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Functionalization of Unprotected Uracil Derivatives Using the Halogen–Magnesium Exchange

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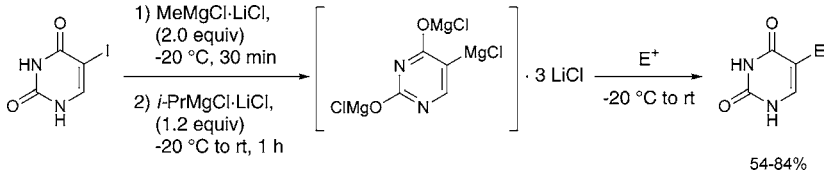
ABSTRACT



The reaction of commercially available 5-iodouracil with 2 equiv of MeMgCl in the presence of LiCl, followed by the addition of *i*-PrMgCl·LiCl, provides the corresponding trimagnesiated species, which reacts with various electrophiles to give selectively 5-functionalized uracil derivatives. This method was also successfully applied to the functionalization of 6-iodouracils including the synthesis of pharmaceutically relevant Emivirine and HEPT precursors.

The functionalization of uracil and related nucleobase derivatives has been extensively investigated, as these systems represent core structural elements for a broad variety of pharmaceutically active compounds.[1] Using uracil-derived organometallic reagents, at least one of the two acidic protons in the uracil moiety has to be protected.[2]

Recently, we have reported a convenient magnesiation of phenol derivatives, avoiding the need for protection of the acidic OH group by generating a bianionic species.[3]

In analogy, we reacted commercially available 5-iodouracil (**1a**) with MeMgCl (2.0 equiv) in the presence of LiCl (2.0 equiv) at −20 °C, followed by the addition of *i*-PrMgCl·LiCl (1.1 equiv) at −20 °C, allowing the mixture to warm to room temperature. The use of MeMgCl as a deprotonating agent proves to be best. Its low activity as an exchange reagent avoids a potential "self-protonation". LiCl plays a double role as it increases the rate of the exchange reaction[4] and, at the same time, drastically improves the solubility[5] (e.g., 5-iodouracil itself is nearly insoluble in THF), resulting in the formation of the triple magnesiated species **2a**, which finally precipitates to give a thick, but still stirrable, slurry.

The use of 3 equiv of LiCl is essential; experiments with fewer equivalents resulted in lower conversions. The magnesium reagent **2a** can be easily trapped by the reaction with different electrophiles. Thus, the reaction with sterically demanding, aliphatic, aromatic, or heteroaromatic aldehydes (1.3 equiv) affords the desired products **3a**−**d** in 55−78% yield (Table 1, entries 1 and 3−5). Similarly, the reaction with allyl bromide in the presence of catalytic amounts of CuCN·2LiCl[6] (1 mol %) proceeds smoothly, giving the

(1) (a) Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737. (b) Newkome, G. R.; Pandler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley: New York, 1982. (c) Botta, M.; Saladino, R.; Lamba, D.; Nicoletti, R. *Tetrahedron* **1993**, *49*, 6053. (d) Asakura, J.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928. (e) Peters, D.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165.

(2) For protection of only one NH function, see: (a) Aso, M.; Kaneko, T.; Nakamura, M.; Koga, N.; Suemune, H. *Chem. Commun.* **2003**, 1094. Or: (b) Schinazi, R. F.; Prusoff, W. H. *J. Org. Chem.* **1985**, *50*, 841. (c) For DABCO-mediated modification of uridine derivatives: Sajiki, H.; Yamada, A.; Yasunaga, K.; Tsunoda, T.; Amer, M. F. A.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 2179.

(3) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, *20*, 2288.

(4) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(5) For the solubilization of lanthanide salts in the presence of LiCl, see: Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.

(6) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

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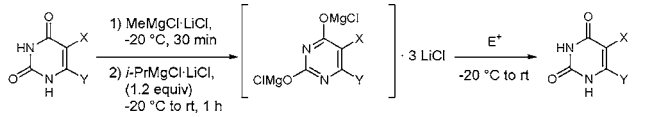
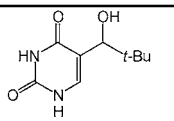
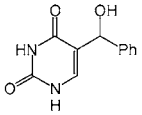
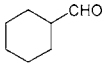
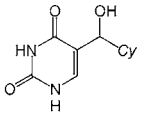
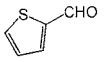
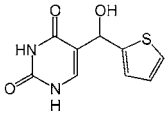
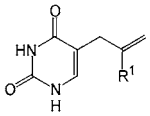
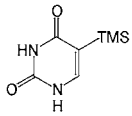
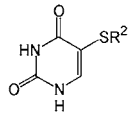
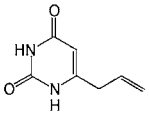
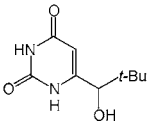
Table 1. Functionalization of Unprotected Uracil Derivatives by Triple Magnesiation and Subsequent Reaction with Electrophiles



1a: X = I; Y = H
1b: X = Br; Y = H
1c: X = H; Y = I

2a: X = MgCl; Y = H
2b: X = MgI-Pr; Y = H
2c: X = H; Y = MgCl

3a: X = E; Y = H
3b: X = E; Y = H
3c: X = H; Y = E

entry	substrate of type **1**	electrophile	product of type **3**		yield[a] [%]
1	**1a**	*t*-BuCHO		**3a**	77
2	**1b**[b]	*t*-BuCHO		**3a**	57
3	**1a**	PhCHO		**3b**	78
4	**1a**			**3c**	70
5	**1a**			**3d**	55
					
6	**1a**	R^1 = H		**3e**	84[c]
7	**1b**[b]	R^1 = Me		**3f**	54[c]
8	**1a**	TMSCl		**3g**	72
		$R^2SSO_2R^2$			
9	**1a**	R^2 = Ph		**3h**	77
10	**1a**	R^2 = Me		**3i**	64
11	**1c**	allyl bromide		**3j**	64[c,d]
12	**1c**	*t*-BuCHO		**3k**	69[d]

[a] Isolated yields of analytically pure compounds. [b] $(i\text{-Pr})_2$Mg·LiCl (1.1 equiv), −20 °C to rt, 2 h. [c] The reaction was conducted in the presence of CuCN·2LiCl (1 mol %). [d] Steps 1 and 2 conducted at −25 °C.

product **3e** in 84% yield (entry 6). The reagent **2a** can also be reacted with TMSCl. In this case, a larger excess of the electrophile (3.3 equiv) was used. After acidic aqueous workup, the desired product, bearing only one TMS group, is isolated in 72% yield (entry 8). The introduction of a sulfur functionality is conveniently accomplished by reacting **2a** with thiosulfonates of the type $R^2SSO_2R^2$.[7] The corresponding thioethers **3h** and **3i** are prepared in 77% and 64% yield, respectively (entries 9 and 10). Also, the cheaper 5-bromouracil (**1b**) can be magnesiated using *i*-Pr_2Mg·LiCl[8] (1.1 equiv). The reactions with standard electrophiles such as *t*-BuCHO or methallyl bromide (2.8 equiv) provide lower yields than using 5-iodouracil (**1a**) as the substrate (compare entries 2 and 7). Similarly, 6-iodouracil[9] (**1c**) can be smoothly metalated using the same reaction sequence. The reactions with allyl bromide and *t*-BuCHO proceed smoothly and give access to the expected products **3j** and **3k** in 64% and 69% yield, respectively (entries 11 and 12).

Artificial nucleobase derivatives have found important applications as drugs, especially for the treatment of HIV, and a broad variety of uracil derivatives have been tested for their activity. Many active compounds bear an alkyl substituent in the 5-position and variable groups in the adjacent position 6.[10] Encouraged by our results with 6-iodouracil (**1c**) as a substrate, we investigated the magnesiation of unprotected 5-alkyl-6-iodouracil derivatives of type **6**. These substrates are easily obtained in a two-step process starting from readily available 5-alkyl barbituric acids (**4**).[11] The chlorination with $POCl_3$ and catalytic amounts of H_3PO_4 at reflux gives access to the 5-alkyl-chlorouracils of type **5** in good yields (Scheme 1).[12] Treatment with sodium iodide in the presence of HI at room temperature affords the corresponding iodides **6a**,**b** in 71−74% yield. The magnesiation according to our protocol occurs smoothly in the case of both the methyl (**6a**) and the isopropyl derivatives (**6b**), affording the triple magnesiated species of type **7**. However, the introduction of a thioether moiety by treating **7a** with $PhSSO_2Ph$ affords **8** in only 40% yield.[13] More efficiently, the reaction of **7b** with benzyl bromide after transmetalation using CuI·2LiCl furnishes the uracil derivative **9** in 57% yield (Scheme 1). The resulting products **8** and **9** are precursors

(7) (a) These electrophiles are easily available: Fujili, K.; Tanifuji, N; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343. (b) The installation of thioether moieties was also recently accomplished by the reaction of chlorouracils with thiolates: Fang, W.-P.; Chedng, Y.-T.; Cheng, Y.-R.; Cherng, Y.-J. *Tetrahedron* **2005**, *61*, 3107.

(8) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 15.

(9) Pfleiderer, W.; Deiss, H. *Isr. J. Chem.* **1968**, *6*, 603.

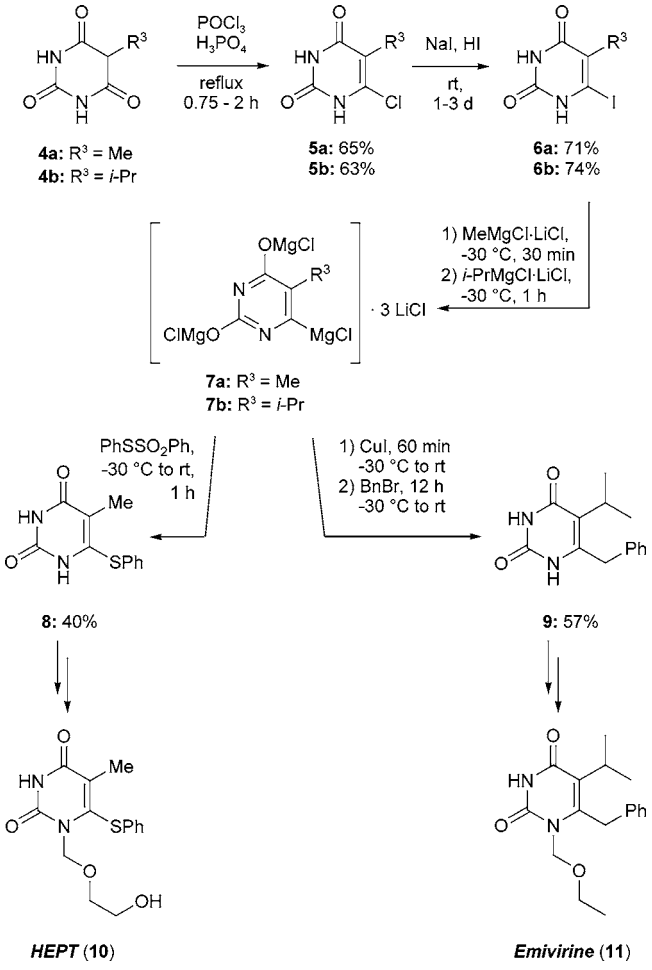
(10) (a) Sun, G.-F.; Chen, X.-X.; Chen, F.-E.; Wang, Y.-P.; De Clercq, E.; Balzarini, J.; Pannecouque, C. *Chem. Pharm. Bull.* **2005**, *53*, 886. (b) Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 349. (c) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1992**, *35*, 4713. (d) El-Brollosoy, N.; Pedersen, E. B.; Nielsen, C. *Arch. Pharm. Pharm. Med. Chem* **2003**, *336*, 236.

(11) **4b** is commercially available, and **4a** was synthesized from diethyl 2-methylmalonate, according to: Puckett, W. E.; Pews, R. G. *J. Fluorine Chem.* **1989**, *42*, 179.

(12) (a) Koroniak, H.; Jankowski; A.; Krasnowski, M. *Org. Prep. Proced. Int.* **1993**, *25*, 563. (b) Gauri, K. K.; Partenheimer, H. *Ger. Offen.* **1962**, 1250829.

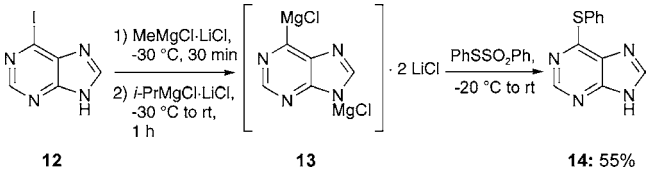
(13) The main side product is the protonolysis product of the organomagnesium reagent **7a**, which suggests the reagent to be quite sensitive and possibly unstable.

Scheme 1. Synthesis of Emivirine and HEPT Precursors



of HEPT (**10**) and Emivirine (**11**), both highly potent agents for the treatment of HIV.[14] Finally, we have applied our protocol to the purine core. An elegant magnesiation of purine derivatives with functionalization of the 6-position has been recently developed by Dvořák and co-workers.[15] Using the "LiCl effect", it is now possible to achieve the magnesiation in position 6 without the need for a protecting group. Thus, 6-iodopurine (**12**) is, after deprotonation, subjected to an iodine/magnesium exchange to produce the magnesium reagent **13**, which reacts with $PhSSO_2Ph$ to give the desired product **14** in 55% yield (Scheme 2).

Scheme 2. Functionalization of 6-Iodopurine



In conclusion, we have developed a new protocol for the selective functionalization of uracil derivatives employing a triple-anionic species as an intermediate. The method was successfully applied during the course of a short synthesis of Emivirine (**11**) and HEPT (**10**) precursors and was also extended to the purine system.

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

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(14) (a) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1995**, *38*, 2860. (b) Pedersen, O. S.; Pedersen, E. B. *Antiviral Chem. Chemother.* **1999**, *10*, 2860.

(15) Tobrman, T.; Dvořák, D. *Org. Lett.* **2006**, *8*, 1291; *Org. Lett.* **2003**, *5*, 4289. For further recent work on the functionalization of the purine core: Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389. Kuchař, M.; Pohl, R.; Votruba, I.; Hocek, M. *Eur. J. Org. Chem.* **2006**, 5083.