ORGANIC LETTERS

2008
Vol. 10, No. 6
1107−1110

LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides

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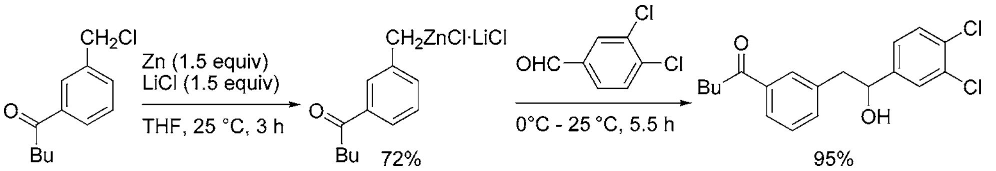
Received December 20, 2007

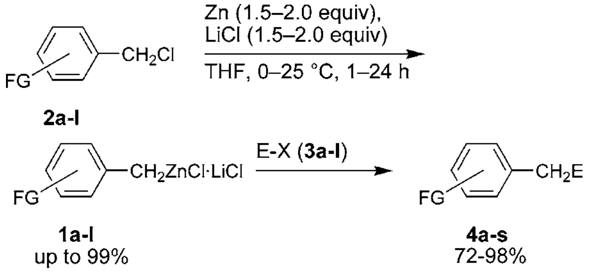
ABSTRACT



In the presence of zinc dust (1.5–2.0 equiv) and LiCl (1.5–2.0 equiv), various benzylic chlorides bearing functional groups (iodide, cyanide, ester, ketone) are smoothly converted at 25 °C to the corresponding zinc reagents without homo-coupling (<5%). The utility of these benzylic zinc reagents is demonstrated by a short synthesis of papaverine.

Zinc organometallics are important intermediates since they combine an excellent functional group compatibility with a high reactivity (in the presence of the appropriate catalyst).[1] Especially functionalized benzylic zinc halides occupy a unique place since the high reactivity of related benzylic lithium and magnesium compounds preclude the presence of most functional groups in these organometallics. Benzylic zinc reagents can be prepared by the direct zinc insertion to benzylic bromides but may require elevated temperatures and the addition of polar cosolvents.[2] These drawbacks hamper a more general application of these organometallics. Recently, we have reported that LiCl facilitates considerably the rate of zinc insertion.[3] Herein, we report an efficient preparation of functionalized benzylic zinc chlorides of type **1** using the LiCl-mediated insertion of commercial zinc dust to functionalized benzylic chlorides of type **2** (Scheme 1 and Table 1). Their reaction with various electrophiles (**3**) provides a range of polyfunctional products of type **4**. Thus, the addition of 2-chlorobenzyl chloride (**2a**, 1.0 equiv) to

Scheme 1. LiCl-Mediated Insertion into Functionalized Benzylic Chlorides



FG = Cl, F, Br, I, CO_2R, CN, COR, OMe

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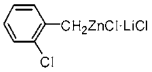
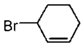
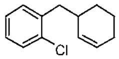
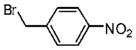
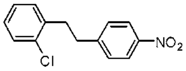
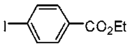
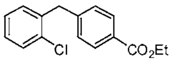
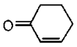
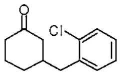
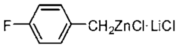
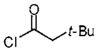
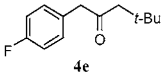
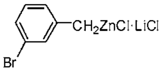
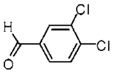
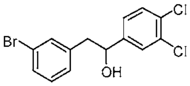
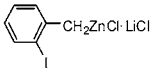
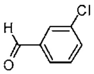
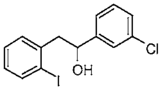
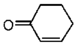
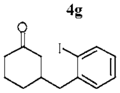
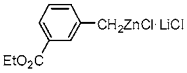
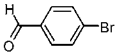
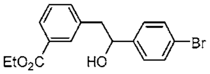
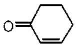
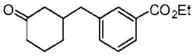
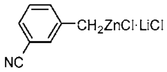
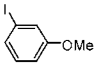
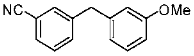
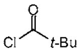
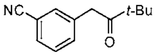
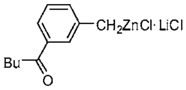
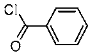
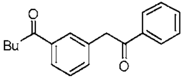
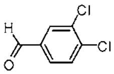
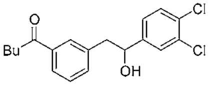
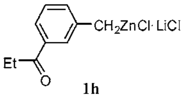
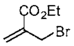
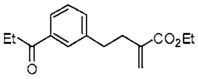
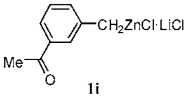
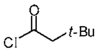
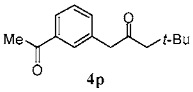
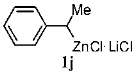
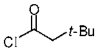
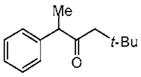
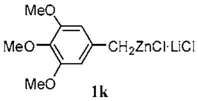
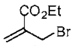
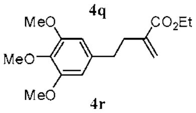
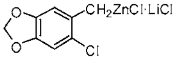
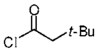
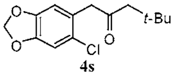
(1) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Knochel, P.; Millot, N.; Rodriguez, A.; Tucker, C. E. *Org. React.* **2001**, *58*, 417. (c) Knochel, P. In *Handbook of Functionalized Organometallics*; Wiley-VCH: New York, 2005. (d) Knochel, P.; Calaza, M. I.; Hupe, E. Carbon-Carbon Bond-Forming Reactions Mediated by Organozinc Reagents. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

(2) (a) Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2004**, *69*, 908. (b) Piazza, C.; Millot, N.; Knochel, P. J. *Organomet. Chem.* **2001**, *624*, 88. (c) Wang, J. X.; Fu, Y.; Hu, Y. L. *Chin. Chem. Lett.* **2002**, *5*, 405. (d) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053. (e) Harada, T.; Kaneko, T.; Fujiwara, T.; Oku, A. *J. Org. Chem.* **1997**, *62*, 8966. (f) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, *5*, 974. For the use of benzylic zinc, see also: (g) Fellahi, Y.; Mandin, D.; Dubois, P.; Ombetta-Goka, J. E.; Guenzet, J.; Chaumont, J. P.; Frangin, Y. *Eur. J. Med. Chem.* **1996**, *31*, 77. (h) Wang, J.-X.; Fu, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2757. (i) Krasovskiy, A.; Gavryushin, A.; Knochel, P. *Synlett* **2006**, *5*, 792. (j) Thorn, S. N.; Gallagher, T. *Synlett* **1997**, 185. (k) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 185.

(3) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

10.1021/ol7030697 CCC: $40.75

Table 1. LiCl-Mediated Insertion into Functionalized Benzylic Chlorides and Reaction with Various Electrophiles

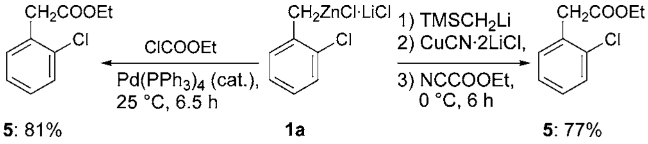
entry	benzylic zinc chloride (**1**)	insertion (h)[a], yield (%)[b]	electrophile (**3**)	temperature (°C), time (h)	product (**4**)	yield (%)[d]
1	 **1a**	2, 99	 **3a**	25, 1.5	 **4a**	94[c,h]
2	**1a**		 **3b**	0, 3	 **4b**	89[e]
3	**1a**		 **3c**	60 °C, 5	 **4c**	97[g]
4	**1a**		 **3d**	−40 to 25, overnight	 **4d**	93[f]
5	 **1b**	24[c], 87	 **3e**	−40 to 25, overnight	 **4e**	95[f]
6	 **1c**	4, 95	 **3f**	0 to 25, 17	 **4f**	98
7	 **1d**	2, 99	 **3g**	0 to 25, 5	 **4g**	87
8	**1d**		 **3d**	−40 to 25, overnight	 **4h**	72[f]
9	 **1e**	3.5[c], 85	 **3h**	0 to 25, 4.5	 **4i**	91
10	**1e**		 **3d**	−40 to 25, overnight	 **4j**	97[f]
11	 **1f**	3, 93	 **3i**	60, 5	 **4k**	88[g]
12	**1f**		 **3j**	−60 to −20, overnight	 **4l**	78[f]
13	 **1g**	3.5, 72	 **3k**	−20, overnight	 **4m**	85[f]
14	**1g**		 **3f**	0 to 25, 5.5	 **4n**	95
15	 **1h**	3, 72	 **3l**	−60 to 0, 1	 **4o**	92[e]
16	 **1i**	3.5, 68	 **3e**	−60 to −20, overnight	 **4p**	74[f]
17	 **1j**	11, 85	 **3e**	−60 to 25, overnight	 **4q**	96[f]
18	 **1k**	3[c], 78	 **3l**	−40 to 0, 1	 **4r**	98[e]
19	 **1l**	1, 93	 **3e**	−60 to 25, overnight	 **4s**	93[f]

[a] Reaction time at 25 °C. [b] Yield as determined by iodometric titration. [c] Zn (2.0 equiv), LiCl (2.0 equiv). [d] Isolated yield of analytically pure product. [e] Catalytic $CuCN\cdot 2LiCl$. [f] Stoichiometric $CuCN\cdot 2LiCl$. [g] $Pd(PPh_3)_4$ (cat.). [h] In this case, the limiting reagent is the benzylic zinc chloride **1a**.

zinc dust[4] (1.5 equiv) and LiCl (1.5 equiv) at 0 °C followed by 2 h of stirring at 25 °C provides almost quantitatively 2-chlorobenzylzinc chloride **1a** (in 99% yield as determined by iodometric titration).[5] In the absence of LiCl, only a slow and incomplete reaction is observed under these reaction conditions. The benzylic zinc reagent **1a** undergoes a range of useful reactions with electrophiles. Thus, Cu(I)-catalyzed cross-couplings with allylic and benzylic bromide such as 3-bromo-1-cyclohexene (**3a**, 1.3 equiv) or 4-nitrobenzyl bromide (**3b**, 0.8 equiv) afford the cross-coupling products **4a** and **4b** in 89−94% yield (entries 1 and 2 of Table 1).

Also, Negishi[6] cross-coupling of ethyl 4-iodobenzoate (**3c**, 0.8 equiv) in the presence of $Pd(PPh_3)_4$ (2 mol %, 60 °C, 5 h) gives the diarylmethane derivative **4c** in 97% yield (entry 3). A copper(I)-mediated 1,4-addition of cyclohexenone (0.8 equiv) using $CuCN{\cdot}2LiCl$[4] (1 equiv, −40 °C to 25 °C, overnight) and TMSCl[7] (2 equiv) provides the Michael adduct **4d** in 93% yield (entry 4). Similarly the 4-fluoro-, 3-bromo, and 2-iodobenzylic zinc chlorides (**1b−d**) were prepared in 87−99% yield. The Cu(I)-mediated reaction of the benzylic zinc chloride **1b** with 3,3-dimethylbutyryl chloride (**3e**, 0.7 equiv) in the presence of $CuCN{\cdot}2LiCl$ (1.0 equiv, −40 °C to 25 °C, overnight) leads to the ketone **4e** in 95% yield. The high reactivity of benzylic zinc chlorides allows an efficient addition to various aldehydes *in the absence of any catalyst*. Thus, the addition of the substituted benzaldehydes (**3f** or **3g**; 0.8 equiv, 0−25 °C, 5−17 h) gave the benzylic alcohols **4f** and **4g** in 87−98% yield (entries 6 and 7). The Cu(I)-mediated Michael addition of **1d** to cyclohexenone furnishes an expected ketone **4h** in 72% yield (entry 8). Various benzylic zinc reagents bearing carbonyl functions have also been prepared (entries 9−16). Thus, the reaction of substituted benzylic chlorides bearing a carbethoxy group, a cyanide, and a ketone group in the meta-position with zinc dust at 25 °C provides smoothly the corresponding zinc reagents (**1e−i**; entries 9−16). Remarkably, the keto group present in the benzylic zinc chlorides **1g−i** is quite stable toward enolization. Thus, the 3-propionyl benzylic zinc chloride (**1h**) has a half-life of 27 days at 25 °C. Even the acetyl-substituted benzylic zinc reagent **1i** is stable for several days ($t_{1/2}$ = 2 days, 25 °C). These zinc reagents react smoothly with typical electrophiles, leading to the functionalized products **4i−p** (74−97%; entries 9−16). Secondary benzylic zinc compounds can be prepared similarly. Thus, the treatment of 1-chloroethylbenzene with zinc dust (1.5 equiv) and LiCl (1.5 equiv) at 25 °C for 11 h provides the expected zinc reagent **1j** in 85% yield. Its acylation with the acid chloride **3e** provides the ketone **4q** in 96% yield. In contrast, cumyl chloride (a tertiary benzylic chloride) did not afford the corresponding zinc species due to competitive elimination. Electron-rich benzylic chlorides, such as 3,4,5-trimethoxybenzyl chloride are easily converted within 3 h at 25 °C (zinc dust 2.0 equiv, LiCl 2.0 equiv) to the benzylic zinc compound (**1k**, 78%). The allylation of **1k** with ethyl (2-bromomethyl)acrylate[8] (0.8 equiv) affords the desired product **4r** in 98% yield (entry 18). Also, the electron-rich benzylic chloride **2l** is readily converted to the corresponding zinc compound **1l** within 1 h (zinc dust 1.5 equiv, LiCl 1.5 equiv) in 93% yield. Acylation of **1l** leads to the ketone **4s** in 93% yield (entry 19). Phenylacetic acid derivatives are common targets in pharmaceutical research.[9] They are readily prepared in two ways using benzylic zinc species of type **1** (Scheme 2). Thus, the Negishi Pd-catalyzed acylation[10] of the benzylic zinc chloride **1a** with ethyl chloroformate in the presence of $Pd(PPh_3)_4$ (5 mol %, 25 °C, 6.5 h) is leading to the phenylacetic acid ethyl ester **5** in 81% yield. Alternatively, a copper mediated acylation is possible.

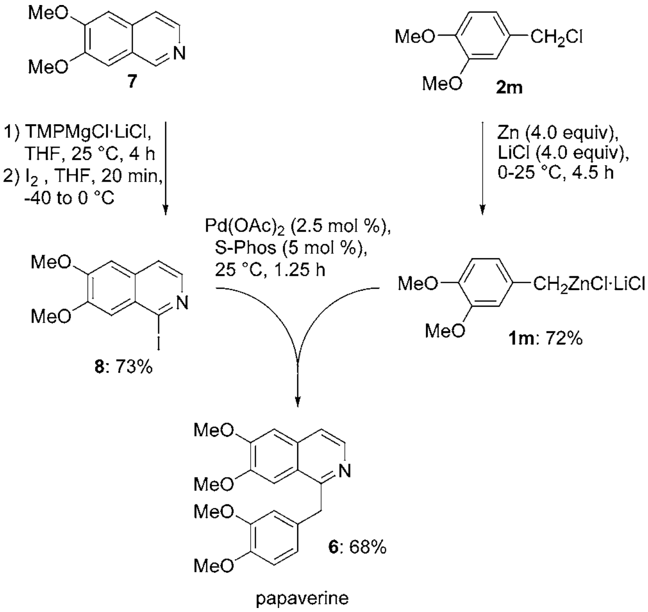
Scheme 2. Synthesis of Phenylacetic Acid Derivatives of Type **5**



Thus, the reaction of **1a** with $TMSCH_2Li$ (−30 °C, 30 min) provides a mixed diorganozinc of the type $ArCH_2ZnCH_2SiMe_3$.[11] Transmetallation to copper ($CuCN{\cdot}2LiCl$, −30 °C, 30 min) and addition of Mander's reagent[12] gives the expected ethyl phenylacetic ester **5** in 77% yield.

As an application, we have prepared papaverine (**6**)[13] starting from the isoquinoline[14] **7** (Scheme 3). Magnesiation

Scheme 3. Synthesis of Papaverine



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of **7** with TMPMgCl·LiCl[15] (TMP = 2,2,6,6-tetramethylpiperidyl; 25 °C, 4 h), followed by iodolysis provides the isoquinoline **8** in 73% yield. Zinc insertion to the benzylic chloride **2m** (25 °C, 4.5 h) gives the expected benzylic zinc reagent **1m** in 72% yield. Pd-catalyzed cross-coupling using $Pd(OAc)_2$ (2.5 mol %) and S-Phos[16] (5 mol %) provides papaverine (**6**) in 68% yield.[17]

In summary, we have reported a mild method allowing the preparation of benzylic zinc chlorides from the corresponding benzylic chlorides using zinc dust and LiCl. Remarkably, these zinc organometallics are compatible with the presence of functional groups including ketones. Further extension of this work to the preparation of heterocyclic analogs is underway.

Acknowledgment. We thank the DFG for a financial support. We thank Umicore AG (Angleur, Belgium) for the generous gift of zinc powder. We also thank Chemetall GmbH (Frankfurt), Evonik Industries AG (Hanau) and BASF AG (Ludwigshafen) for the generous gift of chemicals.

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

OL7030697

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