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Preparation and Reactions of Heteroarylmethylzinc Reagents

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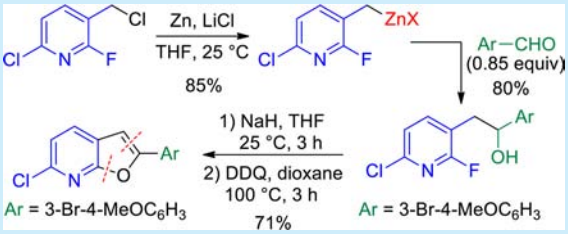
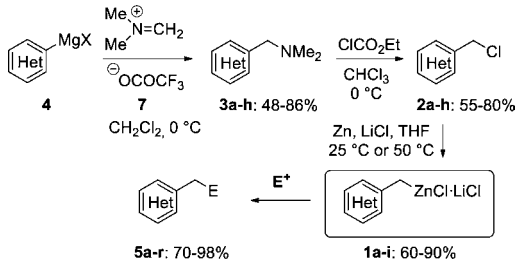
Supporting Information

ABSTRACT: We report a general preparation of heteroarylmethylzinc chlorides by direct zinc insertion into heteroarylmethyl chlorides, along with a facile and straightforward synthesis of these heterocyclic chloromethyl precursors. We demonstrate that heteroarylmethylzinc reagents undergo various reactions including cross-couplings, allylations, acylations, and addition reactions to aldehydes, leading to polyfunctional heterocyclic products. Furthermore, these heteroaromatic zinc compounds prove to be versatile reagents for the preparation of various N- and O-heterocycles and give access to an analogue of a CB1 modifier.



Zinc organometallics are key intermediates in organic synthesis.[1,2] The broad functional group tolerance of the carbon−zinc bond allows the preparation of highly functionalized zinc reagents. Thus, aryl, heteroaryl, and alkylzinc compounds are readily prepared and react with a broad range of electrophiles under appropriate reaction conditions.[3] Recently, we have shown that polyfunctional benzylic zincs are obtained by direct zinc insertion.[4] Since heterocyclic scaffolds are major building blocks for pharmaceuticals and materials, we envisioned the development of a general preparation of heteroarylmethylzinc compounds of type **1**[5] (Scheme 1). Herein, we report a practical synthesis of these

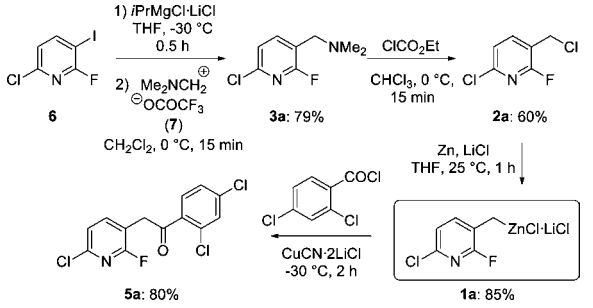
Scheme 1. Preparation of Chloromethyl Heterocycles of Type 2, Their Conversion to Zinc Reagents of Type 1, and Trapping Reactions Leading to Products of Type 5



heterocyclic zinc chlorides **1** as well as of the corresponding heteroarylmethyl chlorides (**2**). These chloromethyl heteroarenes **2** are prepared in a straightforward manner from the *N*,*N*-dimethylaminomethyl heteroarenes of type **3** obtained from readily available heteroaryl organometallics (**4**). The novel heteroarylmethylzinc compounds **1** proved to be stable and practical reagents that react with a wide range of electrophiles leading to polyfunctional heterocyclic products of type **5** (Scheme 1).

A typical preparation of these new heterocyclic zinc reagents is shown in the synthesis of the polyfunctional zincated

Scheme 2. Preparation of Zinc Reagent 1a Followed by a Copper-Mediated Reaction with an Acyl Chloride Leading to the Ketone 5a



pyridine **1a** (Scheme 2). Thus, the I/Mg exchange on 6-chloro-2-fluoro-3-iodopyridine[6] (**6**) with *i*-PrMgCl·LiCl[7] (1.1 equiv) produces an intermediate magnesium reagent which readily reacts with methylene(dimethyl)iminium trifluoroacetate **7**,[8] leading to the benzylic *N*,*N*-dimethylamine **3a** in 79% yield. Treatment with $ClCO_2Et$[9] affords the 3-(chloromethyl)-pyridine[10] **2a** in 60% yield. Subsequent LiCl-promoted zinc insertion furnishes the new pyridylzinc reagent **1a** in 85% yield.[11] Although the metalation of 2- and 4-picolines can be realized with various bases,[12] the direct metalation of 3-picolines is difficult since the resulting cross-conjugated anion is not delocalized onto the nitrogen, therefore leading to a highly reactive anion.[13] Our new approach provides readily metalated 3-picoline derivatives such as **1a**.[14] The acylation of **1a** with 2,4-dichlorobenzoyl chloride in the presence of CuCN·2LiCl[15] (1.1 equiv) gives **5a** in 80% yield (Scheme 2).

Similarly, the zinc reagent **1a** adds rapidly to aldehydes, leading to the alcohol **5b** in 80% yield (entry 1, Table 1). Pd-catalyzed cross-coupling (3 mol % $Pd(dba)_2$ (dba =

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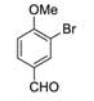
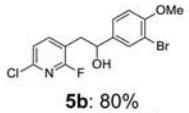
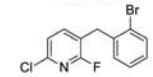
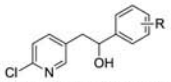
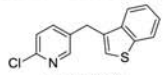
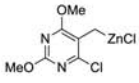
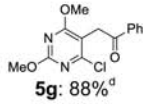
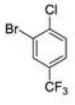
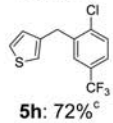
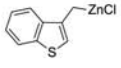
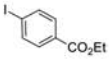
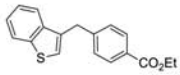
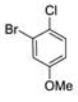
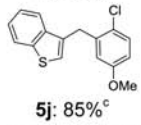
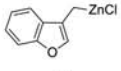
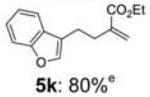
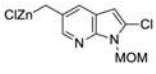
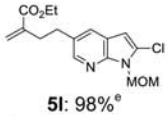
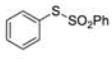
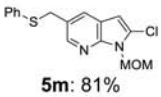
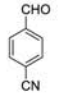
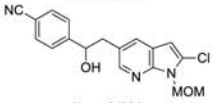
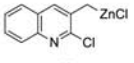
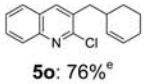
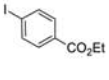
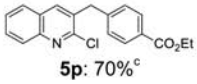
Table 1. Products of Type 5 Obtained by the Reaction of Heteroarylmethylzinc Reagents 1 Followed by Reaction with Electrophiles

entry	zinc reagent[a]	electrophile	product[b]
1	**1a**		 **5b**: 80%
2	**1a**		 **5c**: 70%[c]
3	**1b**		 **5d**: R = *p*-CN, 89% **5e**: R = *o*-NO_2, 91%
4	**1b**		 **5f**: 93%[c]
5	**1c**		  **5g**: 88%[d]
6	**1d**		  **5h**: 72%[c]
7	**1e**		  **5i**: 85%[c]
8	**1e**		  **5j**: 85%[c]
9	**1f**		  **5k**: 80%[e]
10	**1g**		  **5l**: 98%[e]
11	**1g**		 **5m**: 81%
12	**1g**		 **5n**: 85%
13	**1h**		  **5o**: 76%[e]
14	**1h**		 **5p**: 70%[c]

[a]LiCl omitted for sake of clarity. [b]Isolated yield of analytically pure product. [c]Obtained by Pd-catalyzed cross-coupling. [d]Obtained by Cu-mediated acylation. [e]Obtained by Cu-catalyzed allylation.

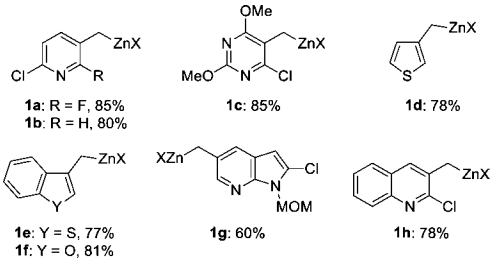


Figure 1. Zinc reagents of type **1** obtained by direct zinc insertion into the corresponding chloromethyl derivatives of type **2**. Yields were determined by iodometric titration.[11] MOM = methoxymethyl. X = Cl·LiCl.

dibenzylideneacetone), 6 mol % tfp (tri-*o*-furylphosphine))[16] with 1-bromo-2-iodobenzene leads to **5c** in 70% yield (entry 2, Table 1). Although the preparation of 3-(chloromethyl)-pyridine can be realized, the corresponding zinc reagent is unstable and polymerizes rapidly. This can be avoided by introducing a chlorine substituent in position 6. The resulting zinc reagent **1b** reacts well with aldehydes to afford **5d–e** in 89–91% yield (entry 3, Table 1). Pd-catalyzed cross-coupling of **1b** with 3-bromobenzothiophene using 1 mol % PEPPSI-IPr[17] provides **5f** in 93% yield (entry 4, Table 1). This reaction sequence is extended to the preparation of biorelevant uracil (**1c**), thiophene (**1d**), benzothiophene (**1e**), benzofuran (**1f**), 7-azaindole (**1g**), and quinoline (**1h**) derived zinc reagents in 60–85% yield (Figure 1).[18]

Thus, the uracil reagent **1c** undergoes a copper-mediated acylation with CuCN·2LiCl[15] and affords the uracil derivative **5g** in 88% yield (entry 5, Table 1). The thienylzinc reagent **1d** smoothly reacts in a Pd-catalyzed cross-coupling (1 mol % PEPPSI-IPr[17]) with 2-bromo-1-chloro-4-(trifluoromethyl)-benzene to furnish **5h** in 72% yield (entry 6, Table 1). Furthermore, the benzothienylzinc reagent **1e** undergoes a smooth Pd-catalyzed cross-coupling (1 mol % PEPPSI-IPr[17]) with aryl halides to give the benzothiophenes **5i,j** in 85% yield each (entries 7 and 8, Table 1). The benzofurylzinc reagent **1f** is allylated using 5 mol % CuCN·2LiCl[15] with ethyl (2-bromomethyl)acrylate[19] to provide **5k** in 80% yield (entry 9, Table 1).

Similarly, the 7-azaindolylzinc reagent **1g** is readily allylated with ethyl (2-bromomethyl)acrylate[19] and reacts smoothly with *S*-benzenesulfonothioate and 4-cyanobenzaldehyde to furnish the desired products **5l–n** in 81–98% yield (entries 10–12, Table 1). Moreover, the quinolylzinc reagent **1h** reacts with 3-bromocyclohexene (5 mol % CuCN·2LiCl[15]) to afford **5o** in 76% yield (entry 13, Table 1). Pd-catalyzed cross-coupling of **1h** (5 mol % PEPPSI-IPr[17]) with ethyl 4-iodobenzoate produces the quinoline derivative **5p** in 70% yield (entry 14, Table 1).

The heterocyclic zinc reagents of type **1** are versatile reagents for the preparation of condensed N-heterocycles such as furopyridines. These heterocycles are of high interest for pharmaceutical applications as enzyme inhibitors, receptors and modifiers.[20] Thus, the furopyridine **8a** is prepared via a cyclization reaction starting from the previously prepared pyridyl alcohol **5b** (entry 1, Table 1). Its treatment with NaH leads to the dihydrofuropyridine **9a** in 86% yield. Oxidation using DDQ[21] (DDQ = 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone) provides **8a** in 82% yield (71% yield over two steps; Scheme 3, **A**).

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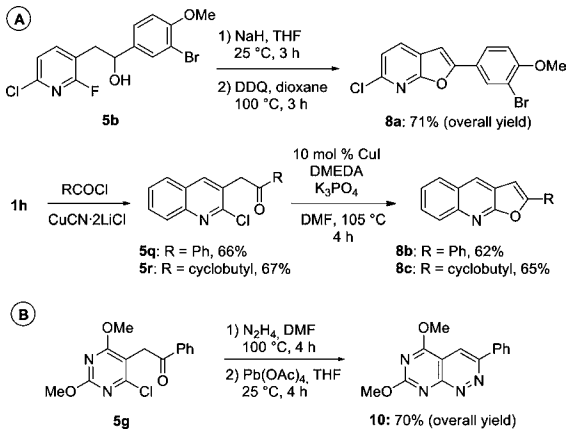
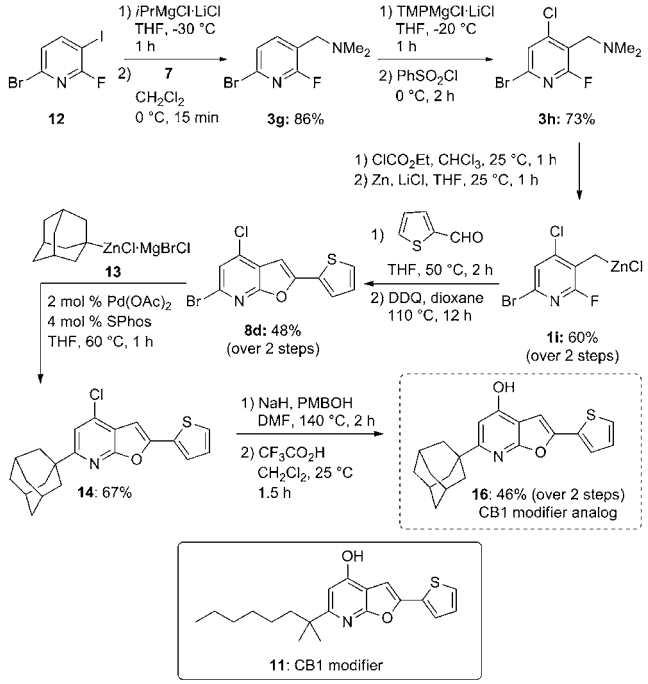
Scheme 3. Preparation of Furopyridines 10a–c Using the Alcohol 5b and the Benzylic Zinc Reagent 1h and Preparation of the Tetra-azanaphthalene 10 from the Benzylic Ketone 5g



Scheme 4. Key Steps in the Synthesis of the CB1 Modifier Analogue 16 Starting from Pyridine 12[a]



[a]LiCl omitted for sake of clarity.

It is noteworthy that such functionalized furopyridines may also be prepared from the appropriate heterobenzylic ketones by a copper-catalyzed ring closure recently reported by Ackermann.[22] Hence, the copper-mediated acylation of the heterocyclic zinc reagent **1h** with acid chlorides such as benzoyl chloride or cyclobutanecarbonyl chloride affords **5q,r** in 66–67% yield (Scheme 3, **A**). Subsequent copper-catalyzed ring closure (CuI, 10 mol %) using K_3PO_4 (2 equiv) and *N,N′*-dimethylethylenediamine (DMEDA, 30 mol %) furnishes the furoquinolines **8b,c** in 62–65% yield (Scheme 3, **A**).[22]

Tetra-azanaphthalenes are biorelevant molecules which have been prepared in a nonstraightforward manner.[23] The ketouracil **5g** reacts with hydrazine to provide the aromatized tetra-azanaphthalene **10** in 70% overall yield after oxidation with $Pb(OAc)_4$[24] (Scheme 3; **B**).

As an application toward the preparation of biorelevant heterocycles, we have prepared an analogue of the CB1 modifier **11** being applicable for various targets in the central nervous system (Scheme 4).[20b] Thus, commercially available 2-bromo-6-fluoropyridine is regioselectively lithiated with LDA (lithium diisopropylamide; 1.05 equiv). Subsequent iodination gives **12** in 82% yield.[25] I/Mg exchange with *i*-PrMgCl·LiCl[7] (1.0 equiv) produces a Grignard reagent, which readily reacts with methylene(dimethyl)iminium trifluoroacetate **7**[8] to furnish the benzylic *N,N*-dimethylamine **3g** in 86% yield (71% yield over two steps). This aminopyridine is regioselectively magnesiated with TMPMgCl·LiCl[6] (1.2 equiv), and subsequent chlorination with $PhSO_2Cl$[26] gives **3h** in 73% yield. Treatment with $ClCO_2Et$[9] (67% yield) and LiCl-promoted zinc insertion (90% yield) affords the new benzylic zinc reagent **1i** in 60% overall yield. Addition of this pyridylzinc reagent to 2-thiophenecarboxaldehyde leads after cyclization to the corresponding dihydrofuropyridine **9b** in 69% yield. Subsequent oxidation with DDQ[21] provides the furopyridine **8d** in 70% yield (48% yield over two steps). To ensure a high lipophilicity of **11**, we have replaced the 1,1-dimethylheptyl group by the highly lipophilic adamantyl group.[27] Pd-catalyzed cross-coupling reaction with the adamantylzinc reagent **13**[28] (1.1 equiv) furnishes **14** in 67% yield. Treatment with sodium (*p*-methoxyphenyl)methanolate[29] (PMBO-Na) affords the alkoxy heterocycle **15** in 63% yield. Subsequent deprotection of the PMB (*p*-methoxybenzyl) group with trifluoroacetic acid[30] leads to the CB1 modifier analogue **16** in 73% yield (46% over two steps; Scheme 4).

In summary, we have developed a general preparation of various chloromethyl heterocycles as well as their elusive zinc derivatives. These new organozinc reagents prove to be versatile organometallic intermediates for the preparation of numerous polyfunctional heterocycles and give a short access to furopyridines, furoquinolines, and tetra-azanaphthalenes as well as to an analogue of the CB1 modifier **11**.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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