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Trifunctionalization of the Purine Scaffold Using Mg and Zn Organometallic Intermediates

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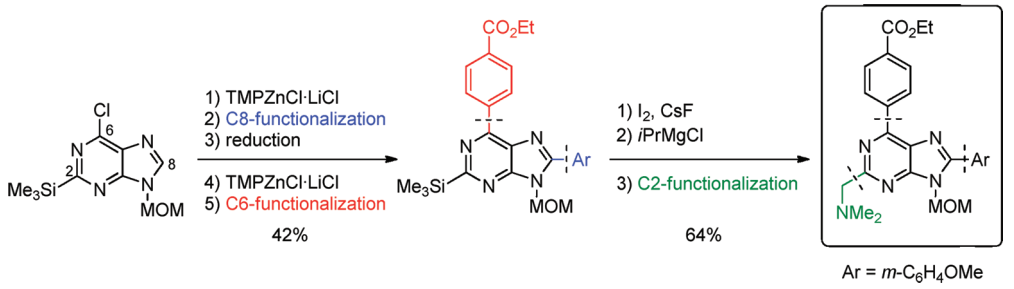
ABSTRACT



Starting from an appropriate 6-chloro-2-TMS-purine derivative, a regioselective functionalization of the purine scaffold was achieved successively at positions 8, 6, and 2 via zinc and magnesium intermediates which were generated either by a direct zincation with TMPZnCl·LiCl or by an I/Mg exchange with *i*PrMgCl.

The purine scaffold functionalization is of great importance since several biologically active compounds bear this heterocyclic unit.[1] For example, purine derivatives **1** and **2** are potential kinase inhibitors[2] or display immunosuppressant[3] activity (Figure 1). Large combinatorial libraries of several types of substituted purines have been prepared by heterocyclizations,[4] direct C−H arylations,[5] or regioselective nucleophilic substitutions of dihalopurines with amines in combination with cross-coupling reactions.[6] Pd-catalyzed cross-couplings as well as Fe-catalyzed alkylations provide access to various simple 6,8-difunctionalized

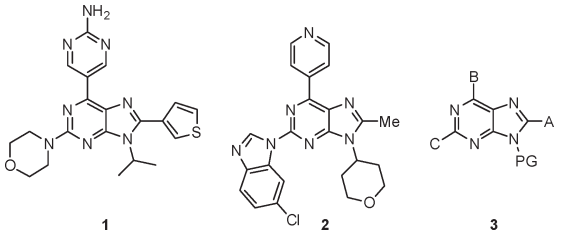


Figure 1. Biologically active purines and metalation precursor of type **3**.

(1) Reviews: (a) Legraverend, M. *Tetrahedron* **2008**, *64*, 8585. (b) Brændvang, M.; Gundersen, L. *Bioorg. Med. Chem.* **2007**, *15*, 7144. (c) Legraverend, M.; Grierson, D. S. *Bioorg. Med. Chem.* **2006**, *14*, 3987. (d) Rosemeyer, H. *Chem. Biodiversity* **2004**, *1*, 361.

(2) Chen, D.; Nagaraj, H. K. M.; Williams, M. WO 2010/114494, 2010.

(3) Neagu, I.; Diller, D.; Kingsbury, C.; Bohnstedt, A. C.; Ohlmeyer, M. J.; Paradkar, V.; Ansari, N. US 20080214580, 2008.

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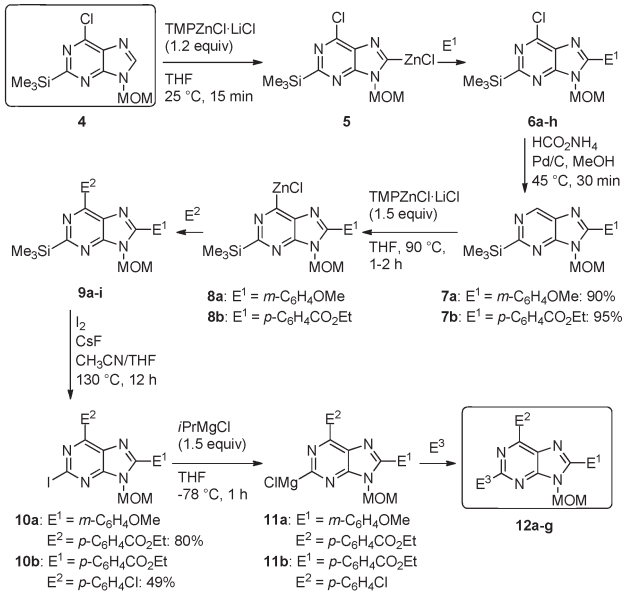
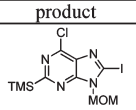
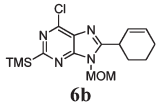
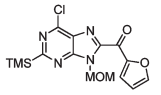
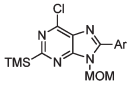
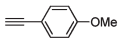
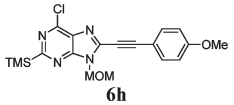
and 2,6,8-trifunctionalized purine derivatives.[5b,6b,6c] The partial functionalization of purines via lithiation,[7] magnesiation,[8] or zincation[9] has also been reported. The successive functionalization of positions 8, 6, and 2 of the same purine scaffold with use of organometallic intermediates is complicated and depends highly on the appropriate choice of the masked functional groups A, B, and C at these positions as well as the protecting group (PG) of purine **3** (Figure 1). After extensive experimentation, we report herein an optimum combination of A, B, C, and PG allowing the successive generation of Zn or Mg intermediates at positions 8, 6, and 2, which finally provides access to a wide range of new polyfunctional purines.

Scheme 1. General Reaction Scheme



Starting from 6-chloropurine, we have prepared the 6-chloro-9-methoxymethyl-2-trimethylsilyl-9*H*-purine (**4**) according to the procedure of Tanaka.[10] Thus, this purine is readily zincated in position 8 by using TMPZnCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidide)[11] within 15 min at 25 °C leading to the zincated purine **5** (Scheme 1). Iodolysis of **5** produces the expected 8-iodopurine (**6a**) in 77% yield (entry 1 of Table 1). Copper(I)-catalyzed allylation[12] (5% CuCN·2LiCl) with 3-bromocyclohexene (−30 to 25 °C, 10 h) leads to the 8-allylated purine (**6b**) in 91% yield (entry 2). Pd-catalyzed acylation (2% $Pd(PPh_3)_4$)[13] with 2-furoyl chloride (0 to 25 °C, 6 h) gave ketone **6c** in 55% yield (entry 3). Negishi cross-coupling reactions[14] with various aryl iodides using 2% $Pd(dba)_2$ and 4% P(*o*-furyl)$_3$[15] afford 8-arylated purines (**6d**−**g**) in 72−91% yield (entries 4−9). An alkynyl group was also introduced via Sonogashira coupling[16] by preparing in situ the iodide **6a**. Its reaction with *p*-anisylacetylene (1.2 equiv of NEt_3, 4% CuI, 2% $Pd(dba)_2$, 4% P(*o*-furyl)$_3$, 25 °C, 3 h) provided the 8-alkynylated purine **6h** in 75% yield. The chloro-substituent in position 6 is then removed by using a Pd-catalyzed reduction with HCO_2NH_4 (20 wt % Pd/C, MeOH/EtOH or MeOH/THF, 45 °C, 15−30 min). Under

Table 1. Functionalization of Position 8 via Zincated Purine **5**

entry	electrophile	product	yield, %[a]
1	I_2	 **6a**	77
2		 **6b**	91[b]
3		 **6c**	55[c]
4	*m*-IC_6H_4OMe	 **6d**: Ar=*m*-C_6H_4OMe	72[d]
5	*p*-$IC_6H_4CO_2Et$	**6e**: Ar=*p*-$C_6H_4CO_2Et$	91[d]
6	*m*-$IC_6H_4CF_3$	**6f**: Ar=*m*-$C_6H_4CF_3$	89[d]
7	*m*-$IC_6H_4NBu_2$	**6g**: Ar=*m*-$C_6H_4NBu_2$	74[d]
8		 **6h**	75[e]

[a] Isolated, analytically pure product. [b] Obtained after addition of 5% CuCN·2LiCl. [c] Obtained by Pd-catalyzed acylation reaction with 2% $Pd(PPh_3)_4$. [d] Obtained by Pd-catalyzed cross-coupling reaction with 2% $Pd(dba)_2$ and 4% P(*o*-furyl)$_3$ as catalyst. [e] Obtained from **6a** by Pd-catalyzed coupling reaction with 1.2 equiv of NEt_3, 4% CuI, 2% $Pd(dba)_2$, and 4% P(*o*-furyl)$_3$.

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(10) Kato, K.; Hayakawa, H.; Tanaka, H.; Kumamoto, H.; Miyasaka, T. *Tetrahedron Lett.* **1995**, *36*, 6507.

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(14) (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

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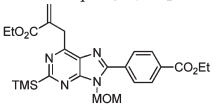
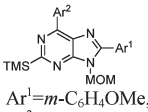
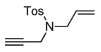
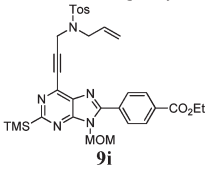
these conditions, the 6-chloropurines **6d**,**e** led to the dechlorinated products **7a**,**b** in 90−95% yield (Scheme 1).

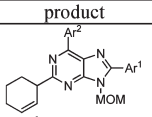
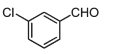
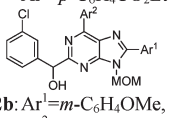
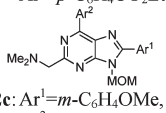
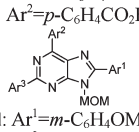
Table 2. Functionalization of Position 6 via Zincated Purines **8a**,**b**

entry	electrophile	product	yield, %[a]
1	I_2	**9a**: Ar=*m*-C_6H_4OMe	64
2	I_2	**9b**: Ar=*p*-$C_6H_4CO_2Et$	76
3		 **9c**	68[b]
4	*p*-$IC_6H_4CO_2Et$	 **9d**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$	64[c]
5	*m*-$IC_6H_4CF_3$	**9e**: Ar^1=*m*-C_6H_4OMe, Ar^2=*m*-$C_6H_4CF_3$	55[c]
6	*m*-$IC_6H_4NBu_2$	**9f**: Ar^1=*p*-$C_6H_4CO_2Et$, Ar^2=*m*-$C_6H_4NBu_2$	62[c]
7	*p*-IC_6H_4Cl	**9g**: Ar^1=*p*-$C_6H_4CO_2Et$, Ar^2=*p*-C_6H_4Cl	55[c]
8	2-iodothiophene	**9h**: Ar^1=*p*-$C_6H_4CO_2Et$, Ar^2=2-thiophenyl	43[c]
9		 **9i**	75[d]

[a] Isolated, analytically pure product. [b] Obtained after addition of 25% CuCN·2LiCl. [c] Obtained by Pd-catalyzed cross-coupling reaction with 2% $Pd(dba)_2$ and 4% P(*o*-furyl)$_3$ as catalyst. [d] Obtained from **9b** by Pd-catalyzed coupling reaction with 1.5 equiv of NEt_3, 4% CuI, 2% $Pd(dba)_2$, and 4% P(*o*-furyl)$_3$.

Purines of type **7** are readily metalated at position 6. Thus, treatment of **7a** with TMPZnCl·$MgCl_2$·LiCl (1.5 equiv) leads to a complete zincation under microwave irridation[11,17] (sealed vessel, 90 °C, 1 h) providing the 6-zincated purine **8a** (E^1 = 3-methoxyphenyl). The purine **7b**, which proved to be more acidic at position 6 than **7a**, reacts with TMPZnCl·LiCl (prepared in the absence of $MgCl_2$) leading to **8b** (E^1 = 4-carbethoxyphenyl, 90 °C, 2 h). The resulting zinc reagents (**8a**,**b**) react with a range of electrophiles (Table 2). Thus, iodolysis produces the 6-iodopurines **9a**,**b** in 64−76% yield (entries 1 and 2 of Table 2). The copper-catalyzed allylation of **8b** with ethyl (2-bromomethyl)acrylate[18] leads to purine **9c** in 68% yield (entry 3). A range of aryl iodides bearing either electron-withdrawing substituents (CO_2Et, CF_3, Cl), electron-donating substituents (NBu_2), or a heterocyclic backbone (2-thienyl) undergo Negishi cross-coupling[14] with **8a**,**b** (25 °C, 8−40 h) affording the 2,6-bis-arylated purines **9d**−**h** in 43−64% yield (entries 4−8). In situ generation of iodide **9b** followed by a Pd-catalyzed cross-coupling with *N*-allyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide[19] affords the 6-alkynylated purine **9i** in 75% yield (entry 9).

Table 3. Functionalization of Position 2 via Magnesiated Purines **11a**,**b**

entry	electrophile	product	yield, %[a]
1		 **12a**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$	68[b]
2		 **12b**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$	94
3	$CF_3CO_2^-$ $CH_2NMe_2^+$	 **12c**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$	86
4	*m*-$IC_6H_4CF_3$	 **12d**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$, Ar^3=*m*-$C_6H_4C F_3$	65[c]
5	*p*-IC_6H_4Br	**12e**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$, Ar^3=*p*-C_6H_4Br	63[c]
6	*p*-IC_6H_4OMe	**12f**: Ar^1=*p*-$C_6H_4CO_2Et$, Ar^2=*p*-C_6H_4Cl, Ar^3=*p*-C_6H_4OMe	58[c]
7	4-iodopyridine	**12g**: Ar^1=*m*-C_6H_4OMe, Ar^2=*p*-$C_6H_4CO_2Et$, Ar^3=4-pyridyl	55[c]

[a] Isolated, analytically pure product. [b] Obtained after addition of 25% CuCN·2LiCl. [c] Obtained after transmetalation with 1.6 equiv of $ZnCl_2$ by Pd-catalyzed cross-coupling reaction with 2% $Pd(dba)_2$ and 4% P(*o*-furyl)$_3$ as catalyst.

After having functionalized positions 8 and 6, we have converted the 2-TMS-substituent of **9d** and **9g** to the corresponding 2-iodopurines (**10a**,**b**) by treatment with I_2 (1.4 equiv, 1:1 CH_3CN:THF, microwave irradiation, sealed vessel, 110−130 °C, 12 h) in the presence of CsF (2 equiv) in 49−80% yield.[20] I/Mg exchange of **10a**,**b** with *i*PrMgCl (1.5 equiv, THF, −78 °C, 1 h) furnishes the Mg- reagents **11a**,**b**. Their reaction with various electrophiles such as allyl bromides (entry 1 of Table 3), aldehydes (entry 2), immonium reagents[21] (entry 3) or a range of functionalized aryl and heteroaryl iodides (entries 4−7) provides the fully 2,6,8-substituted purines in 55−94% yield.

In summary, we have described a novel triple functionalization sequence of the purine scaffold starting from the readily available 6-chloropurine **4** via 8-zincated, 6-zincated, and 2-magnesiated intermediates using either a selective

(17) The kinetic basicity of TMPZnCl·LiCl can be increased by adding $MgCl_2$ (1 equiv), see: Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685.

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(21) Kinast, G.; Tietze, L. F. *Angew. Chem., Int. Ed.* **1976**, *15*, 239.

zincation with TMPZnCl·LiCl[11] or an I/Mg exchange triggered by *i*PrMgCl. Besides cross-coupling reactions, our new functionalization approach of the purine skeleton allows the performance of novel functionalizations such as allylations, acylations, and aminomethylations. In conclusion, this new method offers access to a large variety of highly functionalized purine derivatives. Further applications to prepare biologically active, valuable purines are underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data of all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.