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4-Metalated Condensed Pyrimidines: Their Preparation and Reaction with Aldehydes under Barbier-Type Conditions

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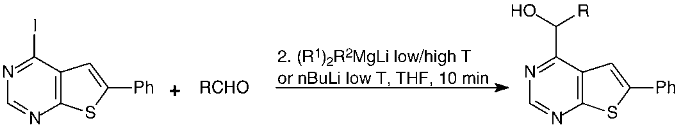
ABSTRACT



1

2a-f

The organometallic intermediate obtained from halogen–metal exchanges of 4-iodo-6-phenylthieno[2,3-*d*]pyrimidine under Barbier-type conditions was reacted with aldehydes to form the corresponding alcohols in moderate yields. The reaction involving an organolithium intermediate proceeded only at low temperature, whereas the reaction involving a magnesium ate intermediate also proceeded at room temperature. A crystal structure confirms that the expected constitutional alcohol isomer is formed, where no migration has taken place. The conditions were also suitable for 9-benzyl-6-iodopurine.

Halogen−metal exchange reactions have evolved as versatile methods over the past decades, and special attention is paid to metalated π-deficient heterocycles as a result of their use in either coupling reactions[1] or nucleophilic addition reactions.[2] The published material is scarce regarding halogen−metal exchange of halo-diazines for use in nucleophilic addition reactions. Some of the best results use methods involving Rieke Mg[3] or metallic Li[4] as metalation agents. The use of organometallic agents has been less successful. This is explained by the low LUMO level in the π-deficient diazines, which makes the systems more prone to attack from nucleophiles.[5] The best results with organometallic agents are obtained with diazines substituted with electron-donating groups, such as methoxy or thiomethoxy groups.[6] Recently, this was further exemplified by halogen−metal exchange of 9-benzyl-6-iodopurine with ^{i}PrMgCl, which produced a stable 6-magnesiated purine at 0 °C, which was subsequently reacted with aldehydes in toluene to give the corresponding

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alcohols in 25−62% overall yield.[7] As the pyrimidine ring in 9-benzyl-6-iodopurine is significantly less π-deficient than in 4-iodo-6-phenylthieno[2,3-*d*]pyrimidine (**1**) the procedure from Tobrman is expected to be less efficient for **1**.

We report here a relatively convenient, effective, and fast method to synthesize either aliphatic or aromatic alcohols (**2a**−**f**) by halogen−metal exchange of **1** in the presence of an aldehyde using Barbier-type conditions.

Conventional metalation attempts on **1** using ^{i}PrMgBr or ^{n}BuLi followed by treatment with an electrophile were unsatisfactory. Although some product was formed at −76 °C, the reaction also formed unacceptable amounts of the 4-hydro (**3a**) and the 4-^{i}Pr (**3b**)/4-^{n}Bu (**3c**) derivatives of **1** (Figure 1).

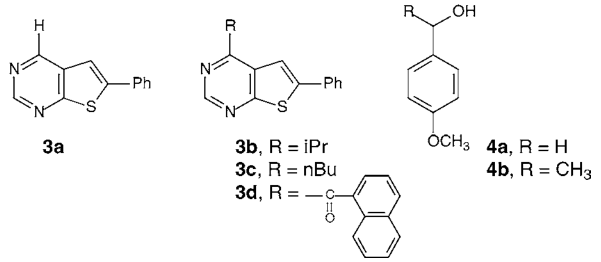


Figure 1. Products occasionally observed in the synthesis of **2a** and the oxidized product, **3d**, obtained in the synthesis of **2e**. Compounds **3a**, **4a**, and **4b** are difficult to separate from **2a**.

The magnesium ate complex $(R^1)_2R^2MgLi$, formed by addition of 2 equiv of R^1Li to 1 equiv of R^2MgX (Scheme 1), is described as being effective in halogen−magnesium exchange of pyridines, and in addition, the reactivity can be tuned by altering the R groups, the reactivity being increased Me < ^{n}Bu < ^{i}Pr.[8,9] Recently, good results were reported using the tributyl-magnesium ate complex as the metallating agent for bromoquinolines, where other conventional Grignard reagents, such as ^{i}PrMgCl, were unsuccessful.[10]

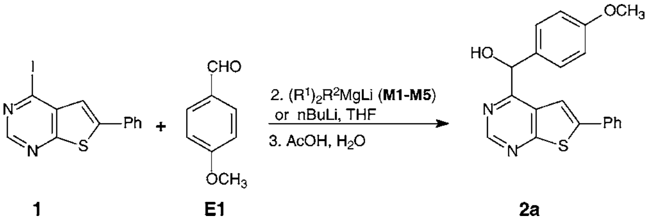
Scheme 1

$$2\,R^1Li + R^2MgX \longrightarrow (R^1)_2R^2MgLi + LiX$$

Preliminary studies using **1** together with an excess of 4-methoxybenzaldehyde (**E1**) and either $Me_2BuMgLi$ (**M1**), Bu_3MgLi (**M2**), $Bu_2PhMgLi$ (**M3**), $Ph_2BuMgLi$ (**M4**), or $Ph_2BnMgLi$ (**M5**) as the metallating agent were performed in THF. A solution of **M1** added to **1** in THF at −76 °C immediately produced a black solution, and immediate quenching with **E1** gave some of the corresponding alcohol **2a** but also a considerable amount of the hydrogen derivative **3a**.

An experiment with an iodobenzene derivative showed that the magnesium ate complex reacted preferentially with the iodo compound rather than an aldehyde already present in the reaction mixture.[8] Taking this result into consideration, the magnesium ate complex **M2** was added to a mixture of **1** and the electrophile **E1** and the corresponding alcohol **2a** was formed in 23% yield (Table 1) with no formation of **3a**. Repeating the experiment with **M1** and **M3** gave **2a** in 60% and 56% yield, respectively. Formation of **3a** was not observed under the Barbier-type conditions. The experiment was repeated using **M1** to explore the outcome of the reaction at different temperatures. It was rather surprising to find that the reaction at room temperature gave **2a** in 62% yield, especially as the reaction mixture turned black (at low temperature the reaction mixture typically turned orange-brown) in an exothermic reaction as **M1** was added.

Table 1. Reaction of **1** with Excess Metallating Agent in the Presence of Excess 4-Methoxybenzaldehyde



$(R^1)_2R^2MgLi$	yield[a] of **2a** at −76 °C	yield[a] of **2a** at 0 °C
M1: $Me_2BuMgLi$	50%[b], 60%[c]	62%[c,f]
M2: Bu_3MgLi	23%[b], 19%[c]	
M3: $Bu_2PhMgLi$	56%[c]	
M4: $Ph_2BuMgLi$	trace[c,d]	38%[c]
M5: $Ph_2BnMgLi$	41%[c]	
^{n}BuLi	57%[e]	0%[e,g]
^{n}BuMgCl	trace[d,e]	trace[e,g]

[a] Yield after chromatographical purification. Occasionally small amounts (0−10%) of alcohol derivatives (**4a** and/or **4b** (using **M1**)) of **E1** were co-isolated with **2a**. The yields tabulated are the corrected yields determined from ^{1}H NMR. A pure product was obtained by recrystallization. [b] 2 equiv of $(R^1)_2R^2MgLi$. [c] 3 equiv of $(R^1)_2R^2MgLi$. [d] No conversion of **1**. [e] 6 equiv of ^{n}BuLi or ^{n}BuMgCl. [f] Reaction at room temperature. [g] Full conversion; **3a** and unidentified products were formed.

The reaction proceeded with lower yields when **M4** and **M5** were used as the metallating agent. **M4** proved to be unreactive toward **1** at −76 °C, but at 0 °C the reaction gave **2a** in 38% yield, whereas using **M5** at −76 °C gave **2a** in 41% yield.

Interestingly, the principle of adding the metallating agent to **1** and **E1** (Barbier-type conditions) also proved valid for ^{n}BuLi at low temperature but not for ^{n}BuMgCl.[6] Using ^{n}BuLi the reaction proceeded at −76 °C to give **2a** in 57% yield, but at 0 °C only **3a** and unidentified products were observed. No significant conversion of **1** was observed using

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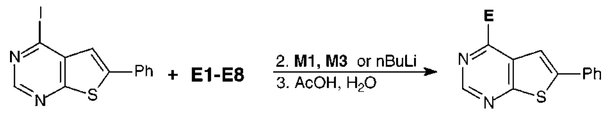
^{n}BuMgCl at −76 °C, but at 0 °C the reaction almost exclusively gave **3a** in preference to **2a**. Full conversion of **1** was observed using ^{n}BuLi as the metallating agent, whereas a trace of **1** still remained unreacted using the magnesium ate complexes (**M1**−**M5**).

To investigate the potential of the reaction a miscellaneous set of electrophiles (**E1**−**E8**, Table 2) was reacted with **1** using the conditions described above. In addition to **E1**, four additional aromatic aldehydes (**E2**−**E5**), some of them having an electron-withdrawing group, were reacted with **1**.

Table 2. Reaction of **1** in the Presence of Excess Electrophile with an Excess of Metalating Agent



1

2a-h

electrophile	product	yield[a] at −76 °C	yield[a] at 0 °C
E1: 4-MeOPhCHO	**2a**	60%[b], 57%[c]	62%[b,d], 0%[c]
E2: PhCHO	**2b**	55%[b]	
E3: 4-NCPhCHO	**2c**	54%[b]	minor[b,e,f]
E4: 3-ClPhCHO	**2d**	28%[g], 52%[c]	
E5: 1-naphthyl.CHO	**2e**	48%[b,h]	minor[b,e,h,i]
E6: *c*-hexaneCHO	**2f**	55%[g], 65%[c]	
E7: HCO_2Et	**2g**	51%[b], 25%[c,j]	0%[c,e,f,g]
E8: PhCOPh	**2h**	0%[c,e,f,g]	0%[c,e,f,g]

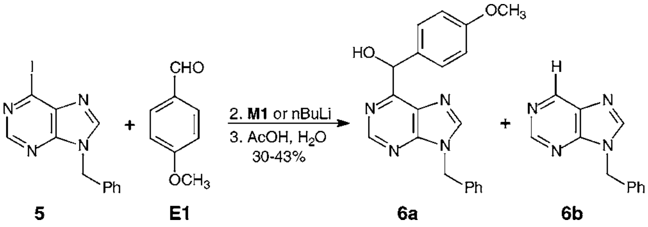
[a] Yield after chromatographical purification. Occasionally small amounts (0−10%) of alcohol derivatives of **E1**−**E6** (analogues to **4a** and **4b** (using **M1**)) were co-isolated with **2a**−**f**. The yields tabulated are the corrected yields determined from ^{1}H NMR. Pure products were obtained by recrystallization. [b] 3 equiv of **M1**. [c] 6 equiv of ^{n}BuLi. [d] Reaction at room temperature. [e] Analyzed by TLC. [f] **3a** and unidentified products formed. [g] 3 equiv of **M3**. [h] Oxidizes over time to the ketone **3d**. [i] **3d** was formed as the major product. [j] **2g** was co-isolated with **3c**.

The alcohol products **2b**−**e** were isolated in 48−55% yield using either the magnesium ate complex (**M1** or **M3**) or ^{n}BuLi at −76 °C (Table 2).

The synthesis of **2c** at 0 °C using **M1** failed, as only a minor quantity of **2c** was formed (analyzed by TLC) along with **3a** and unidentified products. The alcohol product **2e** derived from the reaction with 1-naphthaldehyde proved unstable and oxidized over time to the corresponding ketone, **3d** (Figure 1). Compound **3d** was the main product when the reaction (analyzed by TLC) was carried out at 0 °C. The aliphatic cyclohexanecarboxaldehyde gave the corresponding alcohol **2f** in 55% and 65% yield at −76 °C using **M3** and ^{n}BuLi, respectively. The introduction of the CHO group directly attached to the 4 position of the pyrimidine ring (**2g**) was accomplished smoothly in 51% yield using **M1** and ethyl formate at −76 °C. ^{n}BuLi was not suitable for the synthesis of **2g**, as only a 25% yield of **2g** was co-isolated with a 13% yield of **3c**. Both **M3** and ^{n}BuLi did not give the desired alcohol **2h** when a ketone (benzophenone, **E8**) was used as the electrophile; only **3a** and unidentified products were formed.

The Barbier-type reaction was extended to the purine ring system. 9-Benzyl-6-iodopurine (**5**) was metalated in the presence of 4-methoxybenzaldehyde (**E1**) with either **M3** or ^{n}BuLi (Scheme 2). Full conversion of **5** was observed when ^{n}BuLi at −76 °C was used as the metallating agent, and the alcohol **6a** was isolated in 43% yield.

Scheme 2



5 **E1** **6a** **6b**

When **M3** was used as the metallating agent, only moderate conversion of **5** was observed. At −76 °C, **6a** and

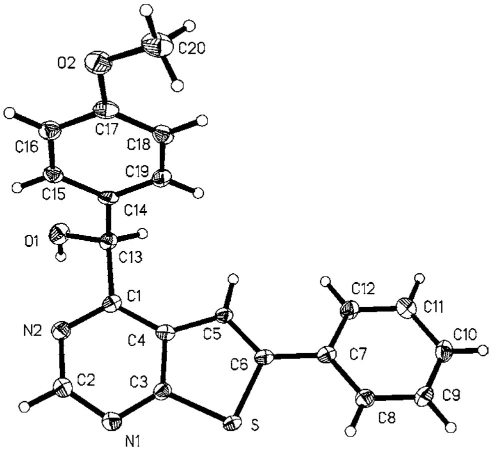
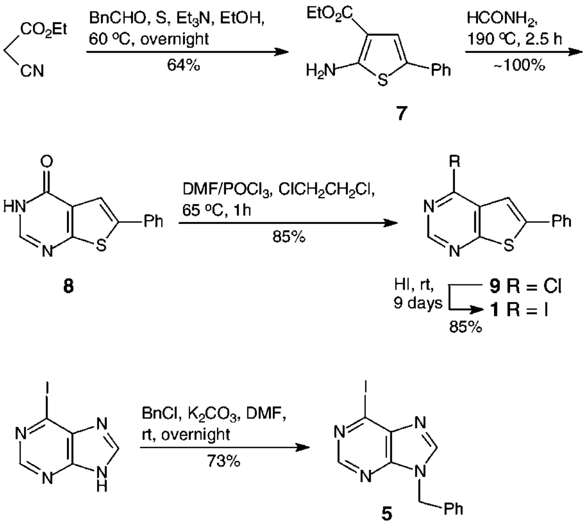


Figure 2. Molecule **2a** as found in the crystal structure.

Scheme 3



7

8

9 R = Cl
1 R = I

5

6b were formed in 20% and 8% yield, respectively. At 0 °C **6a** was formed in 30% yield and 36% of **5** was recovered, whereas **6b** was not formed.

It has previously been described that a relocation of the carbanion from the 6 to the 8 position took place when 6-iodo-9-(tetrahydro-pyran-2-yl)purine was treated with ^{n}BuLi at −76 °C.[11] We observed only a single constitutional isomer in the syntheses of **2a−g** and **6a**, regardless of whether ^{n}BuLi or the magnesium ate complex was used as the metallating agent. Single crystals of **2a** were obtained by crystallization from ethyl acetate/petroleum ether, and the crystal structure was determined by X-ray crystallography. The resultant structure (Figure 2) confirms that the formed product is the expected alcohol where no relocation of the carbanion has taken place before the nucleophilic attack at **E1**.

The synthesis of **1** was completed in four steps in 46% overall yield (Scheme 3). Compound **7**[12] was obtained in 64% yield in a modified procedure. The following ring closure to **8** was quantitative, and **9** was obtained in 85% yield using $POCl_3$/DMF. Compound **1** was obtained in 85% yield after prolonged stirring with HI. Compound **5** was obtained by a selective benzylation of 6-iodopurine in 73% yield (Scheme 3).

Supporting Information Available: Detailed experimental procedures and characterization for the synthesis of **1**, **2a−g**, **5**, **6a**, and **7−9,** as well as crystallographic data (in CIF format) for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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