Zinc Base Assisted Amination of 2-Chloropyrimidines by Aniline Derivatives at Room Temperature

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Abstract: The amination of 2-chloropyrimidines was performed with several aniline derivatives in the presence of tolylzinc bromide as a base. The organozinc compound has a profound effect on the reactivity of the amines, so that the reaction takes place at room temperature. Further studies gave insight into the reaction mechanism and favor a nucleophilic substitution over a catalytic process.

Key words: zinc base, amination, nucleophilic aromatic substitution, 2-anilinopyrimidine, heterocycles

The 2-anilinopyrimidine moiety is an important motif for pharmaceuticals and agrochemicals. It can be found in a variety of biologically active compounds such as anticancer agents pazopanib (Votrient™; **1**) and imitanib (Gleevec™; **2**),[1a,b] fungicide[1c] cyprodinil (**3**), anti-HIV agent[1d] etravirine (Intelence™; **4**) and many more (Figure 1).

The most straightforward strategies[2] to synthesize these structures involve nucleophilic aromatic substitution of 2-chloro-,[3] or more reactive, 2-methylsulfonylpyrimidines[4]

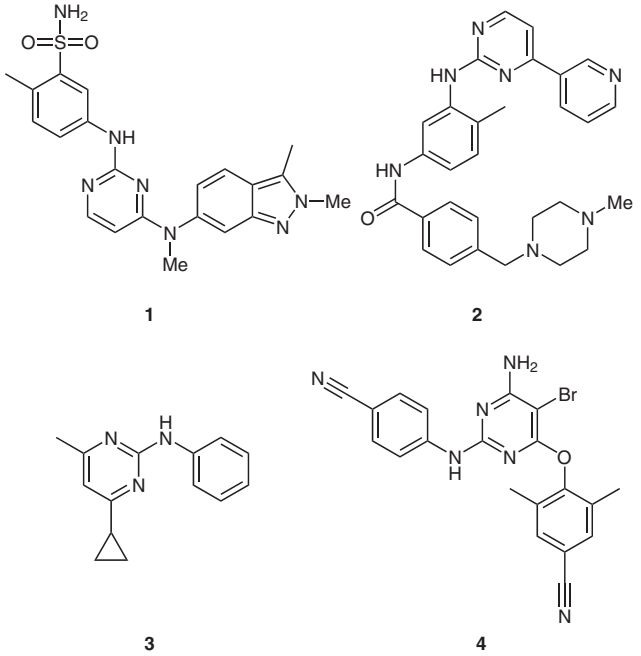
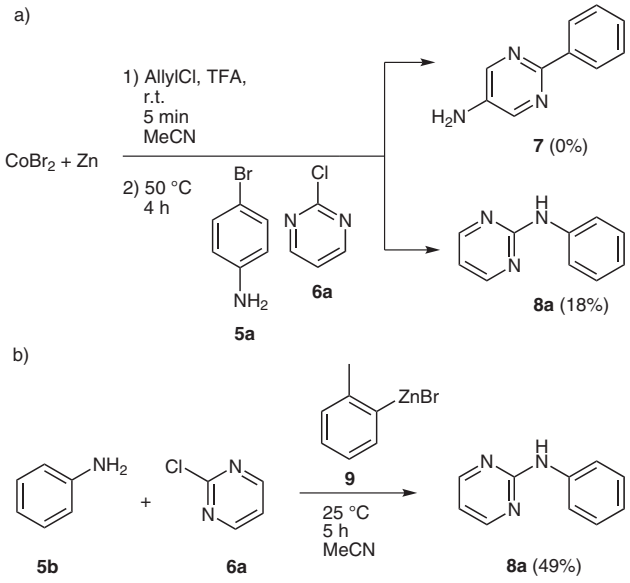


Figure 1 Selection of important, biologically active compounds containing the 2-anilinopyrimidine motif

by aniline derivatives and approaches featuring C–N cross-coupling either via Ullmann-type reaction[5] or by Buchwald–Hartwig amination.[6] All of these methods have harsh reaction conditions in common with reaction temperatures usually over 100 °C. Furthermore noncatalytic reactions give just moderate isolated yields and Buchwald–Hartwig aminations normally rely on an expensive palladium source and sensitive ligands. Despite the impressive progress of amination reactions in recent years, a mild and simple protocol to furnish 2-anilinopyrimidines is still of interest.

In the course of our investigation of cobalt-catalyzed C–C cross-coupling between 2-chloropyrimidines and functionalized arylzinc compounds,[7] we tested if the developed Barbier procedure tolerates amino groups. As anticipated amines, such as 4-bromoaniline (**5a**), are not tolerated under the given conditions, but to our surprise, we found that the reaction yielded 18% of 2-anilinopyrimidine (**8a**) at 50 °C (Scheme 1a).

We were rationalizing that the in situ generated organozinc compound deprotonates the amino group to facilitate either the nucleophilic attack or a C–N coupling with 2-chloropyrimidine (**6a**) by cobalt catalysis. Thus, we decided to design a zinc base, 2-tolylzinc bromide (**9**), that is unable to couple with 2-chloropyrimidine under the giv-



Scheme 1 (a) Barbier procedure for the cobalt-catalyzed C–C coupling in the presence of an amino group; (b) amination in the presence of tolylzinc bromide **9**

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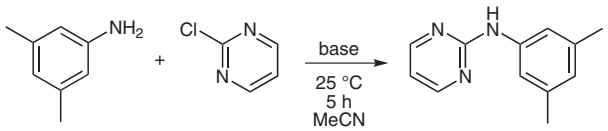
en conditions and does not interfere in a possible amination of halide **6a**. We were pleased to see that the reaction gave 49% yield at room temperature within five hours in the presence of organozinc **9**, which is stable and readily accessible in almost quantitative yield by the protocol for the cobalt-catalyzed zinc insertion developed by our group (Scheme 1b).[8] The base is prepared separately and either filtered or the supernatant is canulated carefully to the reaction flask to guarantee that no remaining zinc is transferred with it.[9] Toluene is generated as the sole by-product after consumption, which can be removed easily once the reaction is finished.

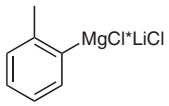
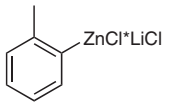
For practical reasons, we decided to optimize the reaction with 3,5-dimethylaniline (**5c**). To study and compare the reactivity of the zinc base, we tested several routinely used bases (Table 1).

The zinc base showed to be much superior to other bases. Common weak organic and inorganic bases gave no reaction under the same conditions (Table 1, entries 2 and 3).

Table 1 Evaluation of Bases for the Amination of 2-Chloropyrimidine with 3,5-Dimethylaniline



5c **6a** **8b**

Entry	Base	Equivalents[a]	Yield (%)[b]
1	none	1	0
2	K_2CO_3	1	0
3	TEA	1	0
4	NaH	1	2[c]
5	LiHMDS[d]	1	5[c]
6	 **10**[d]	1	8[c,d]
7	**9**[e]	1	48
8	**9**[e]	2	68
9	**9**[e]	2 × 1	85
10	 **11**[d]	2 × 1	72
11	**11**[f]	2 × 1	70

[a] Regarding the amount of **5c**.
[b] Isolated yield of the pure product.
[c] GC yield with dodecane as internal standard.
[d] Base preparation and reaction in THF.
[e] Base was prepared by Co catalysis in MeCN.
[f] Reaction was carried out in MeCN after solvent change.

Stronger bases like NaH and LiHMDS yielded only traces of the desired compound (Table 1, entries 4 and 5). We also tested a carbon metal base, tolylmagnesium bromide **10** that should show comparable basicity as **9**. The reaction yielded 8% product, which underlines the necessity of organozinc **9** as the organometallic reagent of choice (Table 1, entry 6). One equivalent of zinc base gave a yield of 48% (Table 1, entry 7). Increasing the equivalents of **9** led to further optimization with two equivalents yielding the desired compound in 68% yield (Table 1, entry 8). Altering the order of addition to one equivalent of **9** followed by another one after two hours of reaction time gave the product in a very good yield of 85% (Table 1, entry 9). With these results in hand we started to study the reaction mechanism. Envisioning that the striking increase in reactivity is due to cobalt catalysis, we synthesized the zinc compound **9** in a cobalt-free matter to verify the role of the remaining cobalt complex in solution. Transmetalation of the corresponding Grignard reagent **10** with $ZnCl_2$ by a modified literature procedure[10] furnished the cobalt-free zinc compound **11**, which was used as such in THF or after a solvent change to acetonitrile as described by Oshima and co-workers.[11] The fact that no significant drop of yield was observed favors a cobalt-independent S_NAr mechanism over a cobalt-catalyzed C–N coupling (Table 1, entries 10 and 11). The solvent change from MeCN to THF did not alter the yield of **8b**. These results give evidence that the reaction is likely to be solvent independent.

Encouraged by these results we turned to analyze the scope of the reaction. With the optimized protocol in hand we were able to obtain 2-anilinopyrimidine (**8a**) in a very good yield of 87% (Table 2, entry 1). The reaction proceeded with anilines bearing different halides in *para*- or *meta*-position, that allowed for further functionalization, in good yields (Table 2, entries 3–5). Anilines functionalized with an ether, an ester or a nitrile group were also well tolerated and gave the desired products in good yields under the given conditions (Table 2, entries 6–8). In the presence of a sensitive keto group the product was furnished in acceptable yields (Table 2, entry 9).

A certain extent of steric hindrance was tolerated in the case of *ortho*-toluidine (**5k**) and the product **8k** was obtained in 54% yield (Table 2, entry 11). However, the secondary aniline **5j** showed only moderate conversion with a yield of 42% despite its higher nucleophilicity (Table 2, entry 10). This could be due to the increase of steric hindrance on the nitrogen. Next we tested several 2-chloropyrimidine derivatives. Reaction of aniline with 2-chloro-5-ethylpyrimidine (**6b**) and 2-chloro-4-(trifluoromethyl)pyrimidine (**6c**) gave the desired product in very good yields (Table 2, entries 12 and 13). Furthermore we could extend the reaction to the trisubstituted triazine **6d**. In this case only one equivalent of the organozinc compound **9** was necessary to achieve an excellent yield of 90% after 2.5 hours reaction time of the triazine **8n**. This result made us speculate that parts of the second equivalent of base are consumed by deprotonation of 2-chloropyrimidine.

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In summary we have developed a mild protocol for the amination of 2-chloropyrimidine and its substituted analogues with functionalized or nonfunctionalized anilines.[12] Tolylzinc bromide dramatically increases the reactivity of the amine towards the halide. Furthermore mechanism studies showed that the reaction does not rely on transition-metal-catalysis. Extension of the scope with further amines and halides is currently ongoing and will be reported in due course.

Table 2 Scope of the Amination of Different 2-Chloropyrimidines with Various Aniline Derivatives under Optimized Conditions

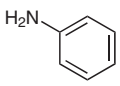
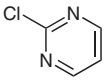
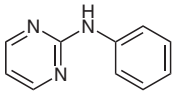
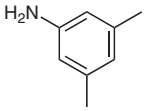
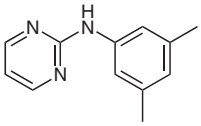
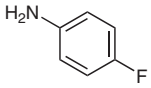
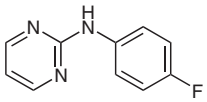
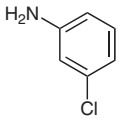
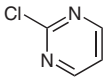
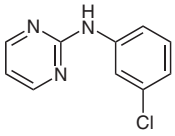
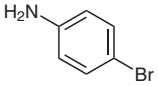
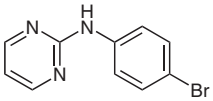
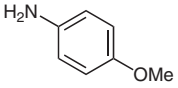
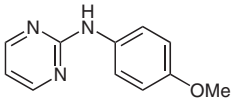
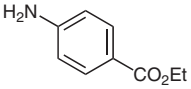
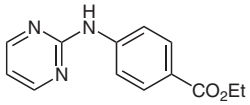
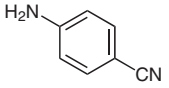
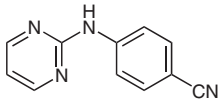
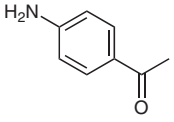
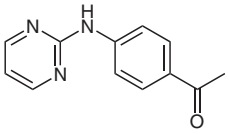
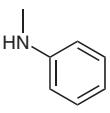
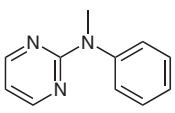
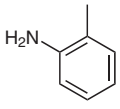
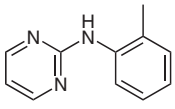
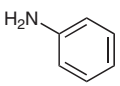
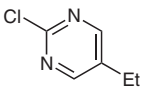
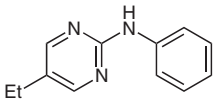
Entry	Amine	Halide	Product	Yield (%)[a]
1	**5b** 	**6a** 	**8a** 	87
2	**5c** 	**6a**	**8b** 	85
3	**5d** 	**6a**	**8c** 	74
4	**5e** 	**6a** 	**8d** 	75
5	**5a** 	**6a**	**8e** 	63
6	**5f** 	**6a**	**8f** 	72
7	**5g** 	**6a**	**8g** 	69
8	**5h** 	**6a**	**8h** 	69
9	**5i** 	**6a**	**8i** 	55
10	**5j** 	**6a**	**8j** 	42[b]
11	**5k** 	**6a**	**8k** 	54[b]
12	**5b** 	**6b** 	**8l** 	81

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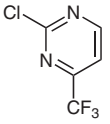
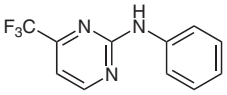
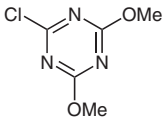
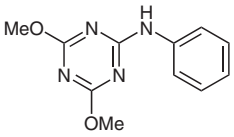
Table 2 Scope of the Amination of Different 2-Chloropyrimidines with Various Aniline Derivatives under Optimized Conditions (continued)

Entry	Amine	Halide	Product	Yield (%)[a]
13	**5b**	**6c** 	**8m** 	88
14	**5b**	**6d** 	**8n** 	90[c]

[a] Isolated yield of the pure product.
[b] Reaction time: 16 h.
[c] Just one equivalent of **9** was used; reaction time was reduced to 2.5 h.

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(12) **General Procedure for the Amination of 2-Chloropyrimidines**: An oven-dried Schlenk flask was equipped with a stirring bar, a septum and was flushed with nitrogen. The flask was charged with a solution of **9** (0.8 M, 3 mL) in MeCN. The amine (2.5 mmol) and 2-chloropyrimidine (3 mmol) were added and the resulting mixture was stirred for 2 h. Another aliquot of the solution of **9** (0.8 M, 3 mL) was added and the reaction mixture was stirred for further 3 h. The reaction was quenched with a sat. NH_4Cl solution (100 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine solution (20 mL) and dried over $MgSO_4$. The drying reagent was filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica or aluminum oxide.

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