Regio- and chemoselective magnesiation of protected uracils and thiouracils using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$†

Marc Mosrin, Nadège Boudet and Paul Knochel*

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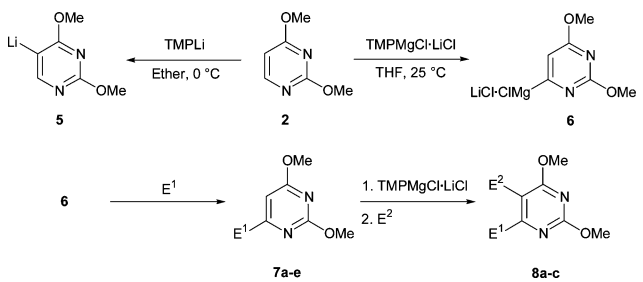
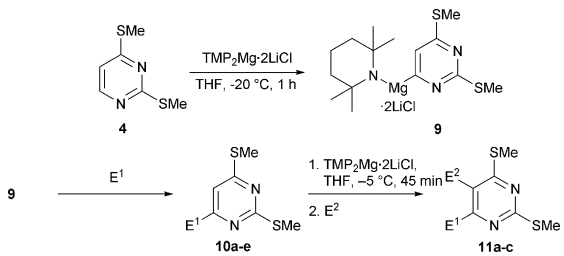
Two successive regio- and chemoselective magnesiations using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ enable the full functionalization of protected uracils and thiouracils in good to excellent yields.

The functionalization of heterocycles like uracils is of great importance for the preparation of bio-relevant molecules, especially with antiviral properties.[1] Wada[2] and Quéguiner[3] have reported the regioselective lithiation of 2,4-dimethoxypyrimidine (**2**) using TMPLi. Recently, we have shown that TMPMgCl·LiCl (**1**; TMP = 2,2,6,6-tetramethylpiperidyl)[4] allows a full functionalization of the pyrimidine scaffold under mild conditions.[5] Herein, we wish to report a complementary metalation procedure of the uracil derivative (**2**) as well as of the thio-analogue of **2** (2,4-bis(methylthio)pyrimidine **4**) using TMPMgCl·LiCl (**1**)[5] or $TMP_2Mg·2LiCl$ (**3**).[6] Whereas the lithiation of dimethoxyuracil (**2**) with TMPLi[3] (ether, 0 °C, 10 min) produces exclusively the 5-lithiated pyrimidine **5**, we have found that the treatment of **2** with TMPMgCl·LiCl (**1**; 1.1 equiv, THF, 25 °C, 15 min) furnishes exclusively the 6-magnesiated uracil derivative **6** (Scheme 1). No trace of 5-magnesiated uracil could be detected after 1 h at 25 °C.



Scheme 1

Thus, the quenching of **6** with various electrophiles such as I_2, Me_3SiCN, 4-ethyl iodobenzoate[7] (after transmetalation with $ZnCl_2$ followed by the addition of $Pd(dba)_2$ and P(*o*-furyl)$_3$), *t*-BuCOCl (after transmetalation with CuCN·2LiCl)[8] and ethyl cyanoformate provides a range of polyfunctional uracil derivatives (**7a–e**) in 70–75% yield (Scheme 1 and Table 1, entries 1–5). Subsequent magnesiation of selected uracils **7** allows a further functionalization in position 5 leading to the 5,6-disubstituted uracils **8a–c** in 78–87% yield (entries 6–8). We have extended our approach to the thiouracil derivative,[9] and have treated 2,4-bis(methylthio)pyrimidine (**4**) with $TMP_2Mg·2LiCl$ (**3**, 1.1 equiv, THF, −20 °C, 60 min), which provides the 6-magnesiated pyrimidine derivative **9** (Scheme 2). No trace of 5-magnesiated thiouracil could be detected. Thus, trapping of **9** with typical electrophiles furnishes the new 6-substituted thiouracils **10a–c** in 76–81% yield (Scheme 2 and Table 1, entries 9–11). The formation of a new carbon–carbon bond is also readily performed by a Negishi[7] cross-coupling providing the 6-arylpyrimidines **10d** and **10e** in 71 and 80% (Table 1, entries 12–13). A further metalation with $TMP_2Mg·2LiCl$ (**3**, 1.1 equiv, THF, −5 °C, 45 min) can be performed at position 5. Quenching with electrophiles such as I_2, PhCOCl (after transmetalation with CuCN·2LiCl)[8] or PhCHO provides the fully substituted pyrimidines **10a–c** in 61–66% yield (entries 14–16).



Scheme 2

In summary, we have reported a new successive regioselective functionalization of protected uracils and thiouracils. This method should find broad applications in the synthesis of pharmaceutically relevant molecules. Further investigations are under way in our laboratories.

Department Chemie, Ludwig-Maximilians-Universität München, Butenandstr. 5-13, Haus F, 81377, München, Germany. E-mail: Paul.Knochel@cup.uni-muenchen.de; Fax: (+49)-89-2180-77680; Tel: (+49)-2180-77681

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Table 1 Products obtained by regio- and chemoselective magnesiation of pyrimidines of type **2** and **4** with TMPMgCl·LiCl (**1**) or $TMP_2Mg·2LiCl$ (**3**) and quenching with electrophiles

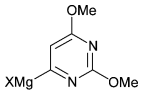
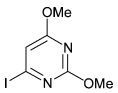
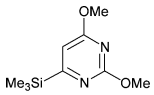
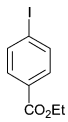
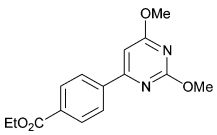
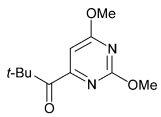
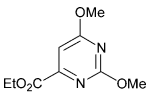
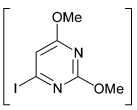
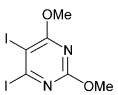
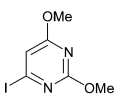
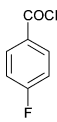
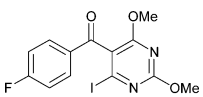
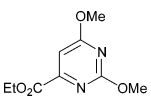
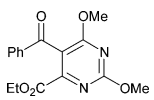
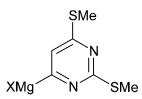
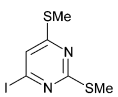
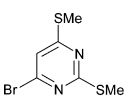
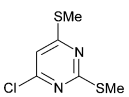
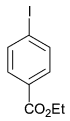
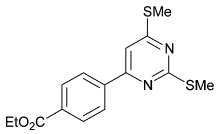
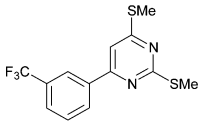
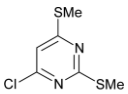
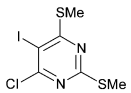
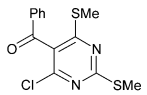
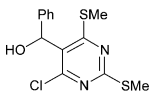
Entry	Mg reagent[a]	Electrophile	Product	Yield (%)[b]
1	 **6**	I_2	 **7a**	74
2	**6**	Me_3SiCN	 **7b**	70
3	**6**		 **7c**	75[d,e]
4	**6**	*t*–BuCOCl[c]	 **7d**	72[c]
5	**6**	NC-CO_2Et	 **7e**	71
6	 **7a**	I_2	 **8a**	87[f]
7	 **7a**		 **8b**	84[c]
8	 **7e**	PhCOCl	 **8c**	78[c]
9	 **9**	I_2	 **10a**	76
10	**9**	$(BrCCl_2)_2$	 **10b**	81
11	**9**	$FCCl_2CClF_2$	 **10c**	78

Table 1 (*Contd.*)

Entry	Mg reagent[a]	Electrophile	Product	Yield (%)[b]
12	**9**		 **10d**	71[d,e]
13	**9**		 **10e**	80[d,e]
14	 **10c**	I_2	 **11a**	61
15	**10c**	PhCOCl	 **11b**	65[c]
16	**10c**	PhCHO	 **11c**	66

[a] X=Cl·LiCl or TMP·2LiCl. [b] Isolated yield of analytically pure product. [c] 1 equiv. of CuCN·2LiCl was added. [d] The Grignard reagent was transmetalated with 1.2 or 2.4 equiv. of $ZnCl_2$ in THF. [e] 3 mol% of $Pd(dba)_2$ and 6 mol% of P(*o*-furyl)$_3$ were added. [f] This reaction was made starting from **7a** in a "one pot" procedure.

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Notes and references

1 D. T. Hurst, *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*, Wiley, Chichester, 1980; D. J. Brown, *The Pyrimidines*, Wiley, New York, 1994; A. R. Katrizky, C. W. Rees and E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford, 1996; G. Gribble and J. Joule, *Progress in Heterocyclic Chemistry, 18*, Elsevier, Oxford, 2007.

2 A. Wada, J. Yamamoto and S. Kanatomo, *Heterocycles*, 1987, **26**, 585.

3 N. Plé, A. Turck, E. Fiquet and G. Quéguiner, *J. Heterocycl. Chem.*, 1991, **28**, 283; for an excellent review, see:; F. Chevallier and F. Mongin, *Chem. Soc. Rev.*, 2008, **37**, 595.

4 A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 2958.

5 M. Mosrin and P. Knochel, *Org. Lett.*, 2008, **10**, 2497.

6 G. C. Clososki, C. J. Rohbogner and P. Knochel, *Angew. Chem., Int. Ed.*, 2007, **46**, 7681.

7 E. Negishi, L. F. Valente and M. Kobayashi, *J. Am. Chem. Soc.*, 1980, **102**, 3298; E. Negishi and M. Kobayashi, *J. Org. Chem.*, 1980, **45**, 5223; E. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340.

8 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.

9 L. Strekowski, D. Harden and R. A. Watson, *Synthesis*, 1988, 70; L. Strekowski, R. A. Watson and M. A. Faunce, *Synthesis*, 1987, 579.