

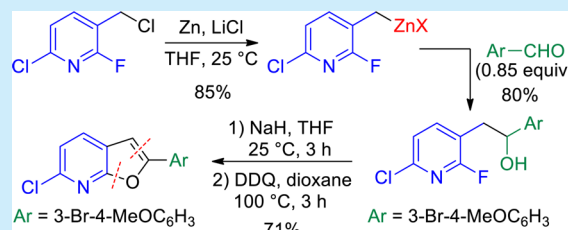
Preparation and Reactions of Heteroarylmethylzinc Reagents

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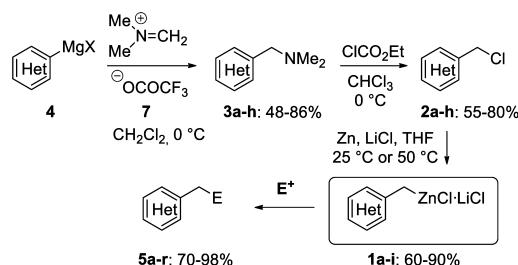
S Supporting Information

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.

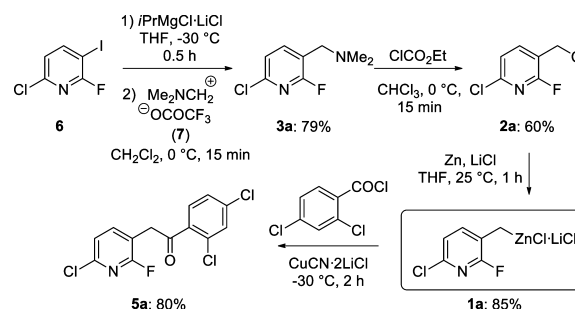


Zinc organometallics are key intermediates in organic synthesis.^{1,2} The broad functional group tolerance of the carbon–zinc bond allows the preparation of highly functionalized zinc reagents. Thus, aryl, heteroaryl, and alkylzinc compounds are readily prepared and react with a broad range of electrophiles 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 1⁵ (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



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) with $i\text{-PrMgCl}\cdot\text{LiCl}$ (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)pyridine¹⁰ 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 $\text{CuCN}\cdot 2\text{LiCl}$ 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 % $\text{Pd}(\text{dba})_2$ (dba =

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

Received: March 17, 2014

Published: April 11, 2014

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

entry	zinc reagent ^a	electrophile	product ^b
1			 5b : 80%
2			 5c : 70% ^c
3			 5d : R = <i>p</i> -CN, 89% 5e : R = <i>o</i> -NO ₂ , 91%
4			 5f : 93% ^c
5			 5g : 88% ^d
6			 5h : 72% ^c
7			 5i : 85% ^c
8			 5j : 85% ^c
9			 5k : 80% ^e
10			 5l : 98% ^e
11			 5m : 81%
12			 5n : 85%
13			 5o : 76% ^e
14			 5p : 70% ^c

^aLiCl omitted for sake of clarity. ^bIsolated yield of analytically pure product. ^cObtained by Pd-catalyzed cross-coupling. ^dObtained by Cu-mediated acylation. ^eObtained by Cu-catalyzed allylation.

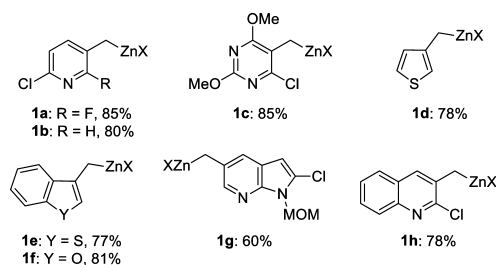


Figure 1. Zinc reagents of type 1 obtained by direct zinc insertion into the corresponding chloromethyl derivatives of type 2. Yields were determined by iodometric titration.¹¹ MOM = methoxymethyl. X = Cl·LiCl.

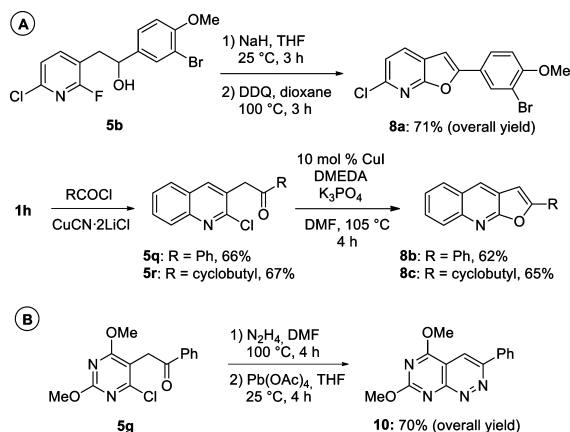
dibenzylideneacetone), 6 mol % tfp (tri-*o*-furylphosphine))¹⁶ with 1-bromo-2-iodobenzene leads to **5c** in 70% yield (entry 2, Table 1). Although the preparation of 3-(chloromethyl)pyridine can be realized, the corresponding zinc reagent is unstable and polymerizes rapidly. This can be avoided by introducing 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-IPr¹⁷ 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·2LiCl¹⁵ 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-IPr¹⁷) with 2-bromo-1-chloro-4-(trifluoromethyl)benzene to furnish **5h** in 72% yield (entry 6, Table 1). Furthermore, the benzothiophenylzinc reagent **1e** undergoes a smooth Pd-catalyzed cross-coupling (1 mol % PEPPSI-IPr¹⁷) with aryl halides to give the benzothiophenes **5i,j** in 85% yield each (entries 7 and 8, Table 1). The benzofuryl zinc reagent **1f** is allylated using 5 mol % CuCN·2LiCl¹⁵ with ethyl (2-bromomethyl)acrylate¹⁹ to provide **5k** in 80% yield (entry 9, Table 1).

Similarly, the 7-azaindoly zinc reagent **1g** is readily allylated with ethyl (2-bromomethyl)acrylate¹⁹ 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 quinoly zinc reagent **1h** reacts with 3-bromocyclohexene (5 mol % CuCN·2LiCl¹⁵) to afford **5o** in 76% yield (entry 13, Table 1). Pd-catalyzed cross-coupling of **1h** (5 mol % PEPPSI-IPr¹⁷) 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 DDQ²¹ (DDQ = 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone) provides **8a** in 82% yield (71% yield over two steps; Scheme 3, A).

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

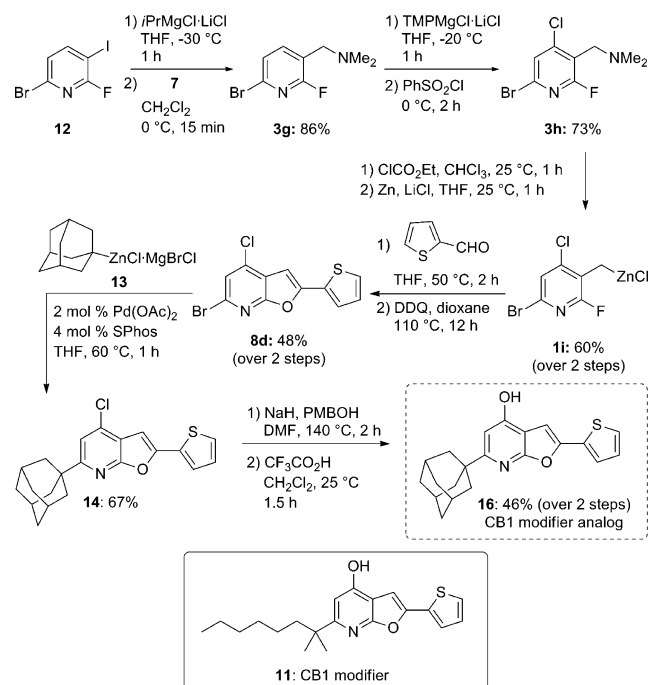


It is noteworthy that such functionalized furopyridines may also be prepared from the appropriate heterobenzylic ketones by a copper-catalyzed ring closure recently reported by Ackermann.²² Hence, the copper-mediated acylation of the heterocyclic zinc reagent **1h** with acid chlorides such as benzoyl chloride or cyclobutanecarbonyl chloride affords **5q,r** in 66–67% yield (Scheme 3, A). Subsequent copper-catalyzed ring closure (CuI, 10 mol %) using K₃PO₄ (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)₄²⁴ (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·LiCl⁷ (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·LiCl⁶ (1.2 equiv), and subsequent chlorination with PhSO₂Cl²⁶ gives **3h** in 73% yield. Treatment with ClCO₂Et⁹ (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 DDQ²¹ 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)methanolate²⁹ (PMBO-Na) affords the alkoxy heterocycle **15** in 63% yield. Subsequent deprotection of the PMB (*p*-methoxybenzyl) group with trifluoroacetic

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



^aLiCl omitted for sake of clarity.

acid³⁰ 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.

■ ACKNOWLEDGMENTS

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) ERC grant agreement no. 227763. We are grateful to BASF SE (Ludwigshafen), W. C. Heraeus (Hanau), and Rockwood Lithium GmbH (Frankfurt) for the generous gift of chemicals. We thank Dr. A. Metzger (Ludwig-Maximilians-Universität Munich, Germany) for preliminary experiments.

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