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New Preparation of TMPZnCl·LiCl by Zn Insertion into TMPCl. Application to the Functionalization of Dibromodiazines

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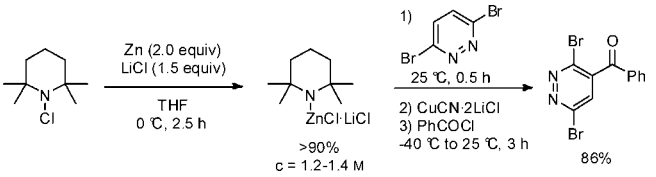
ABSTRACT



A practical zinc insertion starting from cheap commercial zinc powder and TMPCl (1-chloro-2,2,6,6-tetramethylpiperidine) allows a fast and efficient synthesis of the zinc base TMPZnCl·LiCl under mild conditions in high yields. This base is kinetically highly active and was used for the regio- and chemoselective functionalization of dibromodiazines (pyridazines and pyrazines).

The preparation of functionalized aromatic molecules and heterocycles is of great importance due to their potential biological activity. These structures are present in many pharmaceuticals or agrochemicals.[1] Direct metalation has proven to be an excellent tool for the regioselective functionalization of these compounds.[2] Therefore the availability of chemoselective as well as kinetically highly active bases is an important synthetic goal.[3]

Recently, we have shown that TMPZnCl·LiCl (**1**) is an exceptionally active and chemoselective base, allowing highly selective zincations to be performed in a convenient temperature range (typically 0 to 80 °C).[4] The preparation of **1** has been done in two steps starting from 2,2,6,6-tetramethylpiperidine (**2**: TMPH) in >95% yield. Thus, the amine **2** is first deprotonated with *n*-BuLi in hexanes (1 equiv, −10 °C, 1 h) leading to TMPLi (**3**) in quantitative yield. Transmetalation with $ZnCl_2$ (1.05 equiv, −10 to 25 °C, 0.5 h) furnishes after evaporation of the hexanes/THF solvent mixture and redissolution in dry THF 1.2−1.4 M solutions of TMPZnCl·LiCl (**1**). Although the overall yield of this synthesis is high (ca. 90%; Pathway A; Scheme 1), it has several drawbacks. The reaction conditions require the use of dry $ZnCl_2$. Also *n*-BuLi is only available in nonpolar solvents (alkanes or toluene). Since this solvent mixture reduces significantly the solubility of TMPZnCl·LiCl (**1**) and therefore also its metalation power, a tedious solvent evaporation and redissolution are required. These impractical conditions as well as the relatively high price of *n*-BuLi solution and safety considerations led us to design a new synthesis of TMPZnCl·LiCl (**1**) which would be conducted in a more favorable temperature range and involve cheap and safe reagents.[5] TMPH (**2**) is readily converted either by chlorination with NCS or by treatment with an aqueous bleach solution

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(1) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Thieme: Stuttgart, 1995. (b) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1996.

(2) (a) Chatani, N. *Topics in Organometallic Chemistry: Directed Metallation*; Springer: Berlin, 2007. (b) Dyker, G. *Handbook of C−H Transformations*: Wiley-VCH: Weinheim, 2005. (c) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (d) Whisler, M. C.; MacNeil, S.; Beak, P.; Snieckus, V. *Angew. Chem.* **2004**, *116*, 2256. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

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(5) A patent application has been filed.

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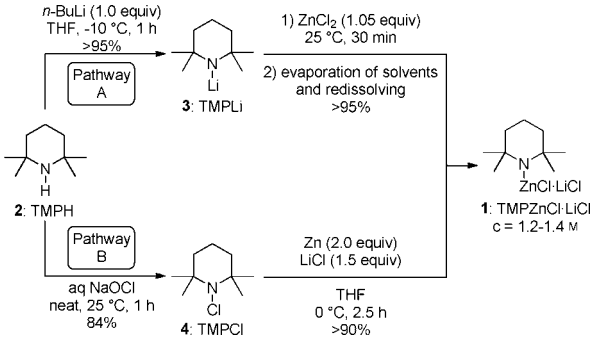
(13% aq NaOCl) at 25 °C to the corresponding chloramine 1-chloro-2,2,6,6-tetramethylpiperidine (**4**: TMPCl) in 84% yield.[6] We have envisioned the direct insertion of a metal (Met) into the nitrogen−chlorine bond of TMPCl (**4**) in the presence of LiCl, which would afford the metallic amides TMPMetCl·LiCl. Preliminary results showed that for, Met = magnesium (turnings or powder), only reduction of the chloroamine (**4**) is observed. However, switching to zinc dust and performing a slow addition of the chloroamine *via* syringe pump at 0 °C allows the preparation of TMPZnCl·LiCl (**1**) in 90% yield as indicated by titration with benzoic acid[7,10c] (Pathway B; 50 mmol scale; Scheme 1).

Scheme 1. Preparation of TMPZnCl·LiCl (**1**)



TMPZnCl·LiCl (**1**) was directly obtained in concentrations that made evaporation of solvents obsolete. The excess of zinc powder can simply be removed by filtration. Thus, a fast preparation of this organozinc base is possible starting from cheap commercial zinc and the *N*-chloroamine TMPCl (**4**).

We have verified that the deprotonation power (temperature, reaction time) of TMPZnCl·LiCl (**1**) prepared by pathways A and B are identical and report herein some new directed zincations of bromo-substituted pyridazine **5a** and pyrazines **5b**−**e**. Pyrazines and pyridazines are biologically highly active, and therefore their functionalization is of great interest since many examples of natural products or pharmaceutically important compounds contain these scaffolds (Figure 1).

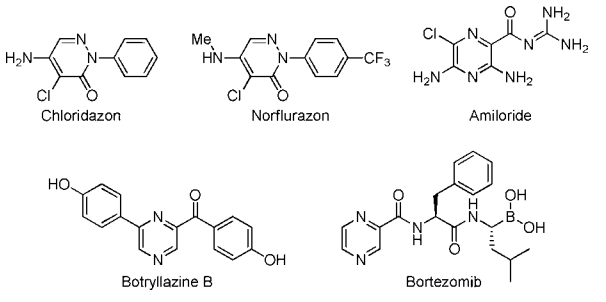
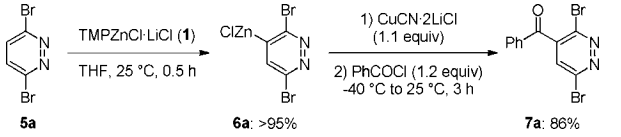


Figure 1. Biologically active compounds containing a pyrazine or pyridazine scaffold.

The high electrophilicity of these heterocycles requires low temperatures for their metalation. TMPZnCl·LiCl (**1**) proved to be especially well suited for zincation of heterocycles of type **5** and related scaffolds since more active bases, such as $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[8] or TMPMgCl·LiCl,[9] lead to the decomposition of these sensitive heterocyclic bromides.[10] In contrast, treatment of the dibromopyridazine **5a**[11] with TMPZnCl·LiCl (**1**; 1.1 equiv, 25 °C, 0.5 h) led to the quantitative formation of the zincated pyridazine **6a** which after transmetalation with $CuCN \cdot 2LiCl$[12] (1.1 equiv) and benzoylation (PhCOCl, 1.2 equiv, −40 to 25 °C, 3 h) provides the ketone **7a** in 86% isolated yield (Scheme 2).

Scheme 2. Directed Zincation of 3,5-Dibromopyridazine (**5a**)



Similary, the zincated pyridazine **6a** reacted smoothly with iodine and allylic bromides, leading to the *N*-heterocycles **7b**−**d** in 71−76% yield (Table 1, entries 1−3).

Equally well 2,5-dibromopyrazine **5b**[13] was zincated with the base **1** (1.1 equiv, 25 °C, 1 h). Copper-mediated acylation with various acid chlorides furnishes the expected acylpyrazines **7e**−**h** in 53−79% yield (Table 1, entries 4−6). The symmetrical 2,6-dibromopyrazine **5c**[14] was readily zincated (**1**, 1.1 equiv, 25 °C, 1 h). It reacts with iodine, allyl bromide, and 1-bromophenylacetylene[15] under standard conditions

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(7) We have applied the method also to other *N*-chloroamines, such as 1-chloro-diisopropylamine, 1-chloro-*tert*-butylisopropylamine, or 1-chloro-piperidine. However, the yields of the corresponding zinc amide drop significantly. A possible reason for this yield decrease could be enamine formation in the course of the insertion. See Supporting Information. Note: *N*-Chloroamines which can readily eliminate HCl are energy-rich compounds that are inherently much less stable than TMPCl, as such considereable care must be taken during their preparation and use.

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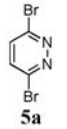
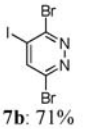
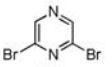
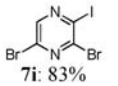
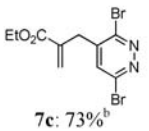
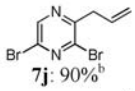
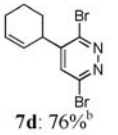
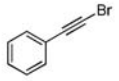
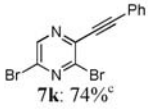
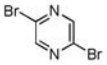
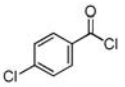
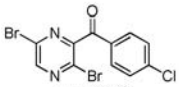
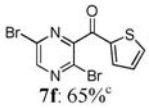
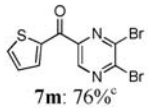
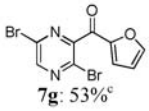
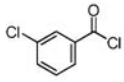
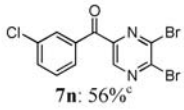
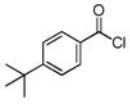
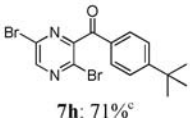
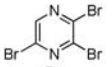
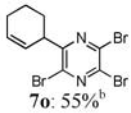
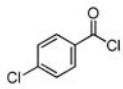
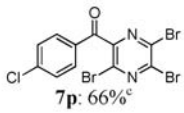
Table 1. Monofunctionalization of Bromodiazines of Type **5**

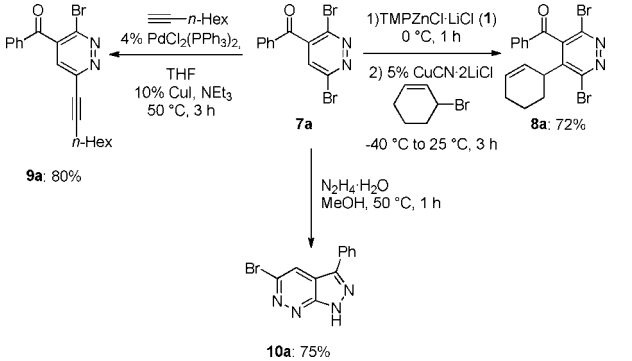
entry	substrate	electrophile	product / yield[a]	entry	substrate	electrophile	product / yield[a]
1	 **5a**	I_2	 **7b**: 71%	8	 **5c**	I_2	 **7i**: 83%
2	**5a**		 **7c**: 73%[b]	9	**5c**		 **7j**: 90%[b]
3	**5a**		 **7d**: 76%[b]	10	**5c**		 **7k**: 74%[c]
4	 **5b**		 **7e**: 79%[c]	11	 **5d**	I_2	 **7l**: 71%
5	**5b**		 **7f**: 65%[c]	12	**5d**		 **7m**: 76%[c]
6	**5b**		 **7g**: 53%[c]	13	**5d**		 **7n**: 56%[c]
7	**5b**		 **7h**: 71%[c]	14	 **5e**		 **7o**: 55%[b]
15	**5e**		 **7p**: 66%[c]				

[a] Yield of analytically pure isolated product. [b] Catalyzed by 5 mol % of CuCN·2LiCl. [c] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv).

providing the trisubstituted pyrazines **7i**–**k** in 74–90% yields (Table 1, entries 8–10). The isomeric 2,3-dibromopyrazine **5d**[16] is only zincated at elevated temperatures with TMPZnCl·LiCl, since no adjacent bromine substituent is available for further acidification of the protons, (**1**; 1.1 equiv, 50 °C, 12 h) leading to the expected zinc reagent which was iodinated to give the iodopyrazine **7l** (71%, Table 1, entry 11). Copper-mediated acylation provides the heterocyclic ketones **7m**–**n** in 56–76% yields (Table 1, entries 12, 13). Finally, the tribromopyrazine **5e**[17] is zincated with TMPZnCl·LiCl (**1**, 1.1 equiv, 25 °C, 1 h) leading to a sensitive zinc reagent. Copper-catalyzed allylation and acylation provide the tetrasubstituted pyrazines in 55–66% yields (Table 1, entries 14, 15).

These diazines can be further functionalized *via* a second zincation. Thus, the treatment of **7a** with TMPZnCl·LiCl (**1**, 1.1 equiv, 0 °C, 1 h) provides an intermediate zinc reagent which was allylated with 3-bromocyclohexene in the presence of 5% CuCN·2LiCl to furnish the fully substituted pyridazine **8a** in 72% yield (Scheme 3).

Scheme 3. Further Functionalizations of (3,6-Dibromopyridazin-4-yl)(phenyl)methanone (**7a**)



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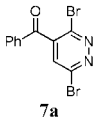
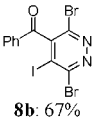
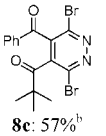
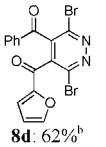
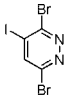
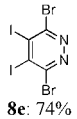
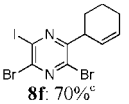
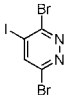
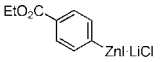
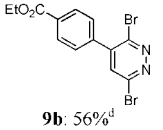
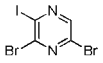
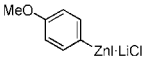
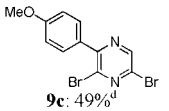
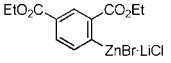
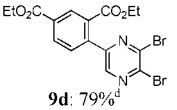
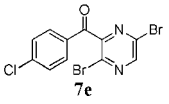
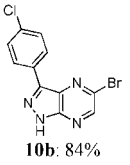
(17) Karmas, G.; Spoerri, P. E. *J. Am. Chem. Soc.* **1957**, *79*, 680.

Table 2. Further Functionalization of Compounds of Type **7**

entry	diazine	electrophile / nucleophile	product / yield[a]
1	 **7a**	I_2	 **8b**: 67%
2	**7a**		 **8c**: 57%[b]
3	**7a**		 **8d**: 62%[b]
4	 **7b**	I_2	 **8e**: 74%
5	 **7i**		 **8f**: 70%[c]
6	 **7b**		 **9b**: 56%[d]
7	 **7i**		 **9c**: 49%[d]
8	 **7l**		 **9d**: 79%[d]
9	 **7e**	$N_2H_4{\cdot}H_2O$	 **10b**: 84%

[a] Yield of analytically pure isolated product. [b] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv). [c] Catalyzed by 5 mol % of CuCN·2LiCl. [d] Obtained by palladium-catalyzed cross-coupling using 2 mol % $Pd(dba)_2$ and 4 mol % P(2-furyl)$_3$.

This zincated pyridazine is also iodinated and acylated providing the expected pyridazines **8b**–**d** in 57–67% yield (Table 2, entries 1–3). Similarly, the iododibromopyridazine **7b** and the iododibromopyrazine **7i** are zincated with TMPZnCl·LiCl (**1**, 1.1 equiv, 0 °C, 1 h) leading after iodolysis or copper catalyzed allylation to the diiododibromopyridazine **8e** and the fully functionalized pyrazine **8f** in yields of 74 and 70%, respectively (Table 2, entries 4 and 5). Furthermore the dibromopyridazine **7a** undergoes a regioselective Pd-catalyzed Sonogashira reaction[18] with 1-octyne in the presence of 4% $PdCl_2(PPh_3)_2$, 10% CuI, and Et_3N (50 °C, 3 h) to afford the pyridazine **9a** in 80% yield. Also, the mixed iodobromopyrazines such as **7b**, **7i**, and **7l** leads as expected to the preferential cross-coupling of the iodide in various Negishi cross-couplings[19] with arylzinc iodides[20] giving the pyrazines **9b**–**d** in 49–79% yields (Table 2, entries 6–8).

Finally, these dibromopyrazines are also regioselectively converted to annulated heterocycles, which are potentially biologically active.[21] Thus, the treatment of **7a** with hydrazine hydrate (MeOH, 50 °C, 1 h) gives the pyrazolopyrazine **10a** in 75% yield (Scheme 3). The same reaction converts the pyrazine **7e** to the condensed heterocycle **10b** in 84% yield (Table 2, entry 9).

In summary, we have described a new practical preparation of the sterically hindered zinc amide TMPZnCl·LiCl (**1**) and demonstrated its utility for the zincation and further functionalization of dibromodiazines. Further extensions to the metalation of related heterocycles are underway.

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

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The authors declare no competing financial interest.