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Groebke–Blackburn–Bienaymé multicomponent reaction in scaffold-modification of adenine, guanine, and cytosine: synthesis of aminoimidazole-condensed nucleobases

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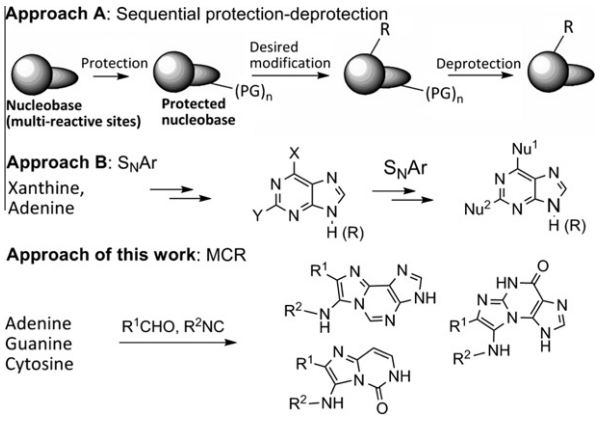
ABSTRACT

A multicomponent method for scaffold-modification of nucleobases (adenine, guanine, and cytosine) was developed. This modification approach, as an alternative to usual synthetic routes involving protection–deprotection or S_NAr of halo (or leaving group-equivalent)-purines, affords in one step therapeutically-relevant substituted aminoimidazole-[*i*]-condensed adenine, [*b*]-condensed guanine, [*c*]-condensed cytosine. These derived nucleobases possess enhanced lipophilicity and solubility and contain the functionalities useful for further chemical manipulations.

The modification/functionalization of nucleobases is important, because the derived products display a wide range of biological activities,[1] for example, agonist/antagonist effects to receptors[2] (such as adenosine and corticotropin-releasing hormone), inhibition of enzymes[3] (such as kinases, HSP90, sulfotransferase, and phosphodiesterases), tubulin polymerization,[4] DNA-stabilization[5], and cellular dedifferentiation.[6] Furthermore, they are valuable as chemical biology tools. The modification/incorporation of substitutions in purines is generally made at positions 2, 6, 8, and/or 9. Since purines contain multiple amine functionalities, these modifications usually necessitate the use of protection–deprotection chemistry[7] or directing groups[8] (Scheme 1, approach A). As an alternative route, the modifications are carried out by S_NAr of halo (or leaving group-equivalent)-purines which are generally prepared from xanthine/adenine in multi-step process (Scheme 1, approach B).[3a,9] While the substitutional modification of nucleobases is common, scaffold-modification toward the synthesis of their heterocyclic-fused[3c,d,10] and heteroaromatic-fused analogs[3e,11] is little known. Recently, Hocek and co-workers[11] introduced an approach of modification at C8–N9 of adenine and 6-methylpurine toward the synthesis of purino[8,9-*f*]phenanthridines. The approach involves the consecutive reactions of N9-arylation of purines (which eventually blocks N9) with 2-bromophenylboronic acid, Suzuki coupling, and the intramolecular C8–H arylation. We report herein an unprecedented one-step direct scaffold-modification of adenine, guanine, and cytosine by a multicomponent reaction (Scheme 1). This affords the preparation of aminoimidazole-condensed nucleobases through the incorporation of therapeutically-relevant substituted aminoimidazole at N^6–N1 in adenine, N^2–N3 in guanine, and N1–N^6 in cytosine, respectively. This modification converts the hydrogen bond donor–exocyclic amine in nucleobases into its acceptor counterpart and introduces one hydrogen bond donor–amine and an alkyl/aryl substituent in N-fused imidazole ring. These derived nucleobases possess enhanced lipophilicity and solubility and contain the functional-



Scheme 1. General approaches for selective structural modifications in nucleobases.

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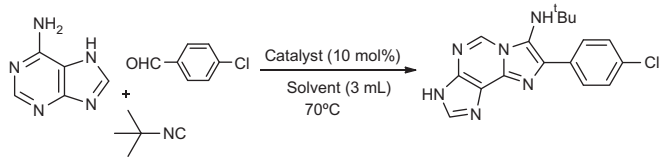
ities useful for further chemical manipulations. This modification approach is thus potentially important in drug discovery research.

Multicomponent reactions (MCRs) offer the elegance of one-pot reaction, atom-, structural- and bond-forming economy, and the feasibility of introducing maximum diversity elements in one chemical event operation.[12] As part of our continuing program to explore the multicomponent methods toward the preparation of therapeutically-relevant heterocycles,[12a,13] we investigated the direct modification of nucleobases. Based on the structural features of adenine, guanine, and cytosine comprising 2-amidine functionality, we speculated that the Groebke–Blackburn–Bienaymé multicomponent reaction (GBB MCR)[13,14] of these nucleobases with aldehyde and isocyanide could afford the incorporation of N-fused aminoimidazole. In an initial experiment, a reaction of adenine with 4-chlorobenzaldehyde and *tert*-butylisocyanide was performed following our developed protocol[13b] for the GBB MCR catalyzed by $ZrCl_4$ in polyethylene glycol at 50 °C. However, the reaction even after 18 h virtually failed leaving adenine, aldehyde, and isocyanide almost intact (Table 1). Increasing the reaction temperature to 70 °C has led to enhanced conversion with the desired product in 41% isolated yield. Further increasing the temperature did not improve yield. When performed in MeOH, the reaction did not take place. As it is well-known that the notorious low solubility of pure purines in many solvents impedes their structural modifications, we focused on finding a suitable reaction solvent along with a catalyst. A series of experiments were then carried out with various catalysts in different solvents. The optimized yields were obtained utilizing adenine (1 mmol), aldehyde (1 mmol), isocyanide (1 mmol), $ZrCl_4$ (10 mol %), and DMSO as solvent (3 mL) at 70 °C. In every case, reaction conversion was not complete. DMSO was found to be a more effective solvent than PEG-400, MeOH, ethylene glycol, or DMSO–H_2O; while DMF and DMA showed similar efficacy as DMSO. A survey of various Lewis and Brønsted acid catalysts ($ZrCl_4$, $CeCl_3{\cdot}7H_2O$, $InCl_3$, $Sc(OTf)_3$, and $HClO_4$) revealed $ZrCl_4$ to be the most effective. Aqueous-extraction of the crude reaction mixtures caused the loss of products because of their partial solubility in water. Direct column chromatographic purification after partial evaporation of DMSO of crude reaction mixture was thus performed and it resulted in

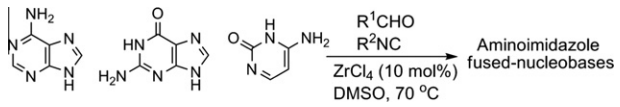
Table 1
Standardization of method

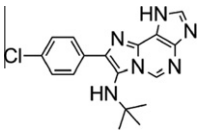
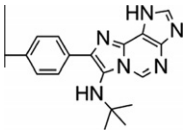
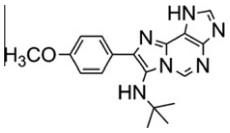
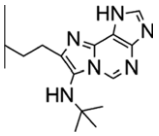
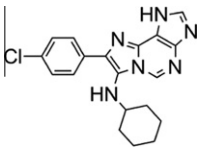
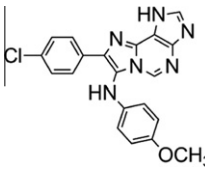
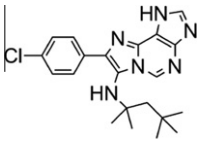
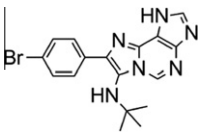
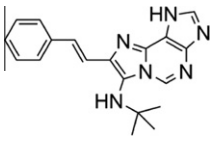
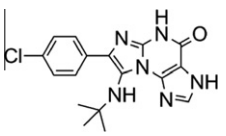
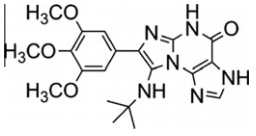


Entry	Catalyst	Solvent	Yield[a] (%)
1	$ZrCl_4$	PEG-400	Trace[b]
2	$ZrCl_4$	PEG-400	41
3	$ZrCl_4$	PEG-400	42[c]
4	$ZrCl_4$	MeOH	0
5	$ZrCl_4$	Ethylene glycol	35
6	$ZrCl_4$	DMSO	68
7	$ZrCl_4$	DMF	62
8	$ZrCl_4$	DMA	60
9	$ZrCl_4$	DMSO/H_2O (1:1)	23
10	$CeCl_3{\cdot}7H_2O$	DMSO	42
11	$InCl_3$	DMSO	47
12	$Sc(OTf)_3$	DMSO	52
13	$HClO_4$	DMSO	43

[a] Isolated yields.
[b] Reaction was carried out at 50 °C.
[c] Reaction was carried out at 90 °C.

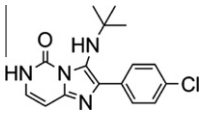
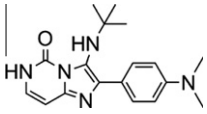
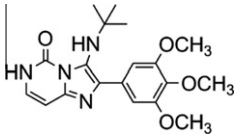
Table 2
Synthesis of aminoimidazole-fused nucleobases[a]



Entry	Aminoimidazole-fused nucleobases[b]	Time (h)	Yield[c] (%)
1		7.5	68
2		6.5	63
3		7	51
4		8	60
5		7	72
6		6	64
7		7.5	57
8		8	50
9		8	50
10		7	25
11		8	15

(*continued on next page*)

Table 2 (*continued*)

Entry	Aminoimidazole-fused nucleobases[b]	Time (h)	Yield[c] (%)
12		6	52
13		12	58
14		6	50

[a] Reaction conditions: nucleobases, aldehydes and isocyanides in 1:1:1 molar ratio, $ZrCl_4$ (10 mol %), DMSO, 70 °C.

[b] All products were characterized by ^1H, ^{13}C, mass and IR, and analyzed by CHN or HRMS.

[c] Isolated yields.

increased yield. We then examined the scope of this method for the multicomponent reactions of adenine, guanine, and cytosine with various aldehydes and isocyanides (Table 2).[15] These reactions furnished corresponding substituted aminoimidazole-[*i*]-condensed adenine (Table 2, entries 1–9), [*b*]-condensed guanine (Table 2, entries 10 and 11), [*c*]-condensed cytosine (Table 2, entries 12–14) in moderate to good yields. The products were characterized by ^1H and ^{13}C NMR, mass and IR spectroscopies, and confirmed by CHN analysis or HRMS. Guanine is known as notoriously difficult-to-protect/modify because of its very poor solubility in almost all common solvents (including water) and its multi-functional/structural nature (imidazole, amide, and guanidine). With the present method guanine was found to undergo modification *albeit* in low yields (Table 2, entries 10 and 11). The reactions of guanine were found to be incomplete even by increasing the reaction temperature or prolonging the reaction. Since a wide range of aldehydes are commercially available and various isocyanides are accessible, this synthetic approach can produce diverse-substituted N-fused aminoimidazole-purines and cytosine derivatives. The modified nucleobases can undergo the post modification at free amines (N9 for adenine and guanine and N1 for cytosine). The tolerance of halogen (Cl and Br) and alkene functionalities in the method provides the opportunity of their various further chemical manipulations. Thus, the modification of nucleobase-motifs in this approach and the possible post-chemical manipulation by usual methods can offer a library of heteroaromatic-fused nucleobases and nucleosides.

In conclusion, we have developed a method for the unprecedented scaffold-modification of adenine, guanine, and cytosine into their aminoimidazole-condensed derivatives. Owing to the therapeutic relevance of the structural modification and the simplicity of the method, being one-step and multicomponent in nature and alternative to usual multi-step synthetic routes involving protection–deprotection or S_NAr, this method may find potential application.

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15. *Representative synthesis of N-tert-Butyl-8-(4-chlorophenyl)-3H-imidazo[1,2-i]purin-7-amine (Table 2, entry 1)*: To a mixture of adenine (0.27 g, 2 mmol) and 4-chlorobenzaldehyde (0.28 g, 2 mmol) in DMSO (5 mL), *tert*-butyl isocyanide (0.17 g, 2 mmol) and $ZrCl_4$ (47 mg, 10 mol %) were added. The mixture was allowed to stir at 70 °C under open air. After 7.5 h of reaction (monitored by TLC), DMSO was partially removed from the resultant mixture by rotary evaporation under reduced pressure (2 mm Hg) at 50–60 °C (water bath temperature). The direct column chromatographic purification of crude product over silica gel (mesh size: 60–120) eluting with EtOAc–hexane afforded *N-tert*-butyl-8-(4-chlorophenyl)-3*H*-imidazo[1,2-*i*]purin-7-amine (0.462 g, 68%); faint yellowish white solid; mp = 229–231 °C; MS (APCI) *m*/*z*: 341 (MH^+); HRMS (*m*/*z*) calcd for $C_{17}H_{17}ClN_6$ 341.1281 (MH^+), found 341.1275; ^1H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 9H), 4.80 (s, NH), 7.48 (d, *J* = 8.4 Hz, 2H), 8.21–8.24 (m, 3H), 9.02 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.8, 55.7, 123.9, 128.0, 129.3, 131.6, 133.5, 134.5, 135.3, 139.6. IR (KBr) ν_{max} = 3650, 3567, 1642, 1486, 1375, 1319, 1196, 1090, 1013 cm^{-1}. Anal. Calcd for $C_{17}H_{17}ClN_6$: C, 59.91; H, 5.03; N, 24.66. Found: C, 59.67; H, 5.06; N, 24.98.
3-(tert-Butylamino)-2-(4-chlorophenyl)imidazo[1,2-c]pyrimidin-5(6H)-one (Table 2, entry 12):Yellowish white solid, mp = 222–224 °C; MS (APCI) *m*/*z*: 317 (MH^+); ^1H NMR (400 MHz, DMSO-d_6): δ 0.96 (s, 9H), 2.98 (s, NH), 4.58 (s, NH), 6.45 (d, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.8, 57.5, 98.3, 128.4, 129.2, 129.4, 129.6, 131.6, 133.3, 134.1, 142.9, 149.2. IR (KBr) ν_{max} = 3337, 3096, 1707, 1546, 1486, 1363, 1305, 1193, 1088 cm^{-1}. Anal. Calcd for $C_{16}H_{17}ClN_4O$: C, 60.66; H, 5.41; N, 17.69. Found: C, 60.28; H, 5.56; N, 18.01.