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Synthesis of 6,7,8-Trisubstituted Purines via a Copper-Catalyzed Amidation Reaction

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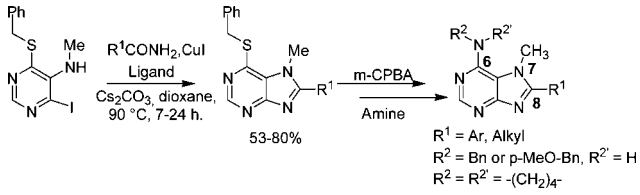
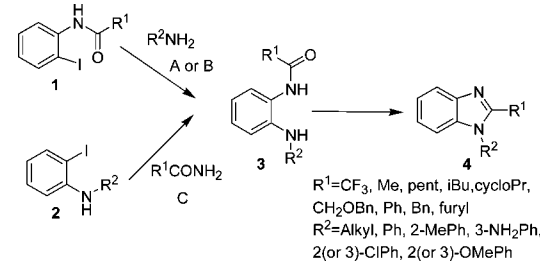


We report herein an efficient method for the synthesis of 6,7,8-trisubstituted purines via a copper-catalyzed amidation reaction from easily accessible starting materials. Furthermore, the resulting 6-benzylsulfanyl-substituted purine derivatives may be readily oxidized for substitution by nucleophiles to give access to 6,7,8- trisubstituted purines for biological screening purposes.

The purine core is a privileged scaffold in medicinal chemistry that is frequently used in the preparation of combinatorial libraries.[1,2] Its seven peripheral atoms may be considered as seven potential points of structural diversity, and a wide variety of interesting inhibitors and modulators of key biological targets have been found among derivatives bearing various combinations of substituents at these centers.[3]

Various methodologies have been developed for the synthesis of polysubstituted purines,[4−7] but some derivatives bearing an aryl or a heteroaryl substituent at position 8 are more difficult to obtain. For example, 2,6,8,9-tetrasubstituted purines can be prepared from 6-chloro-2-alkyl (or 2-aryl)-4,5-diaminopyrimidine precursors by treatement with an alkyl (or aryl) aldehyde or carboxylic acid, but the yield of the resulting 6-chloro-2,8,9-trisubstituted purine is low, due to hydrolysis of the chlorine atom.[8]

SCHEME 1. Known Approaches to the Syntheses of the *N*-Alkyl and *N*-Arylbenzimidazoles[a]



[a] Reagents and conditions—Method A: (1) Cu/L-proline/K_2CO_3, DMSO, rt−50 °C; (2) heat or AcOH, 40−60 °C, 61−97%. Method B: (1) CuI, Cs_2CO_3, DMF, rt; (2) AcOH, 50 °C (without a ligand), 82% only with $R^1 = CF_3$. Method C: (1) CuI/L, Cs_2CO_3, 1,4-dioxane, 90 °C, 2 h; (2) K_3PO_4, *t*-BuOH, 110 °C or AcOH 75 °C, 72−82%.

This was indeed the case in all our attempts to apply this method to introduce more complex substituents at position 8. Although other methods exist for the preparation of purine derivatives, e.g., from 8-halogenopurines,[9−12] or by direct arylation at C-8,[13,14] we wanted to develop a more general method that could lead to a variety of 6,7,8-trisubstituted purines in high yield.

Our attention was drawn by the recent work by Ma and coworkers,[15] who described a Cu-catalyzed aryl amination/condensation process, using 2-iodoacetanilides **1**, which led to a series of 1,2-disubstituted benzimidazoles **4** in high yield (method A). Buchwald simultaneously reported[16,17] a similar copper-catalyzed amination/cyclization of related acetanilide (Scheme 1, $R^1 = CF_3$), but unfortunately, the process lacked generality (method B).

Interestingly, Buchwald developped an improved method involving a copper-catalyzed amidation of a 2-iodoaniline **2**[16] in the presence of a diamine ligand, which led to various *N*-alkyl-2-substituted benzimidazoles **4** in good yields (Method C) (68−93%).

In view of the potential generality of these syntheses of benzimidazoles, we wanted to investigate the use of this strategy in the synthesis of 6,7,8-trisubstituted purines (Scheme 2). In this Note, we report a new efficient method for the three-step synthesis of 6,7,8-trisubstituted purines from a suitable pyrimidine precursor, using a copper-catalyzed amidation.

For this purpose, we required a functionality in the final purine derivative which would allow the introduction of various substituents at position 6. However, our first attempts with 4,6-dihalogenopyrimidines met with little success. When 5-amino-

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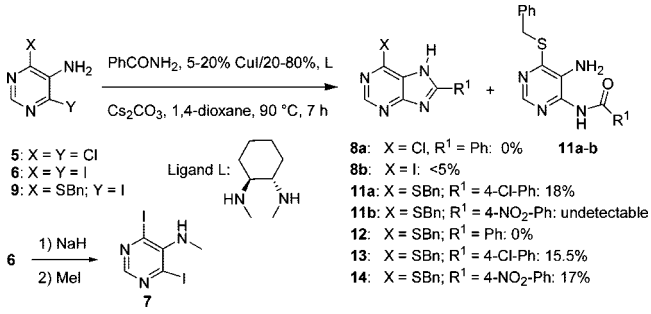
SCHEME 2. Synthesis of 6,8-Disubstituted Purines

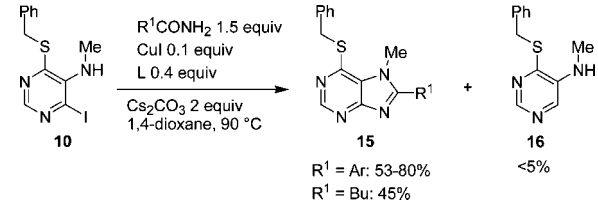


4,6-dichloropyrimidine **5** was treated with CuI (10 mol %) and ligand L (40 mol %) in the presence of benzamide, no purine **8a** was formed (Scheme 2) and significant degradation of the starting material was observed. In the case of 5-amino-4,6-diiodopyrimidine[18] **6** a very low yield (<5%) of 6-iodopurine **8b** (Scheme 2) was obtained, even when the amount of copper and ligand (*trans-N,N′*-dimethylcyclohexane-1,2-diamine) was increased. Experiments with Pd(0) catalyst[19] instead of CuI gave also the cyclization product **8b** in very low yield and required a much longer reaction time in a sealed vessel. Therefore we returned to the CuI/ligand amidation conditions of Buchwald[16] that we applied to the monoiodopyrimidine (**9**), to avoid any diamidation. The choice to substitute one iodo atom in **6** by a benzylsulfanyl group to give **9** was made first for the well-known chemical stability of the benzylthioether under various conditions (SNAr, Pd(0) cross-coupling), and second because it can be activated to the sulfone for subsequent substitution by nucleophiles. Thus, treatment of 5-amino-4-benzylsulfanyl-6-iodopyrimidine (**9**) with 4-chlorobenzamide in the presence of CuI and diamine ligand led to a small amount of purine **13** (16%) as well as a small quantity of pyrimidine **11a** (18%) (Scheme 2). In the case of 4-nitrobenzamide, purine **14** was obtained in low yield (17%) and no pyrimidine intermediate **11b** was detected in the reaction mixture (Scheme 2). In addition, **9** treated with benzamide, in the presence of CuI/ligand, remained unchanged (**12** was not detected) (Scheme 2).

However, we were delighted to observe that a pure product was obtained in 53% yield when the copper-catalyzed amidation reaction was applied to a benzylsulfanyl pyrimidine precursor **10**, in which the 5-amino group was methylated (Table 1, entry 1) (see the Supporting Information for the synthesis of **10** from **7**, which was itself prepared by treating **6** with NaH followed by MeI). The amounts of CuI (10 mol %) and ligand (40 mol %) were optimized in the reaction of benzamide with **10**, heating for 24 h in a sealed tube (Table 1, entry 1). Further increase of CuI led to some degradation and a higher amount of reduced product **16**. The best results were obtained with 1.5 equiv of benzamide, in the presence of 2 equiv of Cs_2CO_3 at 90 °C. No purine was formed in the absence of ligand.

As shown in Table 1 this method was equally efficient with electron-rich and electron-deficient aryl amides, suggesting that the substrate scope for this method is high. A variety of 8-arylpurines **15a−m** were thus obtained in 53−80% yields.

TABLE 1. Scope for Copper-Catalyzed Synthesis of Various 8-Aryl(Bu)-6,7-Substituted Purine Derivatives 15a−n



entry	compd	R^1	yield (%)[a]
1	**15a**	Ph	53
2	**15b**	3-Cl-Ph	68
3	**15c**	4-Cl-Ph	75
4	**15d**	4-MeO-Ph	65
5	**15e**	4-pyridyl	66
6	**15f**	3-pyridyl	61
7	**15g**	3-NO_2-Ph	68
8	**15h**	4-NO_2-Ph	75
9	**15i**	3-F-Ph	67
10	**15j**	4-F-Ph	70
11	**15k**	2-F-Ph	73
12	**15l**	2-tolyl	80
13	**15m**	3-MeO-Ph	75
14	**15n**	*n*-butyl	45

[a] Isolated yields.

The coupling reaction of an alkyl amide was also carried out and led to 8-butyl-substituted purine **15n** in moderate yield (45%).

The total conversion of pyrimidine **10** to purines **15** was achieved in 7 h with all amides with the exception of benzamide, nicotinamide, ortho-substituted benzamides (2-fluorobenzamide and *o*-toluamide), and valeramide which required prolonged reaction time (24 h) (Table 1, entries 1, 11, 12, and 14).

In contrast to the synthesis of *N*-alkylbenzimidazoles (Scheme 1, method C)[16] the presumed pyrimidine intermediates (such as **11**) were not isolated and cyclized spontaneously by dehydration to purine derivatives **15a−n** (Table 1). A trace amount (<5%) of reduced product **16** could be detected in all of these experiments and was characterized by LC-MS and by comparison to an authentic sample prepared from iodo derivative **10** by treatement with *n*-BuLi at −78 °C, followed by quenching with H_2O.

The utility of the 6-benzylsulfanyl group lies in its stability under the amidation conditions and easy oxidation with *m*-chloroperbenzoic acid to the corresponding sulfone for substitution with suitable nucleophiles.[20,21] Examples of 6,7,8-trisubstituted purines **18a−f** bearing amino substituents at position 6 were synthesized by heating the sulfone intermediate **17** in BuOH or THF in the presence of three different amines (Scheme 3).

In conclusion, this method provides a new practical three-step synthesis of 6,7,8-trisubstituted purines from a readily available pyrimidine starting material. It utilizes a key amidation/cyclization step with copper catalyst and diamine ligand (*trans-N,N′*-dimethylcyclohexane-1,2-diamine) and avoids expensive palladium catalysts and phosphine ligands. In addition, as shown previously,[20,21] the presence of a 6-benzylsulfanyl group in compounds **10** or **15** opens the way to solid-phase synthesis of 6,7,8-substituted purines, using a sulfur-linked Merrifield resin

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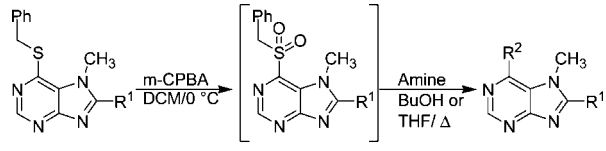
SCHEME 3. Substitution of the 6-Benzylsulfanyl Group by Amine Nucleophiles Following Sulfur Oxidation



15b, d, h, i **17** **18**

18a: R^2 = benzylamino, R^1 = 4-MeO-Ph (69 %)
18b: R^2 = benzylamino; R^1 = 4-NO_2-Ph (66 %)
18c: R^2 = pyrrolidinyl; R^1 = 4-NO_2-Ph (69 %)
18d: R^2 = pyrrolidinyl; R^1 = 4-Cl-Ph (80 %)
18e: R^2 = p-MeO-benzylamino; R^2 = 3-F-Ph(51 %)
18f: R^2 = p-MeO-benzylamino; R^2 = 4-Cl-Ph (60 %)

as a traceless linker. The synthesis reported here has the potential to increase the diversity of the substituents that can be introduced at position 8 for biological screening purposes. We expect it will become a valuable addition to the methods available for the synthesis of combinatorial libraries of purines.

Experimental Section

General Procedure A for the Copper-Catalyzed Couplings of (4-Benzylsulfanyl-6-iodopyrimidin-5-yl)methylamine and Amides. An oven-dried Schlenk was charged with 1 equiv of **10** (100 mg), the corresponding amide (1.5 equiv), cesium carbonate (2 equiv), CuI (0.1 equiv, 10 mol %), (*trans-N,N′*-dimethylcyclohexane-1,2-diamine, **L**) (0.4 equiv, 40 mol %), and degassed dioxane (1.5 mL). The Schlenk was capped with a rubber septum evacuated and backfilled with argon three times, the rubber septum was replaced with a screwcap, and the mixture was stirred for 7−8 h (unless otherwise mentioned) at 90 °C. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane and water, and then extracted twice with dichloromethane. The organic layers were combined dried with $MgSO_4$ and then concentrated under vacum. The crude material was purified by flash chromatography on silica gel eluting with a gradient of ethanol in dichloromethane.

6-Benzylsulfanyl-8-(3-chlorophenyl)-7-methyl-7*H*-purine (15b). A mixture of **10** (100 mg, 0.28 mmol), 3-chlorobenzamide (65.11 mg, 0.41 mmol), Cs_2CO_3 (187 mg, 0.57 mmol), CuI (5.3 mg, 0.027 mmol), **L** (15.78 mg, 0.11 mmol), and dioxane (1.5 mL) was stirred for 7 h at 90 °C (procedure A). After workup, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOH 2%) to afford **15b** as a white solid (yield 68%): mp 161−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.77 (s,1H), 7.64 (d, J = 6 Hz, 1H), 7.48 (m, 7.48, 4H), 7.34 (m, 3H), 4.71 (s, 2H), 4.11 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 153.4, 137.2, 135.4, 131.4, 130.7, 130.6, 130.3, 129.1, 128.3, 128.1, 35.3, 33.9; MS (electrospray) *m/z* (%), 389.0 (100) $[M + Na]^+$. Anal. Calcd for $C_{19}H_{15}ClN_4S$: C, 62.2; H, 4.12; N, 15.27. Found: C, 61.92; H, 4.17; N, 15.21.

6-Benzylsulfanyl-8-(4-chlorophenyl)-7-methyl-7*H*-purine (15c). A mixture of **10** (100 mg, 0.28 mmol), 4-chlorobenzamide (65.11 mg, 0.41 mmol), Cs_2CO_3 (187 mg, 0.57 mmol), CuI (5.3 mg, 0.027mmol), and **L** (15.78 mg, 0.11 mmol) in dioxane (1.5 mL) was stirred for 7 h at 90 °C (procedure A). After workup, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethanol (gradient elution 100/0, and then 98/2) to afford **15c** as a white solid (yield 75%). Mp 202−203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (8.89, s, 1H), 7.7 (d, J = 6 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.45 (d, J = 9 Hz, 2H), 7.3 (m, 3H), 4.7 (s, 2H), 4.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 152.8, 152.7, 137.3, 136.8, 131.1, 129.3, 128.7, 127.6, 127.0, 34.9, 33.5; MS (electrospray) *m/z* (%), 389.0 (100) $[M + Na]^+$, 367,0 (70) $[M + H]^+$. Anal. Calcd for $C_{19}H_{15}ClN_4S$: C, 62.2; H, 4.12; N, 15.27. Found: C, 61.84; H, 4.01; N, 15.19.

General Procedure B for the Preparation of 6-Aminopurines. A solution of commercial *m*-chloroperbenzoic acid (3 equiv) in CH_2Cl_2 (10 mL) was dried over $MgSO_4$ and added dropwise to the corresponding compounds (6-benzylthio-7,8-disubstitued purines) in CH_2Cl_2 at 0 °C, and the resulting mixture was stirred for 8 h in an ice water-bath until disappearence of the starting material as judged by TLC on silica gel in DCM/EtOH 5%. A saturated solution of $Ca(OH)_2$ was added and after workup (extraction with CH_2Cl_2, water washing, and $MgSO_4$ drying of the organic layer), the residue was evaporated under reduced pressure. Compounds were sufficiently pure to be used directly in the next step. The resulting sulfone and 1−2 equiv of the appropriate amine in butyl alcohol (except for compound **18a** where butyl alcohol was replaced by THF) were heated at 110 °C for 4−48 h. After evaporation, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOH 0−6%).

Benzyl-[8-(4-methoxyphenyl)-7-methyl-7*H*-purin-6-yl]amine (18a). 18a was synthesized according to procedure B as a white solid that was recrystallized from EtOH in 69% yield. Mp 227−228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.65 (d, J = 9 Hz, 2H), 7.37 (m, 5H), 7.02 (d, J = 9 Hz), 5.26 (t br, J = 6 Hz), 4.855 (d, J = 3 Hz), 4.01 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 159.5, 156.0, 153.8, 151.0, 139.0, 131.7, 129.3, 128.3, 128.1, 121.4, 114.7, 55.8, 45.5, 34.8; MS (electrospray) *m/z* (%), 368.1 (100) $[M + Na]^+$, 346.2 (70), $[M + H]^+$. HRMS (ESI) calcd for $C_{20}H_{19}N_5O$ $[MH^+]$ 346.1668, Found 346.1665.

8-(4-Chlorophenyl)-7-methyl-6-pyrrolidin-1-yl-7*H*-purine (18d). Procedure B gave a white solid that was recrystallized from heptane/CH_2Cl_2 in 80% of yield. Mp 212−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.78 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 3.49 (s, 3H), 3.79 (m, 4H), 2.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 156.9, 153.0, 152.9, 137.3, 131.6, 129.5, 128.0, 117.0, 50.8, 37.9, 26.0; MS (electrospray) *m/z* (%), 314.2 (40) $[M + H]^+$, 336.1 (100), $[M + Na]^+$; HRMS (ESI) calcd for $C_{16}H_{16}N_5Cl$ $[MH^+]$ 314.1172, Found 314.1168.

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Supporting Information Available: Experimental procedures and spectral data for compounds **6**, **7**, **9**, **10**, **11a**, **13**, **14**, **15a**, **15d**−**n**, **16**, **18b**,**c**, and **18e**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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