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Microwave-Assisted Palladium-Catalyzed Phosphonium Coupling of 2(1*H*)-Pyrazinones

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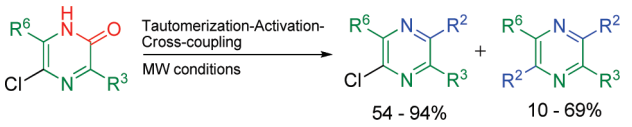

An expedient route for the synthesis of differently substituted 2(1*H*)-pyrazinones applying a microwave-assisted palladium-catalyzed phosphonium coupling procedure is reported. The method has also been successfully extended to some other tautomerizable heterocycles for efficient C−C cross-coupling.

Transition-metal-catalyzed cross-coupling reactions are nowadays indispensable tools for C−C[1] and C−heteroatom[2] bond formation, being particularly useful for the synthesis of diversely functionalized heterocycles. Organic (pseudo)halides[3] and organometallic reagents[4,5] as electrophiles and nucleophiles, respectively, are reacted with each other with the aid of a suitable catalyst. Recently Kang et al. disclosed the palladium-catalyzed cross-coupling reaction of boronic acids with tautomerizable heterocycles via C−OH bond activation using phosphonium salts as activating agents.[6] Pursuant to our long-standing interest in the synthesis and decoration of the 2(1*H*)-pyrazinone scaffold[7] and to our recently described novel and versatile protocol for the generation of asymmetrically tetrasubstituted pyrazines[8] starting from 2(1*H*)-pyrazinones, we envisaged that successive C−OH bond activation[6c,d] of this tautomerizable heterocycle, followed by palladium-catalyzed cross-coupling, would allow the generation of variously substituted pyrazines.

To evaluate this hypothesis, test reactions were carried out using 5-chloro-3-methoxy-6-methylpyrazin-2(1*H*)-one (**1a**) as model substrate with *p*-tolylboronic acid (**2a**) (Table 1). Using the conditions previously described by Kang et al.,[6a] the reaction was performed with (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as phosphonium coupling reagent under conventional heating conditions. A mixture of pyrazinone **1a** (0.25 mmol), PyBOP (1.1 equiv), and Et_3N (2 equiv) in 1,4-dioxane (2 mL) was stirred at room temp for 2 h. Then, $Pd(PPh_3)_2Cl_2$ (5 mol %), *p*-tolylboronic acid (2 equiv), Na_2CO_3 (2 equiv), and water (1 mL) were added, and the mixture was stirred in a sealed tube at 100 °C for 2 h (Table 1, entry 1). However, only the undesired C2,C5-disubstituted compound **5a** together with the C5-monosubstituted pyrazine **4a** were detected in the reaction mixture (GC-MS analysis). Although our first attempt met with failure, this result clearly indicates that the cross-coupling seems to be feasible with the 2(1*H*)-pyrazinone system. The C5-chlorine is far less reactive compared to the C3-chlorine of the 3,5-dichloro-2(1*H*)-pyrazinone system,[7a] but it becomes susceptible to palladium-catalyzed Suzuki cross-coupling reaction once the pyrazine system of **3a** is formed, as we have previously demonstrated.[8] This explains the easy formation of the disubstituted **5a** as soon as **3a** is formed. To circumvent this problem the number of equivalents of the *p*-tolylboronic acid (**2a**) was decreased from 2.0 to 1.05 equiv (Table 1, entry 3). Gratifyingly this resulted in the formation of the desired C2-monosubstituted pyrazine **3a** in a moderate yield of 65%, together with traces of the disubstituted compound **5a**. When switching from PyBOP to bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP), **3a** could be obtained with an excellent yield of 84%, although we were not able to fully suppress the formation

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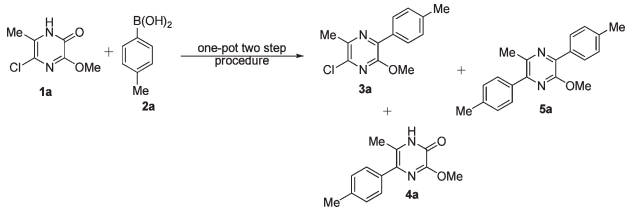
TABLE 1. Optimization of the Tautomerization-Activation-Coupling of 5-Chloro-3-methoxy-6-methylpyrazin-2(1*H*)-one (1a) with *p*-Tolylboronic Acid (2a)[a]



entry	reaction conditions (equiv of reagents)[a]	method	yield (%) **3a**	ratio (**4a/5a**)[b]
1	PyBOP (1.1), Et_3N (2.0), **2a** (2.0), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)	A	trace	10/60
2	PyBOP (1.1), Et_3N (2.0), **2a** (1.2), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)	A	54	−/30
3	PyBOP (1.1), Et_3N (2.0), **2a** (1.05), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)	A	65	−/14
4	**PyBroP (1.1), Et_3N (2.0), 2a (1.05), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)**	**A**	**84**	**2/10**
5	PyBroP (1.1), Et_3N (2.0), **2a** (1.05), $Pd(PPh_3)_4$ (0.05), Na_2CO_3 (2.0)	A	79	−/15
6	PyBrOP (1.1), Et_3N (2.0), **2a** (1.05), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)	B[c]	43	10/30
7	PyBroP (1.1), Et_3N (2.0), **2a** (1.05), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)	B[d]	59	10/20
8	**PyBroP (1.1), Et_3N (2.0), 2a (1.05), $Pd(PPh_3)_2Cl_2$ (0.05), Na_2CO_3 (2.0)**	**B**	**82**	**3/7**
9	PyBroP (1.1), Et_3N (2.0), **2a** (1.05), $Pd(PPh_3)_2Cl_2$ (0.05), K_2CO_3 (2.0)	B	81	−/9

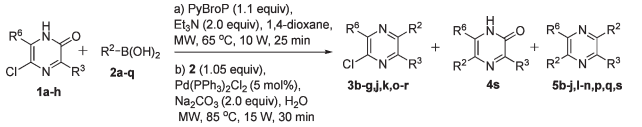
[a]Reaction conditions. Method A: **1a** (0.25 mmol, 1.0 equiv), phosphonium salt (0.275 mmol, 1.1 equiv), Et_3N (0.50 mmol, 2.0 equiv), 1,4-dioxane (2 mL), rt, 2 h; then **2a** (0.262−0.50 mmol, 1.05−2.0 equiv), Pd catalyst (5 mol %), base (0.50 mmol, 2.0 equiv), H_2O (1 mL), 100 °C, 2 h. Method B: **1a** (0.25 mmol, 1.0 equiv), phosphonium salt (0.275 mmol, 1.1 equiv), Et_3N (0.50 mmol, 2.0 equiv), 1,4-dioxane (2 mL), MW, 65 °C, 10 W, 25 min; then **2a** (0.262−0.50 mmol, 1.05−2.0 equiv), Pd catalyst (5 mol %), base (0.50 mmol, 2.0 equiv), H_2O (1 mL), MW, 85 °C, 15 W, 30 min.; [b]The ratio **4a**/**5a** was determined by GC-MS analysis. [c]MW, 65 °C, 10 W, 10 min; then MW, 80 °C, 20 W, 10 min. [d]MW, 65 °C, 10 W, 20 min; then MW, 80 °C, 25 W, 10 min. [PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; PyBroP = bromotripyrrolidinophosphonium hexafluorophosphate]

of the disubstituted compound **5a** as was indicated by GC-MS analysis (Table 1, entry 4). Replacing the $Pd(PPh_3)_2Cl_2$ catalyst by $Pd(PPh_3)_4$, no significant changes in product distribution were noticed (Table 1, entry 5). Next we investigated the application of microwave irradiation. A mixture of pyrazinone **1a** (0.25 mmol), PyBroP (1.1 equiv), and Et_3N (2 equiv) in 1,4-dioxane (2 mL) was irradiated at a ceiling temperature of 65 °C and a maximum power of 10 W for 10 min. Then, $Pd(PPh_3)_2Cl_2$ (5 mol %), *p*-tolylboronic acid (1.05 equiv), Na_2CO_3 (2 equiv), and water (1 mL) were added, and the mixture was irradiated at a ceiling temperature of 80 °C and a maximum power of 20 W for 10 min (Table 1, entry 6). The mono cross-coupled compound **3a** was obtained in 43% yield along with a mixture of **4a/5a** in a ratio of 10/30 according to GC-MS analysis. The optimal conditions were obtained by increasing the irradiation time of the first step to 25 min and that of the second step to 30 min at a slightly higher temperature of 85 °C (Table 1, entry 8). The desired product **3a** was obtained in 82% yield along with a mixture of **4a/5a** in a ratio of 3/7 as indicated by GC-MS analysis.

We next explored the scope of this protocol. An array of substituted 2(1*H*)-pyrazinones **1a**−**h** (Table 2) were reacted with various aryl or (hetero)aryl boronic acids **2a**−**q** using our optimized conditions. In all cases the mono- and/or the C2,C5-disubstituted cross-coupled product was formed. For the substrates bearing a methoxy or amino butyl group at the C3-position, the corresponding C2-monosubstituted product was predominantly formed (Table 2, entries 1−7 and 16−19, with the exception of 7 and 17). The 2(1*H*)-pyrazinones bearing a 4-tolyl- or styryl substituent in the C3-position tend to give the disubstituted product (Table 2, entries 8−15, with the exception of 10 and 11). Substrates bearing an -SPh or $-NH_2$ at the C3-position were less successful by applying these conditions (Table 2, entries 21 and 22).

We also evaluated the phosphonium-mediated Sonogashira−Hagihara-type[9] cross-coupling of 5-chloro-3-methoxy-6-methylpyrazin-2(1*H*)-one **1a** (Scheme 1). A mixture of pyrazinone **1a** (0.25 mmol), PyBroP (1.1 equiv), and Et_3N

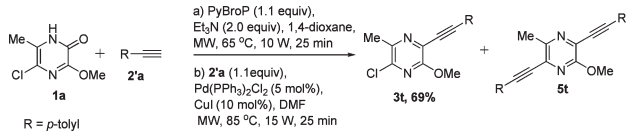
TABLE 2. Evaluation of the Scope of the Optimized Tautomerization-Activation-Coupling[a]



entry	R_3	R_6	R_2	yield (**3**:**4**:**5**) (%)
1	OMe	Me	5-Me-thiophene-2-	85/0/5
2	OMe	Me	4-MeO-C_6H_4	84/0/10
3	OMe	Me	2,4-diCl-C_6H_3	94/0/0
4	OMe	Me	4-$COCH_3$-C_6H_4	82/0/10
5	OMe	Me	2-F-C_6H_4	74/0/12
6	OMe	Me	4-COOEt-C_6H_4	54/0/29
7	OMe	Me	3-MeO-C_6H_4	12/0/69
8	4-tolyl	Me	4-MeO-C_6H_4	0/0/64
9	4-tolyl	Me	4-$COCH_3$-C_6H_4	0/0/59
10	4-tolyl	Me	3-CF_3-C_6H_4	72/0/9
11	4-tolyl	Me	4-$N(CH_3)_2$-C_6H_4	[b]
12	styryl	Bn	4-CN-C_6H_4	0/0/48
13	styryl	Bn	4-COOEt-C_6H_4	0/0/54
14	styryl	Bn	2-BnO-C_6H_4	0/0/45
15	styryl	Bn	4-^{t}Bu-C_6H_4	0/0/64
16	NH-^{n}Bu	Bn	3,5-diMe-C_6H_3	85/0/10
17	NH-^{n}Bu	Bn	3-CHO-thiophene-2-	[c]
18	NH-^{n}Bu	Bn	4-$CONH_2$-C_6H_4	62/0/15
19	NH-^{n}Bu	Bn	4-^{t}Bu-C_6H_4	92/0/0
20	4-MeO-Ph	H	2-F-C_6H_4	trace/60/20
21	S-Ph	H	4-EtO-C_6H_4	[c]
22	NH_2	4-MeO-Ph	4-MeO-C_6H_4	[c]
23	Ph	4-MeO-Ph	4-EtO-C_6H_4	[d]

[a]Reaction conditions. **1a**−**h** (0.25 mmol, 1.0 equiv), PyBroP (0.275 mmol, 1.1 equiv), Et_3N (0.50 mmol, 2.0 equiv), 1,4-dioxane (2 mL), MW, 65 °C, 10 W, 25 min; then **2a**−**q** (0.262 mmol, 1.05 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), Na_2CO_3 (0.50 mmol, 2.0 equiv), H_2O (1 mL), MW, 85 °C, 15 W, 30 min. [b]Sluggish reaction due to instability of the boronic acid. [c]No starting material or product were detected according to GC-MS analysis due to sluggish reaction mixture. [d]Only starting material **1h** was recovered after completion of the reaction.

SCHEME 1. Phosphonium-Mediated Sonogashira−Hagihara-Type Cross-Coupling Reaction



(2 equiv) in 1,4-dioxane (2 mL) was irradiated at a ceiling temperature of 65 °C and a maximum power of 20 W for 25 min. Then, $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and *p*-tolyl acetylene (**2′a**) (1.1 equiv) in DMF (1 mL) were added, and the mixture was irradiated at a ceiling temperature of 85 °C and a maximum power of 15 W for 25 min. The corresponding monoalkynylated product **3t** was obtained in 69% yield next to 5% disubstituted alkynylated product **5t** as determined by GC-MS analysis (Scheme 1).

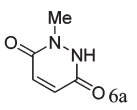
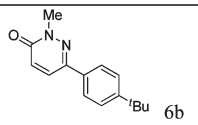
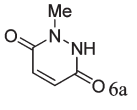
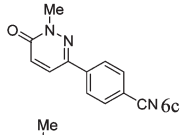
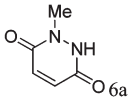
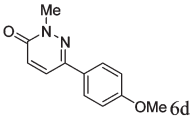
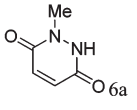
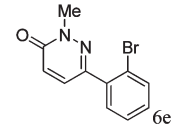
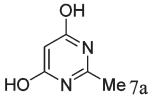
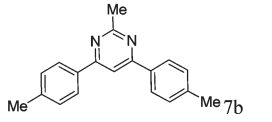
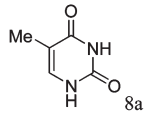
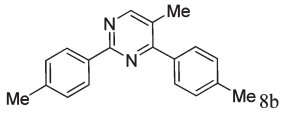
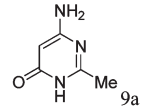
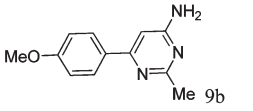
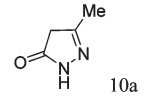
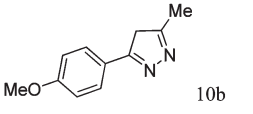
Having successfully established the optimized condition for the pyrazinone scaffold, we next explored the scope of the protocol for some other tautomerizable heterocycles.[6b,10] We selected the pyridazinone scaffold **6a** as this is present in a wide range of commercially important drugs and agrochemicals such as the antiplatelet clotting agent Zardaverine, the anti-inflammatory Emorfazone,[11a] and the COX-2 inhibitor ABT-963,[11b] as well as the herbicide Norflurazon. Gratifyingly, applying our optimized protocol, the corresponding arylated products **6b−d** were obtained in excellent yields starting from **6a** upon reaction with various boronic acids (Table 3, entries 1−3). However, the arylation did not proceed when 2-bromo-phenylboronic acid was applied probably because of steric hindrance (Table 3, entry 4). When 2-methylpyrimidine-4,6-diol **7a** was reacted with **2a**, the corresponding disubstituted product **7b** was obtained in 72% yield (Table 3, entry 5). However, when the thymine derivative **8a** or 6-amino-2-methylpyrimidin-4(3*H*)-one **9a** was used, the corresponding cross-coupled product was not formed, and all starting material was recovered (Table 3, entries 6 and 7). Similarly no reaction occurred when 3-methyl-1*H*-pyrazol-5(4*H*)-one was used (Table 3, entry 8).

In conclusion, we have demonstrated that 2(1*H*)-pyrazinones are good tautomerizable substrates for performing a cross-coupling protocol through PyBroP-mediated, palladium-catalyzed arylation. This efficient one-pot, two-step protocol gives access to asymmetrically substituted pyrazines, although symmetrical 2,5-disubstitution is difficult to control. We have also demonstrated the applicability of the optimized protocol for some other tautomerizable heterocycles.

Experimental Section

Typical Procedure for the Microwave-Assisted Palladium-Catalyzed Phosphonium Coupling. Synthesis of 2-Chloro-6-methoxy-3-methyl-5-*p*-tolylpyrazine, 3a (Method B). To a 10 mL oven-dried microwave vial were added pyrazinone **1a** (44 mg, 0.25 mmol), PyBroP (128 mg, 0.275 mmol), Et_3N (67 μL, 0.5 mmol), and 1,4-dioxane (2 mL). The reaction tube was sealed and irradiated at a ceiling temperature of 65 °C using 10 W maximum power for 25 min. The reaction mixture was cooled with an air flow for 3 min, and $Pd(PPh_3)_2Cl_2$ (8.8 mg, 5 mol %), boronic acid **2a** (36 mg, 0.262 mmol), Na_2CO_3 (53 mg, 0.5 mmol), and H_2O (1 mL) were successively added. The reaction tube was sealed again and irradiated at a ceiling temperature of 85 °C using 15 W maximum power for 30 min. The reaction mixture as cooled with an air flow. The mixture was washed with brine (50 mL) and extracted with dichloromethane (2 × 50 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography over silica gel using EtOAC/heptane (5:95) to afford the corresponding monosubstituted product **3a** (51 mg) in 82% yield as a light yellow solid: mp 58−60 °C. R_f = 0.47. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93−7.91 (d, J = 6.0 Hz, 2H), 7.26−7.24 (d, J = 6.0 Hz, 7H), 4.01 (s, 3H), 2.60 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 155.3,

TABLE 3. Application of the Optimized Phophonium Coupling for Some Other Heterocycles[a]

entry[a]	reactant	product	yield (%)
1	 6a	 6b	92
2	 6a	 6c	88
3	 6a	 6d	96
4	 6a	 6e	0[b]
5	 7a	 7b	72[c]
6	 8a	 8b	0[b]
7	 9a	 9b	0[b]
8	 10a	 10b	0[b]

[a]Reaction conditions: **6a−10a** (0.25 mmol, 1.0 equiv), PyBroP (0.275 mmol, 1.1 equiv), Et_3N (0.50 mmol, 2.0 equiv), 1,4-dioxane (2 mL), MW, 65 °C, 10 W, 25 min; then **2** (0.275 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), Na_2CO_3 (0.50 mmol, 2.0 equiv), H_2O (1 mL), MW, 85 °C, 15 W, 30 min. [b]No cross-coupled product was observed, and the starting material was fully recovered. According to GC-MS analysis no homocoupled boronic acid was formed during the reaction. [c]PyBroP (0.55 mmol, 2.2 equiv), Et_3N (0.50 mmol, 2.0 equiv), and **2a** (0.55 mmol, 2.2 equiv) were used.

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(10) We selected some tautomerizable heterocycles other than those described in ref 6b to evaluate the possibility of this newly developed condition.

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142.4, 141.6, 140.2, 139.4, 132.3, 129.1, 129.0, 54.5, 21.5, 20.8. HRMS (EI): calcd for $C_{13}H_{13}ON_2Cl$ 248.0716, found 248.0711.

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Supporting Information Available: Experimental procedure and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.