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Regio- and Chemoselective Multiple Functionalization of Pyrimidine Derivatives by Selective Magnesiations using TMPMgCl·LiCl

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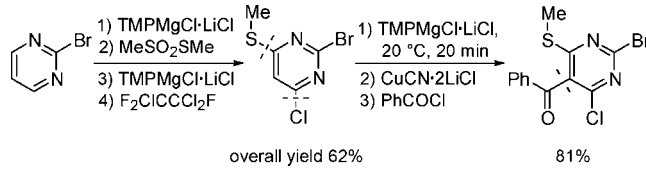
ABSTRACT



Successive regio- and chemoselective magnesiations of pyrimidines using TMPMgCl·LiCl furnish, after trapping with various electrophiles, highly functionalized derivatives in good to excellent yields. Applications to the synthesis of antiviral and anti-inflammatory agents such as p38 and sPLA2 kinase inhibitors are reported.

Pyrimidines are important scaffolds for the preparation of various biologically active compounds.[1] The direct functionalization of these heterocycles by lithiation is difficult due to the electrophilic character of the ring, which readily undergoes the addition of various organometallics in positions 4 and 6.[2] This implies that low temperatures are often required for the metalation of pyrimidines.[3] Recently, we have reported the new powerful base TMPMgCl·LiCl (**1**; TMP = 2,2,6,6-tetramethylpiperidyl), which allows direct magnesiation of a number of arenes and heteroarenes.[4]

Herein, we report a procedure allowing *selective functionalization of all positions* of the pyrimidine ring starting from simple compounds such as 2-bromopyrimidine[5] (**2**) by performing successive magnesiations using TMPMgCl·LiCl (**1**; Scheme 1).

Thus, the treatment of 2-bromopyrimidine (**2**) with TMPMgCl·LiCl (**1**; 1.1 equiv, −55 °C, 1.5 h) leads to the 4-magnesiated pyrimidine (**3**), which can be trapped by various electrophiles such as $MeSO_2SMe$, $PhSO_2SPh$, I_2, $BrCCl_2CCl_2Br$, and TMSCN leading to the expected products of type **4a**−**e** in 67−85% (Scheme 1). The formation of a new carbon−carbon bond is readily performed by a Negishi[6] cross-coupling or a Sonogashira[7] reaction of *in situ* generated 2-bromo-4-iodopyrimidine (**4c**) providing the 4-substituted heterocycles **4f**−**h** in 71−81% (Scheme 1).

A subsequent magnesiation is readily achieved at position 6 by the addition of TMPMgCl·LiCl (**1**) to various 4-sub-

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(3) (a) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron Lett.* **2001**, *57*, 4489. (b) Schlosser, M.; Lefebvre, O.; Ondi, L. *Eur. J. Org. Chem.* **2006**, *6*, 1593.

(4) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673.

(5) 2-Bromopyrimidine is commercially available from Acros, Aldrich, Fluka ($15 for 1 g).

10.1021/ol800790g CCC: $40.75
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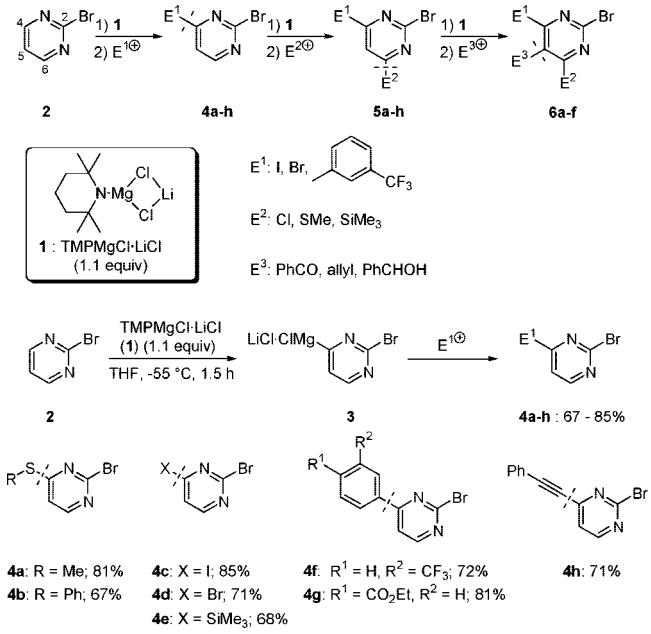
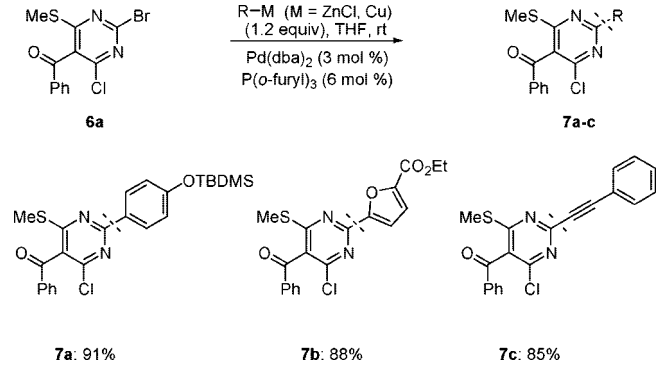
Scheme 1. Magnesiation of 2-Bromopyrimidine (**2**) at Positions 4, 6, and 5 using TMPMgCl·LiCl (**1**; 1.1 equiv)



stituted 2-bromopyrimidines. Thus, the 2-bromo-4-(methylthio)pyrimidine[8] **4a** is converted within 5 min at 20 °C to the 6-magnesiated species, which is chlorinated by reaction with FCl_2CCF_2Cl[9] leading to the chloropyrimidine **5a** in 76% yield (entry 1 of Table 1). Reaction with $BrCl_2CCCl_2Br$ furnishes the bromo-pyrimidine **5b** in 81% yield (entry 2). An iodolysis using I_2 leads to the 2-bromo-4-iodopyrimidine derivative **5c** in 78% yield (entry 3). Similarly, the 4-arylated-2-bromopyrimidine **4f** is magnesiated quantitatively with TMPMgCl·LiCl (**1**; 1.1 equiv, −40 °C, 45 min) and reacted with FCl_2CCF_2Cl, TMSCN, or $MeSO_2SMe$ affording the expected 4,6-disubstituted 2-bromopyrimidines **5d**−**f** in 72−91% yield (entries 4−6).

Other 2-bromopyrimidines substituted at position 4 with an alkynyl group or an iodine (**4c**, **4h**) are magnesiated under mild conditions. Quenching with typical electrophiles furnishes the polyfunctional pyrimidines **5g** and **5h** in 84−93% yield (entries 7 and 8). The last position (position 5) can be magnesiated as well between −5 and 20 °C within 20−30 min with TMPMgCl·LiCl (**1**; 1.1 equiv). Trapping with iodine, PhCOCl (after transmetalation with CuCN·2LiCl[10] (1.1 equiv)), allyl bromide, PhCHO, or $MeSO_2SMe$ provides the fully substituted

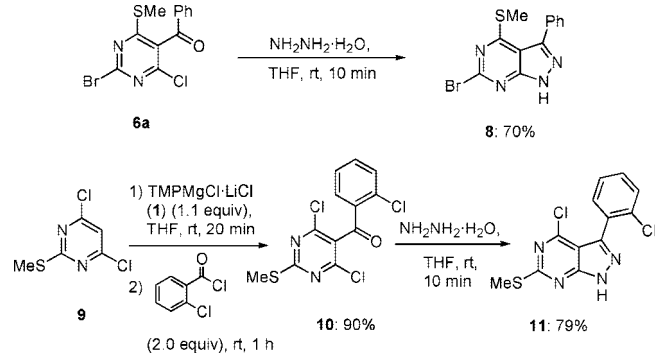
Scheme 2. Negishi and Sonogashira Cross-Coupling Reactions at Position 2 Leading to Fully Substituted Pyrimidines **7a**−**c**



pyrimidines **6a**−**f** in 67−92% yield (entries 9−14). The bromine attached at position 2 can be readily substituted using a Negishi[6] or a Sonogashira[7] reaction giving the 2-substituted pyrimidines **7a**−**c** in 85−91% yield (Scheme 2).

This method is of great utility for the preparation of pharmaceutically active heterocycles such as pyrazolopyrimidines.[11] Thus, the treatment of tetrasubstituted pyrimidine **6d** with $NH_2NH_2{\cdot}H_2O$ in THF (rt, 10 min) leads to the pyrazolopyrimidine **8** in 70% yield (Scheme 3). As

Scheme 3. Application to the Synthesis of Pyrazolopyrimidines and Synthesis of a p38 Kinase Inhibitor (**11**)



an application, we have prepared a p38 kinase inhibitor[12] (useful as an anti-inflammatory and antiviral agent) starting from 4,6-dichloro- 2-(methylthio)pyrimidine[13] (**9**).

(6) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E.; Kobayashi, M. *J. Org. Chem.* **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (d) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(7) (a) Benderitter, P.; de Araujo, J. X., Jr.; Schmitt, M.; Bourguignon, J. J. *Tetrahedron* **2007**, *63*, 12465. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. (d) Sonogashira, K. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 3.

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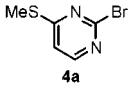
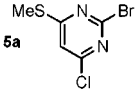
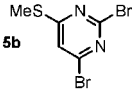
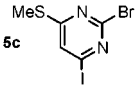
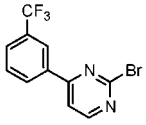
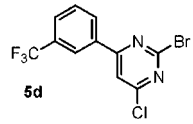
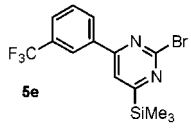
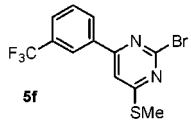
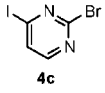
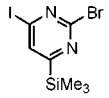
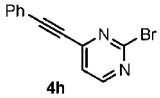
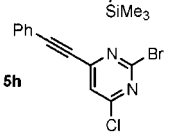
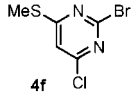
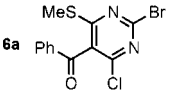
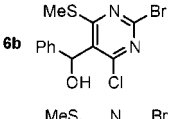
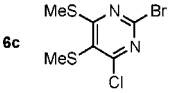
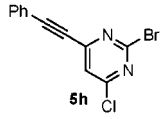
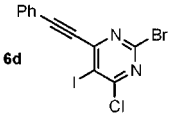
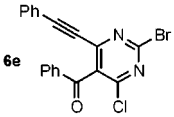
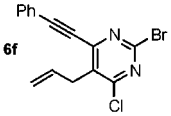
(13) 4,6-Dichloro-2-(methylthio)pyrimidine is commercially available.

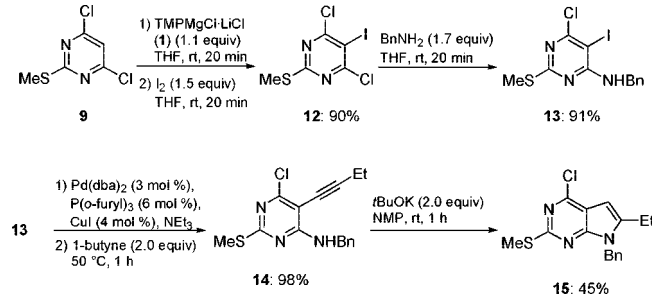
Table 1. Products Obtained by Regioselective Magnesiation of Pyrimidines of Type **4** and **5** with TMPMgCl·LiCl (**1**) and Quenching with Electrophiles

entry	substrate of type **4** and **5**	electrophile	product	yield, %[a]
1	 **4a**	FCl_2CCF_2Cl	 **5a**	76
2	**4a**	$(BrCl_2C)_2$	 **5b**	81
3	**4a**	I_2	 **5c**	78
4	 **4f**	FCl_2CCF_2Cl	 **5d**	91
5	**4f**	Me_3SiCN	 **5e**	72
6	**4f**	$MeSO_2SMe$	 **5f**	76
7	 **4c**	Me_3SiCN	 **5g**	93
8	 **4h**	FCl_2CCF_2Cl	 **5h**	84
9	 **4f**	PhCOCl[b]	 **6a**	81
10	**4f**	PhCHO	 **6b**	75
11	**4f**	$MeSO_2SMe$	 **6c**	92
12	 **5h**	I_2	 **6d**	71
13	**5h**	PhCOCl[b]	 **6e**	69
14	**5h**	allyl bromide[c]	 **6f**	67

[a] Isolated, analytically pure product. [b] Transmetalation with 1.1 equiv of CuCN·2LiCl. [c] Transmetalation with 5 mol % of CuCN·2LiCl.

The magnesiation of **9** with TMPMgCl·LiCl is complete within 20 min at 25 °C. Transmetalation with CuCN·2LiCl[10] (1.1 equiv) and acylation with 2-chlorobenzoyl chloride (2 equiv, rt, 1 h) provides the tetrasubstituted pyrimidine **10** in 90% yield. Subsequent treatment with $NH_2NH_2 \cdot H_2O$ furnished the p38 kinase inhibitor **11** in 79% yield (Scheme 4).

Scheme 4. Synthesis of an sPLA2 Inhibitor (**15**) by Chemoselective Magnesiation



Similarly, we performed the synthesis of an sPLA2 inhibitor **15** having anti-inflammatory properties.[14] Thus, the iodination of the dichloropyrimidine **9** is leading to the iodopyrimidine derivative **12** in 90% yield. The substitution of the chlorine at position 6 with benzylamine[15] (1.7 equiv, THF, 25 °C, 20 min) leads to the aminopyrimidine **13** in 91% yield. The Sonogashira[7] cross-coupling of the pyrimidine **13** with 1-butyne affords the 5-alkynyl-6-aminopyrimidine **14** in 98% yield. Smooth cyclization with KO*t*Bu[16] (2 equiv, NMP, 25 °C, 1 h) finally provides the sPLA2 inhibitor **15** in 45% yield (Scheme 4).

In summary, we have reported the multiple functionalization[17] of the pyrimidine scaffold using TMPMgCl·LiCl as an effective magnesium base. This method displays a large scope and allows functionalization of all positions of a pyrimidine unit. It should find broad applications to

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(15) Baindur, N.; Chadha, N.; Player, M. R. *J. Comb. Chem.* **2003**, *5*, 653.

(16) (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.

(17) **Procedure for Synthesis of (2-bromo-4-chloro-6-(methylthio)-pyrimidin-5-yl)(phenyl)methanone (6a).** A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated TMPMgCl·LiCl (**1**) (0.89 M in THF, 1.24 mL, 1.1 mmol, 1.1 equiv). 2-Bromo-4-chloro-6-(methylthio)pyrimidine (**5a**) (240 mg, 1.0 mmol) dissolved in THF (2 mL) was dropwise added at 25 °C, and the resulting mixture was stirred for 20 min. The reaction mixture was cooled to −30 °C and after addition of CuCN·2LiCl (1.00 M solution in THF, 1.1 mL, 1.1 mmol) was stirred for 30 min. Then, benzoyl chloride (281 mg, 2.0 mmol) was slowly added at −30 °C, and the resulting mixture was stirred at room temperature for 45 min. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL), and dried (Na_2SO_4). After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished (2-bromo-4-chloro-6-(methylthio)-pyrimidin-5-yl)-(phenyl)methanone (**6a**) as a white solid (276 mg, 81% yield).

the synthesis of pharmaceutically relevant molecules. Extensions to the preparation of new materials are currently under investigation in our laboratories.

Acknowledgment. We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) for financial support. We also thank BASF AG (Ludwigshafen), Evonik Degussa AG (Hanau), and Chemetall GmbH (Frankfurt) for the generous gift of chemicals.

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

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