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Highly selective mono-substitution in Pd-catalyzed cross-coupling reactions of 3,6-dichloropyridazine with organozinc compounds

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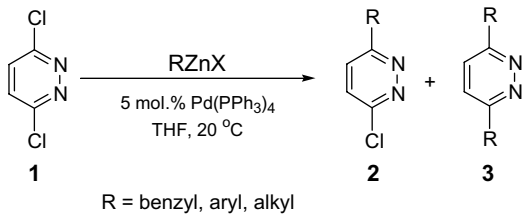
Abstract—Pd-catalyzed cross-coupling reactions of 3,6-dichloropyridazine (**1**) with benzyl, aryl, and alkyl organozinc compounds led to selective mono-substitution of one of the chlorine atoms. The subsequent cross-coupling of the resulting monochlorides with RZnCl afforded unsymmetrical 3,6-carbon-disubstituted pyridazines.

Pyridazine derivatives continue to attract considerable attention due to the wide range of their biological activity.[1,2] Most of the bioactive compounds are 3,6-disubstituted pyridazines. The readily available 3,6-dichloropyridazine (**1**) seems to be an appropriate starting material for these compounds. It is well known that selective mono-substitution of a single chlorine atom in **1** can be achieved when **1** is allowed to react with oxygen,[3–9] sulfur,[10] nitrogen[3,6,11–13] or halogen nucleophiles.[14] To our knowledge, selectivity (mono- vs disubstitution) in carbon–carbon bond formation reactions of **1** has been studied to a much lesser extent. The treatment of **1** with α-lithiated nitriles afforded 'one to one' alkylation products exclusively.[1,15–19] Pd-catalyzed Stille reactions of **1** with (α-alkoxyvinyl)stannanes also led to the mono-substitution products in high yield.[20,21] On the other hand, Suzuki cross-coupling with phenylboronic acid[22] and Sonogashira reactions with terminal acetylenes[23] suffered from a lack of selectivity. To our knowledge, there are no effective and general protocols in the literature for highly selective mono-substitutions of a single chlorine atom in **1** with an alkyl, aryl, benzyl or allyl fragment.[24] However, for combinatorial chemistry applications one needs facile and rapid access to a library of various 3,6-carbon-disubstituted pyridazines.

Here we report our results on the palladium catalyzed cross-coupling reactions of commercially available 3,6-dichloropyridazine (**1**) with a range of organozinc compounds prepared in situ by the treatment of $ZnCl_2$ with the corresponding organolithiums or organomagnesiums.[25–27] We chose zinc derivatives because they are non-toxic, readily available, tolerant to functional groups (ester-, nitrile-, etc.)[26,28], and have proved to be effective partners in cross-couplings with various heteroaryl halides.[29,30] All reactions were carried out in THF in the presence of $Pd(PPh_3)_4$ (Scheme 1 and Table 1).

As represented by the results shown in Table 1, the reactions of **1** with 1.05 equiv of benzyl and phenylzinc bromides afforded the corresponding mono-substitution



Scheme 1.

Keywords: 3,6-Dichloropyridazine; Organozinc compounds; Palladium; Cross-coupling reactions.
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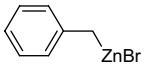
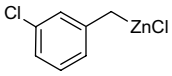
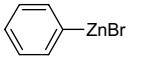
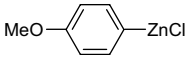
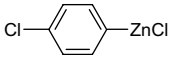
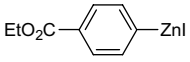
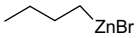
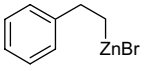
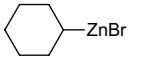
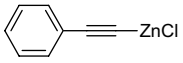
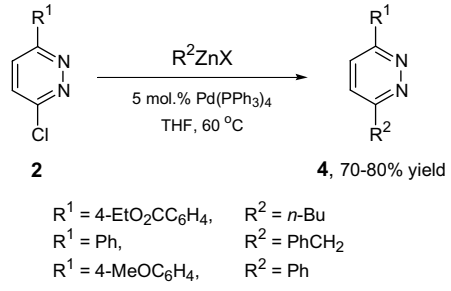
Table 1. Reactions of 3,6-dichloropyridazine (**1**) with organozinc compounds[a]

Entry	RZnX	RZnX/**1**	**2**+**3**, %[b]	**2**/**3**[c]
1		1.05	65[e]	>98:2
2		1.05[d]	71	86:14
3		1.6	86	88:12
4		1.6	64	>98:2
5		1.05	37[e]	>98:2
6		1.6	72	92:8
7		1.6	92	96:4
8		1.6	86	92:8
9		1.05[f]	61	>98:2
10		1.6	87	>98:2
11		1.6	63	>98:2
12		2	27	>98:2
13		3.2	49[e]	80:20

[a] All reactions were carried out in THF at 20 °C for 24 h under Ar unless stated otherwise.
[b] Total yields of **2**+**3** isolated by column chromatography.
[c] According to GC-MS and ^{1}H NMR data.
[d] At 50 °C.
[e] 25%, 51%, and 42% of **1** (for entries 1, 5, and 13 respectively) remained in the crude reaction mixtures according to GC-MS data.
[f] Commercial (Aldrich®) 0.5 M solution of RZnI in THF was used.



2 **4**, 70-80% yield

R^1 = 4-$EtO_2CC_6H_4$, R^2 = *n*-Bu
R^1 = Ph, R^2 = $PhCH_2$
R^1 = 4-$MeOC_6H_4$, R^2 = Ph

Scheme 2.

products **2** in moderate yields and with more than 98% selectivity (entries 1 and 5). According to NMR analysis of the crude reaction mixtures, significant amounts of **1** remained in both cases. Note that prolonged reaction times or additional amounts of the Pd-catalyst did not increase the conversion of **1**. Increasing the temperature or the use of 1.6 equiv of RZnBr in the reactions of **1** with $PhCH_2ZnBr$ and PhZnBr, although improving conversion, led to formation of detectable (8–14%) amounts of the di-substitution products **3** (entries 2, 3, and 6). The reactions of **1** with 1.6 or 1.05 equiv of the other benzyl and aryl organozinc compounds afforded the mono-substitution products **2** in high yields and more than 92% selectivity (entries 4, 7, 8, and 9).[†] To our delight, the primary alkylzinc compounds proved to be excellent reaction partners giving almost exclusively the corresponding monochlorides **2** in good yields (entries 10 and 11). However, with cyclohexylzinc bromide the yield of **2** decreased to 27% due to formation of a complex mixture of unidentified side-products (entry 12). In comparison with benzyl, aryl, and alkyl organozinc compounds, the reaction of **1** with (phenylethynyl)ZnCl proceeded more slowly (42% of **1** was recovered from the reaction mixture even when 3.2 equiv of RZnX was used) and with less selectivity (entry 13).

The possibility of a subsequent cross-coupling of the monochlorides **2** with another equivalent of an organozinc reagent was demonstrated by the reactions represented in Scheme 2. In all cases the unsymmetrical 3,6-carbon-disubstituted pyridazines **4**[31] were obtained in good yields when the reaction temperature was increased from 20 to 60 °C.

In conclusion, in this letter we have shown that palladium catalyzed cross-coupling reactions of 3,6-dichloropyridazine (**1**) with benzyl, aryl, and alkyl organozinc compounds represents an effective and practical method for the synthesis of various 3,6-disubstituted pyridazines where both the substituents can be varied independently.[‡]

References and notes

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[†] In the absence of Pd-catalyst only the starting dichloride (>90%) was isolated from the reaction of **1** with 1.6 equiv of PhZnCl (THF, 20 °C). However, treatment of **1** with 1.6 equiv of PhMgBr led to a complex mixture of products (where the desired product of mono-substitution was completely absent).

[‡] *Typical experimental procedure* (Table 1, entry 6): to a stirred solution of bromobenzene (252 mg, 1.60 mmol) in THF (6.0 mL), *n*-BuLi (1.00 mL, 1.6 M in hexanes) was added dropwise at −78 °C. The resulting solution was stirred for 30 min at −78 °C, then a solution of $ZnCl_2$ (218 mg, 1.60 mmol) in THF (2.0 mL) was added, the cooling bath was removed, and the reaction mixture was stirred for 30 min at room temperature. A solution of **1** (149 mg, 1.00 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (2.0 mL) was added via syringe. After stirring for 24 h at 20 °C the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (5 mL) and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Small amounts of unreacted **1** were removed by sublimation in vacuo (0.1 mmHg, 50 °C, 2 h). The residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 30:1) to give 3-chloro-6-phenylpyridazine (140 mg, 72% yield), as a white solid, mp 157 °C. Spectral data were in exact agreement with those reported.[14]

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31. The identity of the obtained compounds was confirmed by spectral data including ^{1}H and ^{13}C NMR, IR, and MS as well as elemental analysis data.