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Synthesis of C8–N9 Annulated Purines by Iron-Catalyzed C–H Amination

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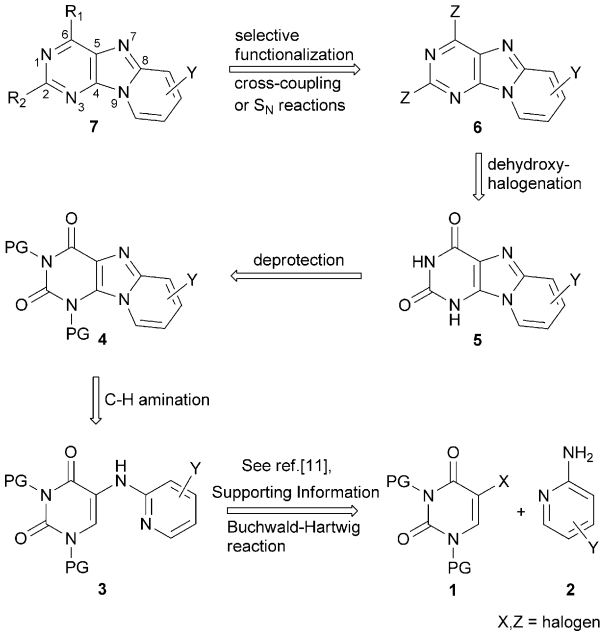
Purine derivatives display a wide variety of biological activities and the purine nucleus has been used as a template for addressing a variety of biological targets.[1,2] Not surprisingly, the development of efficient functionalization processes for the purine nucleus is a very active area of research.[3,4] The biggest challenge in obtaining good purine-based enzyme inhibitors and receptor (ant)agonists is to overcome the lack of selectivity for a specific enzyme/receptor. Modification of the substitution pattern and altering the purine core can both result in an improved selectivity, as well as an increased activity. Synthetic methods to construct new purine-based scaffolds, which are easily post-decorated, are thus very important. In this respect, it is surprising that heteroarenes annulated to C8–N9 of the purine core, in contrast to their C8–N7 regioisomers,[5] have been rarely documented.[6–8] Derivatives of the pyrido[1,2-*e*]purine core have been reported as phosphodiesterase type 5 (PDE5) inhibitors,[7] of which some had a better selectivity over PDE6 and PDE1 than sildenafil,[7a] and as anti-neoplastics.[8] However, the synthetic strategy to construct the scaffold does not allow an efficient post-modification of the pyrimidine substitution pattern. Given the potential of substituted pyrido[1,2-*e*]purines to interact selectively with enzymes and receptors, we developed a short synthesis for substituted 1,3-bis(4-methoxybenzyl)pyrido[1,2-*e*]purine-2,4(1*H*,3*H*)-diones (**4**) based on an Fe-catalyzed direct amination reaction on easily accessible 5-(pyridin-2-ylamino)pyrimidine-2,4(1*H*,3*H*)-diones (**3**; Scheme 1). Oxygen (O_2), the most sustainable oxidant available, could be used as oxidase in the process.[9] Compounds **4** potentially allow further decoration in a late stage of the synthesis by N-deprotection and subsequent dehydroxyhalogenation, making them especially useful for library synthesis.



Scheme 1. Retrosynthesis of substituted pyrido[1,2-*e*]purines.

Intramolecular Cu-catalyzed direct amination of arenes with amidines involving sp^2 C–H activation using O_2 as oxidase has been reported by the groups of Buchwald (*N*-arylbenzamidines),[10a] Zhu (*N*-arylpyridin-2-amines),[10b] and Maes (*N*-arylpyridin-2-amines).[10c] When these reaction conditions were applied to our test substrate, 1,3-bis(4-methoxybenzyl)-5-(pyridin-2-ylamino)pyrimidine-2,4(1*H*,3*H*)-dione (**3a**), a low yield of 1,3-bis(4-methoxybenzyl)pyrido[1,2-*e*]purin-2,4(1*H*,3*H*)-dione (**4a**) was obtained under the Buchwald (25%) and Zhu conditions (28%; Table 1, entries 1 and 2, respectively). Moreover, starting material remained in the latter case, even with a higher catalyst loading in comparison to the other literature procedures (Table 1, entries 1–3). Application of the conditions reported by our group gave a moderate yield of target compound **4a** (57%) but a significant amount of a side compound, *N,N*-bis(4-methoxybenzyl)tricarbanodiimidic diamide (**8**), was isolated (20%; Table 1, entry 3).[12] A closer look at the reaction mixtures conducted under the Buchwald and Zhu conditions revealed that this side compound was also formed in 34% and 26% yield, respectively. To address this selectivity problem, we turned our attention to the use of another base metal. Iron was selected because it has advantages from the perspective of availability and price in comparison to copper;[13] the crustal abundance of iron is around 1000 times higher and its price is more than hundred times lower than that of copper. Moreover, chemoselectivity of iron over copper in the framework of benzylic oxidations has been previously shown by our group.[14]

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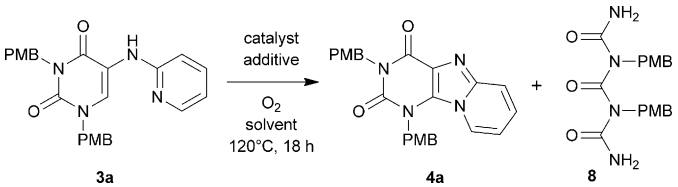
Table 1. Optimization of the direct amination of **3a**.[a]



3a **4a** **8**

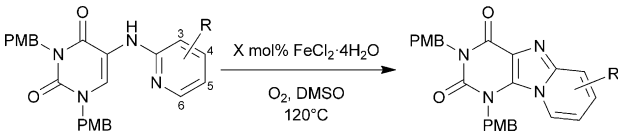
	Catalyst	Yield of **4a** [%][b]	Yield of **3a** [%][b]	Yield of **8** [%][b]
1[c]	$Cu(OAc)_2$	25	0	34
2[d]	$Cu(OAc)_2$	28	15	26
3[e]	$Cu(OAc)_2{\cdot}H_2O$	57	0	20
4	none	0	100	0
5	**$FeCl_2{\cdot}4H_2O$**	**68**	**0**	**0**
6	**$FeCl_3{\cdot}6H_2O$**	**64**	**0**	**0**
7	$FeCl_2$ (99.998%)	68	0	0
8[f]	$FeCl_2{\cdot}4H_2O$	73	4	12
9[g]	$FeCl_2{\cdot}4H_2O$	19	29	21
10	$[Fe(acac)_3]$[h]	0	51	22
11	$Fe(NO_3)_3{\cdot}9H_2O$	58	0	19
12	$Fe(OAc)_2$	25	33	24
13	FeF_2	0	89	0
14	$Fe(ClO_4)_2{\cdot}H_2O$	25	30	34
15	$Fe_2(SO_4)_3{\cdot}H_2O$	30	6	36
16	Fe_2O_3	27	40	11
17	$(NH_4)_2Fe^{II}(SO_4)_2{\cdot}6H_2O$	12	50	20
18	$K_4[Fe^{II}(CN)_6]{\cdot}3H_2O$	17	30	7

[a] Conditions: Substrate (0.5 mmol), catalyst (15 mol%), DMSO (1 mL), O_2 atmosphere (balloon), 120°C, 18 h. [b] Yield of isolated product. [c] $Cu(OAc)_2$ (15 mol%), AcOH (5 equiv), DMSO (1 mL), O_2 atmosphere (balloon), 100°C, 20 h (ref. [10a]). [d] $Cu(OAc)_2$ (20 mol%), $Fe(NO_3)_3{\cdot}9H_2O$ (10 mol%), PivOH (5 equiv), DMF (1 mL), O_2 atmosphere (balloon), 130°C, 28 h (ref. [10b]). [e] $Cu(OAc)_2{\cdot}H_2O$ (15 mol%), 3,4,5-trifluorobenzoic acid (TFBA; 15 mol%), DMSO (1 mL), O_2 atmosphere (balloon), 120°C, 18 h (ref. [10c]). [f] 15 mol% PivOH as additive. [g] PivOH (5 equiv) as additive. [h] acac = acetylacetone.

Although Cu-catalyzed C–N bond forming reactions involving C–H activation (sp^2 and sp^3) have received considerable interest,[10,15–17] the number of reported processes based on iron as a catalyst is very limited.[18–26] The known Fe-catalyzed sp^3 and sp^2 C–H amination reactions generally involve nitrenoid formation. These intermediates are generated from preactivated primary amines (e.g., from azides,[18] PhI=NTs,[19] PhNO and PhNHOH,[20] by in situ oxidation of a primary amine with *N*-bromosuccinimide (NBS)[21] or $PhI(OAc)_2$,[22] or by ring opening of an 2*H*-azirine[23]). However, the stoichiometric preactivation of the nitrogen reagent is still a drawback from a sustainability perspective.[26] Moreover, this methodology cannot be applied to secondary amines. Interestingly, our substrates **3** feature a secondary amine (upon tautomerism).

A catalyst screening was performed on test substrate **3a** (Table 1). $FeCl_2{\cdot}4H_2O$ proved to be the best catalyst as full conversion was obtained after 18 h at 120°C, providing **4a** in a good isolated yield (Table 1, entry 5). $FeCl_3{\cdot}6H_2O$ gave a similar result, suggesting an initial oxidation occurs when Fe^{II} salts are used (Table 1, entry 6). To exclude the possibility that a Cu impurity in the Fe catalyst was performing the actual catalysis, a highly pure source was tested, which gave the same result (Table 1, entry 7). The addition of pivalic acid (PivOH) in a catalytic amount had no significant effect on the yield of **4a** (Table 1, entry 8); however, excess acid decreased the yield significantly (Table 1, entry 9). Other Fe^{II} and Fe^{III} salts gave a lower or zero yield of the target molecule (Table 1, entries 10–18), and in several cases a substantial amount of side compound **8** was formed. With $FeCl_2{\cdot}4H_2O$, only a trace of this side productwas detected in the crude reaction mixture (by LC-MS). A solvent screening (dimethylacetamide (DMA), DMF, anisole, *ortho*-xylene) with the best catalyst ($FeCl_2{\cdot}4H_2O$) at 120°C revealed that

Table 2. Scope of the direct amination of **3**.[a]



3b–t **4b–t**

	R	Cat. [mol%]	*t* [h]	Substrate	Product	Yield of **4** [%][b]
1	3-Me	20	24	**3b**	**4b**	90
2	4-Me	20	24	**3c**	**4c**	76
3	5-Me	20	24	**3d**	**4d**	60
4	5-Me	15	24	**3d**	**4d**	57
5	6-Me	20	24	**3e**	**4e**	0[c]
6	3-OMe	20	24	**3f**	**4f**	59[d]
7	3-OMe	40[e]	48	**3f**	**4f**	71
8	3-OMe	40	48	**3f**	**4f**	42[f]
9	4-OMe	20	24	**3g**	**4g**	39
10	5-OMe	20	24	**3h**	**4h**	64
11	3-Br	20	24	**3i**	**4i**	30[g]
12	3-Br	40[e]	48	**3i**	**4i**	59
13	3-Br	40	48	**3i**	**4i**	73
14	4-Br	20	24	**3j**	**4j**	64
15	5-Br	20	24	**3k**	**4k**	76
16	6-Br	20	24	**3l**	**4l**	0[h]
17	4-Cl	20	24	**3m**	**4m**	57[i]
18	4-Cl	40[e]	48	**3m**	**4m**	82
19	4-Cl	40	48	**3m**	**4m**	51
20	5-Cl	20	24	**3n**	**4n**	77
21	$5\text{-}CF_3$	20	24	**3o**	**4o**	39[g]
22	$5\text{-}CF_3$	40[e]	48	**3o**	**4o**	33[j]
23	$5\text{-}CF_3$	40	48	**3o**	**4o**	46[k]
24	4-COOMe	20	24	**3p**	**4p**	49[l]
25	4-COOMe	40[e]	48	**3p**	**4p**	59[i]
26	4-COOMe	40	48	**3p**	**4p**	39[f]
27	5-COOMe	20	24	**3q**	**4q**	6[j]
28	5-COOMe	40[e]	48	**3q**	**4q**	5[m]
29	5-COOMe	40	48	**3q**	**4q**	35[n]
30	3-Et	20	24	**3r**	**4r**	86
31	3-Et	15	24	**3r**	**4r**	85
32	3-Ph	20	24	**3s**	**4s**	91
33	3-Ph	15	24	**3s**	**4s**	84
34	isoquinolin-1-yl	20	24	**3t**	**4t**	93

[a] Conditions: Substrate (0.5 mmol), $FeCl_2{\cdot}4H_2O$ (X mol%), DMSO (1 mL), O_2 atmosphere (balloon), 120°C, Y h. [b] Yield of isolated product. [c] No substrate recovered. [d] 24% substrate recovered. [e] In two batches of 20 mol%, 2×24 h. [f] 6% substrate recovered. [g] 33% substrate recovered. [h] Only substrate recovered. [i] 19% substrate recovered. [j] 52% substrate recovered. [k] 29% substrate recovered. [l] 37% substrate recovered. [m] 49% substrate recovered. [n] 14% substrate recovered.

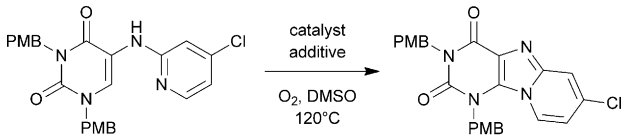
only in DMSO were good results achieved (See the Supporting Information).

Next, the compatibility of our method for substrates with substitution at the pyridine ring was probed. Both electron-donating (Me, Et, Ph, OMe) and electron-withdrawing groups (Cl, Br, COOMe, CF_3) were tested (Table 2). A uniform catalyst loading (20 mol% $FeCl_2{\cdot}4H_2O$) and a reaction time of 24 h were selected for these substituted substrates. The catalyst loading was not optimized for each substrate, although in several cases this could definitely be reduced as exemplified by the selected cases that were tested (Table 2, entries 4, 31, and 33). Gratifyingly, under these conditions the corresponding substituted 1,3-bis(4-methoxybenzyl)-pyrido[1,2-*e*]purin-2,4(1*H*,3*H*)-diones (**4b–t**) were generally obtained in moderate to good yields (Table 2), thus supporting a wide functional group compatibility of the new protocol. C6 substitution, which blocks the α-position to nitrogen, was not tolerated, as exemplified for a methyl and a bromo substituent (Table 2, entries 5 and 16). However, no steric effect due to substituents in the challenging C3 position (Me, Et, Ph; compare Table 2 entries 1, 30, and 32) was observed. Heteroatom-based groups in this position (OMe, Br; Table 2, entries 6 and 11) require a higher catalyst loading (40 mol%) and longer reaction time (48 h) to obtain full conversion (Table 2, entries 7 and 13). For pyridine substitution featuring stronger electron withdrawing groups (Cl, CF_3, COOMe), these conditions were usually also required (Table 2, entries 17–29). The very challenging ester and trifluoromethyl groups were tolerated by the protocol, although under the best conditions some starting material remained (Table 2, entries 23, 25, and 29). Interestingly, often it was beneficial to add the additional catalyst in two portions because it suppressed the formation of side compound **8** and increased the yield of **4** (See Table 2, entries 7 and 8, 18 and 19, 25 and 26, and the Supporting Information for yield of **8**). The protocol is chemoselective as halogens were generally tolerated (Table 2, entries 11–20). Regioisomeric halopyrido[1,2-*e*]purin-2,4(1*H*,3*H*)-diones (**4i–n**) are very interesting compounds as they allow post functionalization by Pd-catalyzed cross-coupling chemistry.

For substrates **3m**, which did not convert completely under the standard conditions (20% $FeCl_2{\cdot}4H_2O$, 24 h), we reinvestigated the use of copper. The reactions were performed with the best copper-based catalytic system ($Cu(OAc)_2{\cdot}H_2O$, 3,4,5-trifluorobenzoic acid (TFBA)) that was identified for **4a** synthesis, and with the same catalyst loading as that used for the iron catalysis (Table 3, entries 1–3). Copper catalysis resulted in systematically lower yields of the target compound and complete decomposition of the starting material, irrespective of the catalyst loading applied (Table 3, entries 4–6). These results further support the superior role of iron catalysts for the cyclization under study.

To gain insight into the reaction mechanism of the Fe-catalyzed direct amination reaction we performed a number of

Table 3. Comparison of iron versus copper in the direct amination of **3m**.[a]

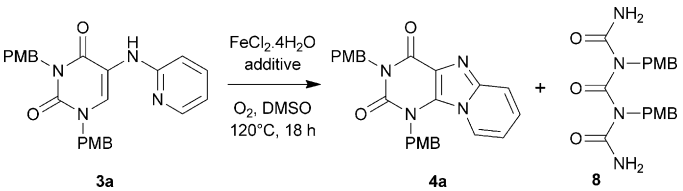


3m **4m**

	Catalyst	Additive	Cat. [%]	*t* [h]	Yield of **4m** [%][b]	Yield of **3m** [%][b]	Yield of **8** [%][b]
1	$FeCl_2{\cdot}4H_2O$	-	20	24	57	19	10
2	$FeCl_2{\cdot}4H_2O$	-	40[c]	48	82	7	9
3	$FeCl_2{\cdot}4H_2O$	-	40	48	51	0	28
4	$Cu(OAc)_2{\cdot}H_2O$	TFBA	20	24	35	0	13
5	$Cu(OAc)_2{\cdot}H_2O$	TFBA	40[c]	48	29	0	15
6	$Cu(OAc)_2{\cdot}H_2O$	TFBA	40	48	30	0	6

[a] Conditions: Substrate (0.5 mmol), catalyst (X mol%), additive (X mol%), DMSO (1 mL), O_2 atmosphere (balloon), 120°C, Y h. [b] Yield of isolated products. [c] In two batches of 20 mol%, 2×24 h.

Table 4. Fundamental studies on **3a**.[a]



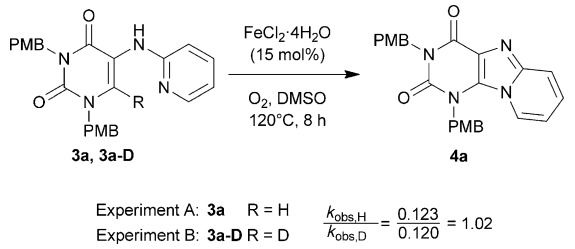
3a **4a** **8**

	Additive	Yield of **4a** [%][b]	Yield of **3a** [%][b]	Yield of **8** [%][b]
1	–	68	0	0
2	TEMPO	8	69	7
3	Galvinoxyl	9	57	9

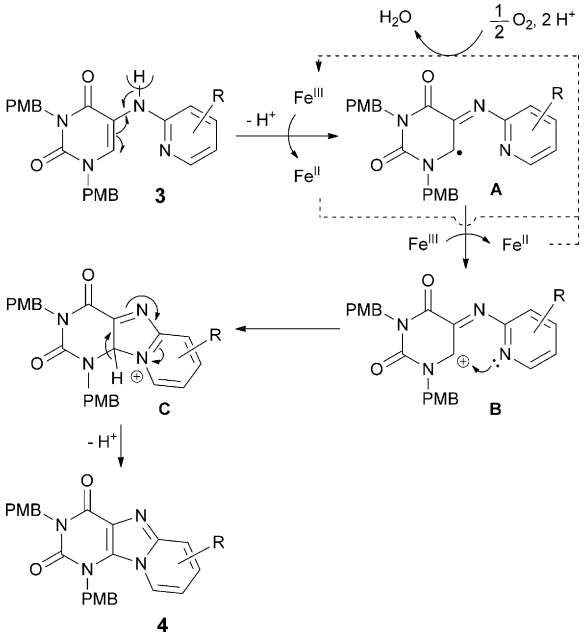
[a] Conditions: Substrate (0.5 mmol), catalyst (15 mol%), additive (1 equiv), DMSO (1 mL), O_2 atmosphere (balloon), 120°C, 18 h. [b] Yield of isolated product.

fundamental experiments on substrate **3a** (Table 4). Radical inhibitors (TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl], Galvinoxyl) were added to the cyclization reaction of **3a** and gave a significant reduction in conversion, hereby supporting a radical reaction mechanism (Table 4, entries 2–3). When a direct amination experiment was performed under an Ar atmosphere with 40 mol% of $Fe^{II}Cl_2{\cdot}4H_2O$, no **4a** was formed. Interestingly, a similar experiment with 40 mol% of $Fe^{III}Cl_3$ gave an 18% yield of **4a.** This experiment indicates that Fe^{III} initiates the catalytic cycle and that two metal ions are required to make one molecule of the reaction product. Oxygen acts as an oxidase, bringing reduced iron into the original oxidation state and allowing a catalytic process to occur. An intermolecular kinetic isotope effect with both non-deuterated (**3a**) and deuterated substrate (**3a-D**), executed in two different flasks, showed no kinetic isotope effect and therefore the rupture of the C–H bond is not involved in the rate-determining step (Scheme 2).

In accordance with these fundamental experiments, the catalytic cycle in Scheme 3 is proposed. A radical mechanism is also in accordance with the more difficult reactions



Scheme 2. Determination of intermolecular KIE. PMB = *para*-methoxybenzyl.



Scheme 3. Proposed catalytic cycle.

observed with electron-withdrawing groups as substituents, because in this case, the intermediate radical A and cation B are less stabilized by resonance in the pyridine ring. The difference in ring-closure efficiency between C3- and C5-substituted substrates featuring a heteroatom (OMe and Br) might be due to an intramolecular hydrogen bonding inhibiting radical formation. After all, electronic effects for C3 and C5 substituents are expected to be similar. Alternatively, a non-planar orientation in the case of C3 substitution, which only exerts an inductive effect resulting in destabilization (steric inhibition of resonance), can explain these observations.

In summary, we have developed a sustainable direct amination protocol for substituted pyrido[1,2-*e*]purine synthesis based on base-metal catalysis that does not require the preactivation of nitrogen and uses O_2 as oxidant. The method has excellent functional-group compatibility and the chemoselectivity towards halogens will allow post-functionalization in the annulated ring. Further investigations to improve the efficiency of the direct amination protocol (lower catalyst loading, better tolerance of electron-withdrawing groups) are currently underway in our laboratory. In addition extending the scope of the base-metal-catalyzed protocol for the synthesis of other annulated purine scaffolds and study of the pyrimidine post-functionalization potential are under study.

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Keywords: amination · C–H activation · homogeneous catalysis · iron · purine

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Amination

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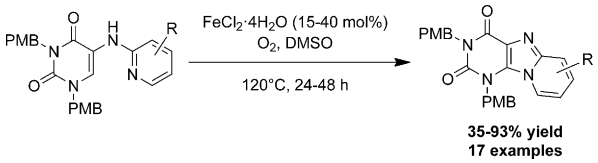
Synthesis of C8–N9 Annulated Purines by Iron-Catalyzed C–H Amination



Purine and simple: A short synthesis for substituted annulated purine derivatives based on an Fe-catalyzed direct amination reaction using oxygen as oxidant was developed (see scheme). Interestingly, iron proved to be superior to copper catalysis.

