solvent selected. Alternatively, ethanol was added in the second step. The two procedures exhibited good and consistent yields (49–52%), with a global efficiency similar to that of method A.

The synthesis of precursors **2/3** from imidazoles **1** suffers from experimental problems associated with the manipulation of these compounds. In fact, these yellow-orange solids are highly soluble and unstable, undergoing rapid intramolecular cyclization to give 6-cyanopurines **9** after ca. 4–6 hours in solution (Scheme 1). A fast acyl migration also occurs leading to imidazoles **10** (Scheme 2). Finally, degradation with formation of dark polymeric materials was often observed, a problem particularly important in the scale-up process.



Scheme 1

To prevent synthesis and manipulation of **2/3**, the one-pot, three-step sequence, starting from imidazoles **1**, was examined (method C). Treatment of **1** with anhydrides was carried out in acetonitrile at 0 °C or room temperature. When imidazole **1** was consumed, addition of an excess of amine was followed by dilution with ethanol and heating under reflux. Most of the adenines **6/7** were isolated in 50–67% yield, an improved global yield for the one-pot reaction. Methods B and C were compared for the synthesis of **7f** and demonstrated the higher global yield of the last method (50% vs. 63%).

A final approach to optimize the three-step sequence involved the activation of the anhydride by the use of DMAP in acetonitrile. An instantaneous acylation occurred, with precipitation of the ammonium salt, removed from solution by filtration. Addition of the appropriate amine followed by reflux in ethanol provided adenines **6a**,**i**,**j** and **7j** (method D). A much faster first step was observed, and cleaner reaction mixtures were obtained, facilitating the workup process in a highly efficient reaction (52–88%).

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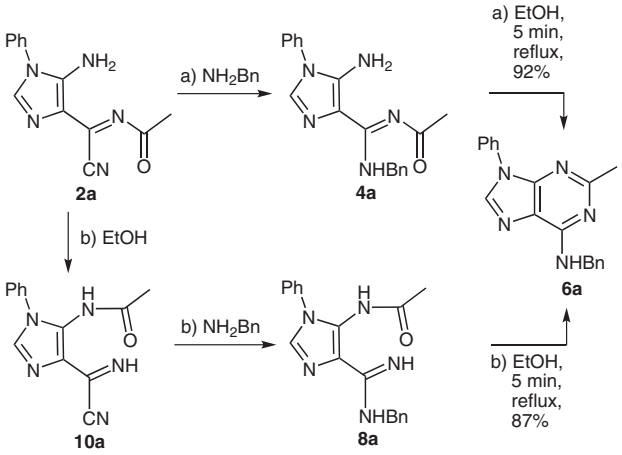
The structures **6/7** were confirmed by their spectral data. In the ^{1}H NMR spectra, a broad NH band was always present, and the chemical shift depends on the amine substituent. For example, the spectrum of **6b** showed the NH signal as a broad triplet (J = 5.4 Hz) at δ = 8.06 ppm, and the corresponding signal for the methylene protons appeared as a broad duplet. This confirmed the presence of the $NHCH_2Ph$ group and supported the structure assigned to the *N*6-substituted isomer. This was reinforced by the solitary HMBC three-bond correlation of the methylene protons with the C6 signal of the purine ring.

Inspired in previous work,[11g] a different synthetic sequence was designed (Scheme 2 – pathway b) to generate compound **8a**.[15] Migration of the acetyl group was induced by stirring an ethanolic solution of imidazole **2a** at room temperature. The product **10a** was allowed to react with benzylamine in situ leading selectively to structure **8a**. This compound was fully characterized, confirming the structure previously assigned.

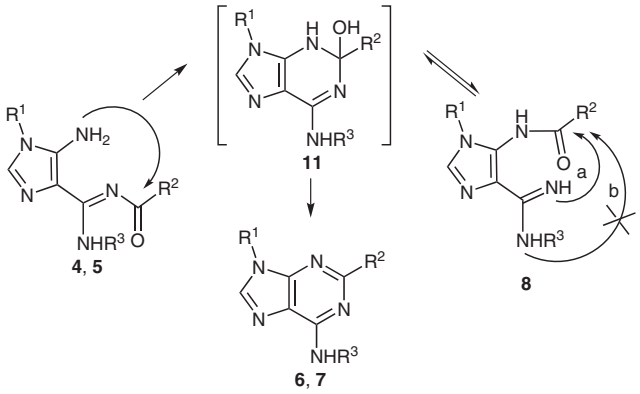
To examine the involvement of product **8** in the synthesis of adenines **6/7**, two parallel experiments were conducted: (a) cyclization of imidazole **4a** under reflux in ethanol; (b) cyclization of imidazole **8a** under the same conditions (Scheme 2). Both reactions were complete after five minutes and adenine **6a**[16] was isolated in 92% and 87% from both experiments.



Scheme 2 Two alternative pathways for the synthesis of adenine **6a**

In order to establish the reaction mechanism, a solution of imidazole **4a** in DMSO-d_6 was maintained at room temperature and followed by ^{1}H NMR. After ca. 24 hours, the starting imidazole **4a** was totally consumed leading to the formation of **8a** and traces of the corresponding adenine **6a**. Conversion of imidazole **8a** into purine **6a** could also be demonstrated upon heating the sample tube at a temperature close to the boiling point of the solvent (ca. 5–15 min).

These results prompted us to postulate the mechanism for the conversion of imidazoles **4/5** into adenines **6/7** (Scheme 3). The reaction is initiated by nucleophilic attack of the 5-amino group to the carbonyl carbon atom of the acyl group, providing the cyclic tetrahedral intermediate **11**. At room temperature, intermediate **11** mainly evolves to the kinetic product **8**. Above 40–80 °C, dehydratation of **11** leads to the thermodynamic product **6/7**. A dynamic equilibrium, between imidazole **8** and intermediate **11**, results in the complete evolution to the adenine derivative. The formation of a single isomer, the *N*6-subtituted adenine **6/7** can be rationalized by a selective nucleophilic attack by the unsubstituted nitrogen atom of the amidine group (a, Scheme 3), governed by the thermodynamic stability of the final product.



Scheme 3 Proposed mechanism for the formation of adenines **6/7**

In conclusion, a general, regioselective, and efficient three-step method was developed to prepare a series of different 2,6,9-substituted adenines **6** and **7** from the easily accessible imidazoles **1**, acetic and benzoic anhydrides, and various alkyl amines. These products could be obtained by multistep synthesis involving *N*-acylamidino imidazoles **4** and **5** as intermediates, in a moderate yield. The one-pot, two-step, and three-step synthetic approaches offered superior results. A particularly easy and efficient one-pot method was devised through a three-step sequence in the presence of DMAP. A wide range of *N*9-substituents, including alkyl, aryl, and hydroxyalkyl groups, was incorporated in the purine ring.

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References and Notes

(1) Verma, S.; Mishra, A. K.; Kumar, J. *Acc. Chem. Res.* **2010**, *43*, 79.
(2) (a) Legraverend, M.; Grierson, D. S. *Bioorg. Med. Chem.* **2006**, *14*, 3987; and references therein. (b) Legraverend, M. *Tetrahedron* **2008**, *64*, 8585; and references therein.
(3) Baraldi, P. G.; Tabrizi, M. A.; Gessi, S.; Borea, P. A. *Chem. Rev.* **2008**, *108*, 238.
(4) (a) Zhang, C.; Shokat, K. M. *Tetrahedron* **2007**, *63*, 5832. (b) Huang, H.; Mab, J.; Shi, J.; Meng, L.; Jiang, H.; Ding, J.; Liu, H. *Bioorg. Med. Chem.* **2010**, *18*, 4615.
(5) Zacharie, B.; Fortin, D.; Wilb, N.; Bienvenu, J.-F.; Asselin, M.; Grouix, B.; Penney, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 242.

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(6) Tang, Y.-b.; Peng, Z.-g.; Liu, Z.-y.; Li, Y.-p.; Jiang, J.-d.; Li, Z.-r. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6350.
(7) (a) Tunçbilek, M.; Ates-Alagöz, Z.; Altanlar, N.; Karayel, A.; Özbey, S. *Bioorg. Med. Chem.* **2009**, *17*, 1693. (b) Geng, B.; Breault, G.; Comita-Prevoir, J.; Petrichko, R.; Eyermann, C.; Lundqvist, T.; Doig, P.; Gorseth, E.; Noonan, B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4368.
(8) Goswami, P.; Das, B. *Tetrahedron Lett.* **2009**, *50*, 2384.
(9) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Rad, M.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M.; Zare Parhami, A. *Tetrahedron* **2008**, *64*, 1778. (c) Aguado, L.; Thibaut, H. J.; Priego, E.-M.; Jimeno, M.-L.; Camarasa, M.-J.; Neyts, J.; Perez-Perez, M.-J. *J. Med. Chem.* **2010**, *53*, 316. (d) Giorgi, I.; Biagi, G.; Livi, O.; Leonardi, M.; Scartoni, V.; Pietra, D. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 81.
(10) (a) Montgomery, J. A.; Thomas, H. J. *J. Med. Chem.* **1972**, *15*, 182. (b) Kadir, K.; Shaw, G.; Wright, D. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2728.
(11) (a) Alves, M. J.; Booth, B. L.; Freitas, A. P.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 913. (b) Booth, B. L.; Dias, A. M.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2119. (c) Alves, M. J.; Booth, B. L.; Proença, M. F. *J. Heterocycl. Chem.* **1994**, *31*, 345. (d) Booth, B. L.; Coster, R. D.; Proença, M. F. *Synthesis* **1988**, 389. (e) Alves, M. J.; Booth, B. L.; Carvalho, M. A.; Pritchard, R. G.; Proença, M. F. *J. Heterocycl. Chem.* **1997**, 739. (f) Al-Azmi, A.; Booth, B. L.; Carpenter, R. A.; Carvalho, M. A.; Marrelec, E.; Pritchard, R. G.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2532. (g) Booth, B. L.; Cabral, I. M.; Dias, A. M.; Freitas, A. P.; Matos-Beja, A. M.; Proença, M. F.; Ramos-Silva, M. *J. Chem Soc., Perkin Trans. 1* **2001**, 1241. (h) Carvalho, M. A.; Esteves, T. M.; Proença, M. F.; Booth, B. L. *Org. Biomol. Chem.* **2004**, *2*, 1019. (i) Carvalho, M. A.; Álvares, Y.; Zaki, M. E.; Proença, M. F.; Booth, B. L. *Org. Biomol. Chem.* **2004**, *2*, 2340. (j) Carvalho, M. A.; Esperança, S.; Esteves, T.; Proença, M. F. *Eur. J. Org. Chem.* **2007**, 1324. (k) Dias, A. M.; Cabral, I.; Vila-Chã, A. S.; Costa, D. S.; Proença, M. F. *Eur. J. Org. Chem.* **2007**, 1925. (l) Alves, M. J.; Carvalho, M. A.; Carvalho, S.; Dias, A. M.; Fernandes, F. H.; Proença, M. F. *Eur. J. Org. Chem.* **2007**, 4881. (m) Correia, C.; Carvalho, M. A.; Proença, M. F. *Tetrahedron* **2009**, *65*, 6903. (n) Ribeiro, A.; Carvalho, M. A.; Proença, M. F. *Eur. J. Org. Chem.* **2009**, 4867. (o) Bacelar, A. H.; Carvalho, M. A.; Proença, M. F. *Eur. J. Org. Chem.* **2010**, 3234.
(12) (a) Dias, A. M.; Cabral, I. M.; Vila-Chã, A. S.; Proença, M. F. *Synlett* **2007**, 1231. (b) Dias, A. M.; Cabral, I. M.; Vila-Chã, A. S.; Cunha, D.; Senhorães, N.; Nobre, S.; Sousa, C.; Proença, M. F. *Synlett* **2010**, 2792.

(13) **General Procedure for the Synthesis of 4a–d**

Benzylamine (1.1 equiv for **4a**,**b**), methylamine (for **4c**), or isopropylamine (for **4d**) was added to a suspension of the acylated imidazole **2** (0.59–2.82 mmol) in MeCN (0.5 mL), and the mixture turned immediately into a beige solution. The mixture was stirred at 0 °C (20 min for **4a**, 10 min for **4b**, and 5 min for **4c**) or at r.t. (10 min for **4d**). Bright white solids precipitated and were filtered and washed with MeCN and Et_2O to give compounds **4a**–**d** (44–63%). The structure of the products was confirmed by elemental analysis, ^1H NMR, and ^{13}C NMR spectroscopy.

Characterization of *N*-[(5-Amino-1-phenyl-1*H*-imidazol-4-yl)benzylaminomethylene]acetamide (4a)

Mp 159.1–160.2 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.69 (br s, 1 H), 7.58 (m, 2 H), 7.52–7.47 (m, 3 H), 7.49 (s, 1 H), 7.40–7.30 (m, 5 H), 7.30 (br s, 2 H), 5.32 (br s, 2 H), 1.98 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 182.93, 161.94, 147.19, 139.09, 131.30, 129.91, 129.05, 128.51, 128.28, 127.23, 126.19, 124.97, 111.32, 47.41, 28.19. Anal. Calcd for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.51; H, 5.61; N, 21.41. IR (mull): 3374, 3256, 1620, 1549, 1455 cm^{-1}.

(14) **General Procedure for the Synthesis of 7c**

Method B

A beige suspension of the imidazole **3** (0.82 mmol) in MeCN (2 mL) stirred at r.t. was combined with benzylamine (1.2 equiv). After 2 h, the mixture turned to an orange solution and was heated under reflux for 7 h. After cooling, the product precipitated out of solution, and the solid was filtered and washed with MeCN and Et_2O to give compound **7c** (50% yield).

Method C

Benzoic anhydride (2 equiv) was added to a beige suspension of imidazole **1** in MeCN (4 mL), and the mixture was stirred at r.t. for 5 h, when the mixture turned into an orange suspension. Benzylamine (1.2 equiv) and EtOH (4 mL) were added, and the mixture was heated under reflux for 5 h. After cooling, a solid precipitated out of solution and was filtered and washed with MeCN, EtOH, and Et_2O to give compound **7c** (63%).

Characterization of *N*-Benzyl-2-phenyl-9-(*p*-tolyl)-9*H*-purin-6-amine (7c)

Mp 199.8–200.7 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.57 (s, 1 H), 8.56 (br s, 1 H), 8.34 (d, *J* = 7.2 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 7.47–7.41 (m, 3 H), 7.38 (d, *J* = 7.6 Hz, 2 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 4.85 (br s, 2 H), 2.39 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.00, 154.29, 149.49, 140.35, 139.96, 138.38, 136.85, 132.73, 129.66, 129.14, 128.19, 128.12, 127.64, 127.39, 126.62, 122.84, 118.73, 43.17, 20.57. Anal. Calcd for $C_{25}H_{21}N_5$: C, 76.70; H, 5.41; N, 17.89. Found: C, 76.70; H, 5.24; N, 17.64. IR (mull): 3270, 3084, 1623, 1571, 1529, 1519, 1496 cm^{-1}.

(15) **General Procedure for the Synthesis of 8a**

A yellow suspension of imidazole **2** (1.82 mmol) in EtOH (50 mL) was stirred at r.t. for 50 min. Benzylamine (1.1 equiv) was added to this solution and 10 min later, the mixture was evaporated in vacuum (30 °C). The residual oil was cooled and a solid precipitated by addition of acetone. The solid was filtered and washed with EtOH and Et_2O to give compound **8a** (91%).

Characterization of *N*-{4-[(benzylamino)(imino)methyl]-1-phenyl-1*H*-imidazol-5-yl}acetamide (8a)

Mp 160.6–161.5 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.81 (s, 1 H), 7.46–7.43 (m, 5 H), 7.43–7.34 (m, 5 H), 4.50 (s, 2 H), 1.72 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.83, 155.80, 148.66, 138.73, 136.01, 134.17, 129.08, 128.32, 127.44, 126.92, 124.09, 115.21, 45.52, 24.78. Anal. Calcd for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.41; H, 5.75; N, 20.86. IR (mull) 3370, 3251, 1631, 1551 cm^{-1}.

(16) **General Procedure for the Synthesis of 6a**

(a) **Method A**

A white suspension of **4a** (1.75 mmol) in EtOH (2 mL) was heated at reflux for 5 min. The solution was evaporated in vacuum and after cooling, a white solid precipitated out of solution. The bright white solid was filtered and washed with EtOH and Et_2O to give compound **6a** (92%).

(b) A suspension of imidazole **8a** in EtOH (2 mL) was heated under reflux for 5 min. After that, the solution was evaporated in vacuum and, after cooling, a solid precipitated out of solution. The bright white solid was filtered and washed with EtOH and Et_2O to give compound **6a** (87% yield). The structure of the product obtained was confirmed by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy.

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Method D

Acetic anhydride (1.2 equiv) and DMAP (1.5 equiv) were added to a beige suspension of **1** (1.80 mmol) in MeCN (1 mL) at 0 °C. The mixture immediately turned in an orange solution and 3 min later, a white solid precipitated out of solution. The solid was filtered and benzylamine (1.2 equiv) and EtOH (2 mL) were added, and the mixture was heated under reflux for 1 h. After cooling, a white solid precipitated out of solution and it was filtered and washed with EtOH and Et_2O to give compound **6a** (76% yield).

Characterization of *N*-Benzyl-2-methyl-9-phenyl-9*H*-purin-6-amine (6a)

Mp 175.6–176.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.48 (s, 1 H), 8.30 (br s, 1 H), 7.85 (d, *J* = 7.8 Hz, 2 H), 7.57 (t, *J* = 7.8 Hz, 2 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.38 (d, *J* = 6.9 Hz, 2 H), 7.30 (t, *J* = 6.9 Hz, 2 H), 7.20 (t, *J* = 6.9 Hz, 1 H), 4.80 (br s, 2 H)), 2.42 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.84, 154.32, 149.39, 140.21, 139.11, 135.15, 129.46, 128.19, 127.61, 127.60, 126.19, 123.15, 117.95, 42.60, 26.11. Anal. Calcd for $C_{19}H_{17}N_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.21; H, 5.28; N, 22.06. IR (mull): 3270, 3223, 3063, 1617, 1598, 1581, 1530 cm^{-1}.

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