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Copper(II)-Mediated Cross-Coupling of Arylboronic Acids and 2(1*H*)-Pyrazinones Facilitated by Microwave Irradiation with Simultaneous Cooling

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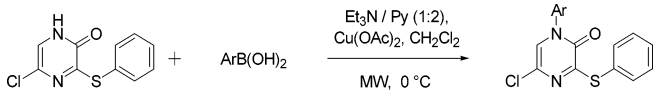
ABSTRACT



Optimized conditions for the decoration of the 2(1*H*)-pyrazinone scaffold were developed by applying the Chan–Lam protocol. It was demonstrated that this Cu(II)-mediated cross-coupling reaction resulted in significantly improved yields and rates when performed under microwave irradiation with simultaneous cooling at 0 °C, applying a mixture of bases Et_3N/pyridine.

The 2(1*H*)-pyrazinones have received considerable interest due to their valuable application as scaffolds for the generation of a diverse array of biologically interesting compound libraries. Some of the recently developed 2(1*H*)-pyrazinone-derived molecules show very promising activities as nonnucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) (Figure 1),[1] μ-opioid receptor agonists,[2] and selective tissue factor VIIa inhibitors.[3] Furthermore, the 2-azadiene system of the pyrazinone skeleton easily undergoes an inter- and intramolecular hetero-Diels−Alder reaction with acetylenes to generate a number of richly functionalized heterocyclic targets such as pyridines and pyridinones, α-carbolines and β-carbolinones, (benzo)furo/pyrano-pyridines and -pyridinones, and pyrrolopyridin(on)es and naphthyridin(on)es.[4] Diels−Alder reactions of 2(1*H*)-pyrazinones with ethylene[5] afford bicyclic products which provide access to various scaffolds of pharmaceutical interest such as β-turn mimics.[6]

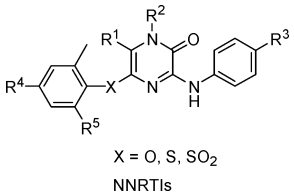


Figure 1. 2(1*H*)-Pyrazinone series with nonnucleoside HIV-1 reverse transcriptase inhibitory activity (NNRTIs).

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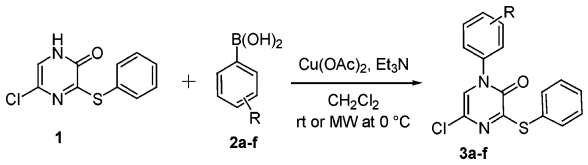
Recently, our group has developed a microwave-assisted, transition-metal-mediated decoration of the 2(1*H*)-pyrazinone scaffold in solution phase and on solid support.[7] As part of these studies toward the development of new NNRTIs (Figure 1), we started to explore the Cu(II)-mediated Chan−Lam cross-coupling reaction[8] for generating a variety of N1-arylated pyrazinones. However, we found that these reactions were rather sluggish at room temperature, affording the final compounds in moderate yields. During the course of our explorations, we observed that the rate and the yield of these couplings could be greatly improved when performed under microwave irradiation in combination with simultaneous cooling at 0 °C. In this contribution, we would like to disclose the preliminary results of our investigations.

The Chan−Lam cross-coupling classically allows Cu(II)-mediated aryl carbon−heteroatom bond formation via an oxidative coupling of arylboronic acids, stannanes, or siloxanes with amines, alcohols, or thiols and may be conducted at room temperature in air. To evaluate the decoration of the N1-position of the 2(1*H*)-pyrazinone scaffold applying the Chan−Lam protocol, we chose the coupling between pyrazinone **1**[4] and 3-(trifluoromethyl)phenylboronic acid **2a** (Table 1). Pyrazinone **1** was chosen as a model because the thiophenyl group at C3 will allow further decoration of the scaffold via substitution, after being activated by oxidation to the corresponding sulfone.[9] In a typical run, a mixture of pyrazinone **1** (0.21 mmol), boronic acid **2a** (2.0 equiv), and $Cu(OAc)_2$ (2.0 equiv) as catalyst was stirred at room temperature using Et_3N (2 equiv) as base in CH_2Cl_2, without any precaution to exclude air and moisture. The reaction was found to proceed slowly over 12 h affording the N-arylated product **3a** in a moderate yield of 33% (Table 1, entry 1). This prompted us to investigate the cross-coupling of pyrazinone **1** with a number of differently functionalized arylboronic acids **2b**−**f** under similar conditions (Table 1, entries 2−6). However, we found that the yields were not satisfactory in most cases, yielding even a mere 28% in the case of boronic acid **2d** (Table 1, entry 4). To improve the yields, we investigated the cross-coupling of pyrazinone **1** with 3-(trifluoromethyl)phenylboronic acid **2a** at elevated temperature applying conventional heating conditions as well as focused microwave irradiation (50 W maximum power). In both cases, when the reaction was carried out at 60 °C for 30 s, the same low yield of 36% was obtained. When the reaction time was increased to 2 min, the yield sharply decreased to a mere 16% under conventional heating conditions and to 19% upon microwave irradiation. Interestingly, reducing the reaction time to less than 30 s leads to incomplete conversion of pyrazinone **1**. These results clearly show that, under these reaction conditions, the product **3a** is rapidly decomposing after formation, when the reaction is run at elevated temperature.

Table 1. N-Arylation of Pyrazinone **1** with Various Boronic Acids **2a**−**f**



			yield (%)[a]	
entry	R	product **3**	rt[b]	0 °C, MW[c]
1	3-CF_3	**a**	33	69
2	3-ClPh	**b**	75	90
3	3-BrPh	**c**	36	49
4	3-EtO	**d**	28	64
5	4-MeO	**e**	44	69
6	Ph	**f**	64	87

[a] Reactions were run on a 0.21 mmol scale of pyrazinone **1** with 2.0 equiv of boronic acid, 2.0 equiv of $Cu(OAc)_2$, and 2 equiv of Et_3N in 3 mL of CH_2Cl_2. [b] rt, 12 h. [c] 0 °C, MW irradiation continuously at the maximum power of 300 W for 1 h; the temperature was measured with a fiber optic device inserted into the reaction vessel.

We therefore decided to investigate the reaction upon microwave irradiation with simultaneous cooling. As advocated in the literature,[10] this should allow for higher levels of microwave energy to be introduced into the reaction mixture, while maintaining the bulk of the material at a relatively low temperature by cooling the vial with a stream of compressed air or a microwave transparent cooling liquid. To our knowledge, only a limited number of publications dealing with this topic have appeared in the literature,[10] describing higher product yields and new pathways compared with the uncooled experiments. As high temperature seemed to be disadvantageous for our coupling, we decided to investigate the reaction upon microwave irradiation, keeping the temperature at 0 °C.[11] This should also allow us to maintain the maximum power input of 300 W during the

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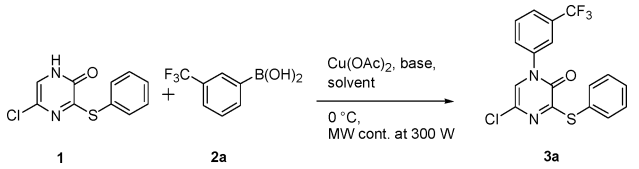
(11) Experiments were carried out in an open and cooled vial applying a dedicated CEM-Discover-Coolmate monomode microwave apparatus operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W (CEM Corporation, P.O. Box 200, Matthews, NC 28106).

full run of the irradiation. To ensure a correct temperature measurement, a fiber optic sensor was used. Using the same reagent ratios and solvent as those for the reactions run at room temperature, we performed the coupling of pyrazinone **1** with arylboronic acids **2a**−**f** upon microwave irradiation with simultaneous cooling at 0 °C (Table 1, entries 1−6). The cross-couplings proceeded smoothly, furnishing the corresponding N-arylated products in increased yields of 49−90%; this is 13−36% higher compared to the conventional reactions at room temperature. It is noteworthy that the reactions could be performed using continuously the full irradiation power of 300 W during the total run, as the high power level was needed to maintain the temperature at 0 °C because of the efficient external cooling. The differences in yield could be attributed to a lower rate of decomposition of the compounds when using simultaneous cooling.

Because the literature advocates the significance of the base in Cu(II)-mediated couplings,[12] we investigated the influence of this parameter on the outcome of the reaction. Thus, the cross-coupling of pyrazinone **1** and 3-(trifluoromethyl)phenylboronic acid **2a** was carried out under the microwave-assisted conditions with simultaneous cooling at 0 °C, switching the base from Et_3N to pyridine (Table 2, entries 1 and 4). However, no significant improvement of the yield was observed. Increasing the concentration of the pyridine had no notable effect on the yield (Table 2, entries 4−6). On the contrary a high concentration of Et_3N was found to inhibit the reaction (Table 2, entry 3). To our surprise, we found that simultaneous use of Et_3N and pyridine improved the yield significantly when an equivalent ratio of 1:2 of the respective bases was used (Table 2, entry 8). The success of this mixture of bases could probably be explained in terms of the different roles of the two bases in the mechanistic pathway of the reaction. Although Et_3N is a better base in capturing the N−H proton and thus promoting the formation of the Cu(II) complex of the substrate, pyridine could form a complex with the catayst, making it probably more efficient in the catalytic cycle. It could be reasoned that the use of the combination fulfills both aspects and therefore is a better choice in comparison with their individual use.

Table 2. Investigation of the Influence of the Base and the Solvent Applying MW + Cooling (0 °C) Conditions



1 **2a** **3a**

entry	base	equiv	solvent	yield (%)[a]
1	Et_3N	1.2	CH_2Cl_2	69
2	Et_3N	3.0	CH_2Cl_2	60
3	Et_3N	5.0	CH_2Cl_2	39
4	Py	1.2	CH_2Cl_2	70
5	Py	5.0	CH_2Cl_2	70
6	Py	10.0	CH_2Cl_2	68
7	Et_3N + Py	1 + 1	CH_2Cl_2	72
8	Et_3N + Py	1 + 2	CH_2Cl_2	93
9	Et_3N + Py	2 + 1	CH_2Cl_2	67
10	Et_3N + Py	2 + 2	CH_2Cl_2	66
11	Et_3N + Py	1 + 2	EtOH	38[b]
12	Et_3N + Py	1 + 2	MeCN	12[b]

[a] All reactions were run on a 0.21 mmol scale of pyrazinone **1** with 2.0 equiv of 3-(trifluoromethyl)phenylboronic acid **2a** and 2.0 equiv of $Cu(OAc)_2$, in 3.0 mL of the appropriate solvent, at 0 °C under MW irradiation continuously at the maximum power of 300 W for 1 h. [b] The starting material could not be completely reacted, as determined by CI−MS.

When the cross-coupling of pyrazinone **1** with boronic acid **2a** was run under conventional conditions at room temperature, using the same 1:2 mixture of Et_3N and pyridine (applying the same ratios and solvent as those for entry 8, Table 2), a yield of only 52% was obtained, which is indeed better compared to the 33% yield obtained under conventional conditions with Et_3N (2 equiv, same ratios and solvent; Table 1, entry 1) but represents a much lower yield than the 93% obtained upon microwave irradiation with simultaneous cooling at 0 °C (Table 2, entry 8). Moreover, when this reaction was tried at 0 °C without microwave irradiation, no reaction was observed. This clearly proves that the increase in yield could be ascribed not only solely to the use of a mixture of Et_3N and pyridine but also to the application of the technique of microwave irradiation with simultaneous cooling, which is most probably advantageous for the stability of the formed compound **3a**.[13]

Altering the solvent from CH_2Cl_2 to EtOH or MeCN resulted in a retardation of the reaction (Table 2, entries 11 and 12). Attempts to improve the yields by prolonging the reaction time to even 2 h were not effective.

We then explored this optimized protocol[14] for the cross-coupling of pyrazinone **1** with boronic acids **2b**−**f**. Strongly increased yields were observed ranging from 84 to 97% (Table 3, entries 2−6). To further investigate the scope and limitations of our optimized conditions, the coupling of pyrazinone **1** was investigated with the structurally and electronically diverse boronic acids **2g**−**l** (Table 3, entries 7−12). Although the reactions with the 4-phenoxy- and 2-naphthylboronic acids **2i**,**j** worked satisfactorily (Table 3,

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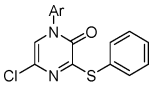
(13) A solution of **3a** (0.13 mmol) in CH_2Cl_2 (2 mL) was brought to 50 °C by conventional heating or microwave irradiation (50 W maximum power) and checked by TLC after 5 and 60 min; only starting material was found without any trace of decomposition. To a solution of **3a** (0.13 mmol) in CH_2Cl_2 (2 mL) were added all reagents as to perform the arylation according to the procedure described in footnote 14. This mixture was brought to 50 °C by conventional heating or microwave irradiation and checked by TLC after 5 and 60 min; partial decomposition of **3a** was noticed.

(14) To a suspension of pyrazinone **1** (0.05 g, 0.21 mmol) in CH_2Cl_2 (3 mL) were added boronic acid **2a**−**f**,**i**,**j** (0.42 mmol, 2 equiv), $Cu(OAc)_2$ (0.076 g, 0.42 mmol, 2 equiv), Et_3N (0.025 g, 0.25 mmol, 1 equiv), and pyridine (0.033 g, 0.84 mmol, 2 equiv). The mixture was irradiated at 0 °C continuously at the maximum power of 300 W for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel, *n*-hexane−CH_2Cl_2 (1:1)] to furnish the products **3a**−**f**,**i**,**j**.

Table 3. N-Arylation of Pyrazinone **1** Applying Optimized MW + Cooling (0 °C) Conditions



3a-l

entry	boronic acid	product	yield (%)[a]
1	3-(trifluoromethyl)phenylboronic acid **2a**	**3a**	93
2	3-chlorophenylboronic acid **2b**	**3b**	97
3	3-bromophenylboronic acid **2c**	**3c**	88
4	3-ethoxyphenylboronic acid **2d**	**3d**	84
5	4-methoxyphenylboronic acid **2e**	**3e**	89
6	phenylboronic acid **2f**	**3f**	94
7	2-bromophenylboronic acid **2g**	**3g**	traces[b]
8	2-fluorophenylboronic acid **2h**	**3h**	traces[b]
9	4-phenoxyphenylboronic acid **2i**	**3i**	83
10	2-naphthylboronic acid **2j**	**3j**	91
11	pyridine-4-boronic acid **2k**	**3k**	no reaction[c]
12	5-methylthiophene-2-boronic acid **2l**	**3l**	no reaction[c]

[a] Reactions were run on a 0.21 mmol scale of pyrazinone **1**, with 2.0 equiv of boronic acid, 2.0 equiv of $Cu(OAc)_2$, 1 equiv of Et_3N, and 2 equiv of pyridine in 3 mL of CH_2Cl_2 at 0 °C under MW irradiation continuously at the maximum power of 300 W for 1 h; the temperature was measured with a fiber optic device inserted into the reaction vessel. [b] Determined by CI−MS. [c] Starting material was recovered.

entries 9 and 10), only trace amounts of the desired compounds **3g**,**h** were observed (Table 3, entries 7 and 8). This can presumably be attributed to the steric hindrance caused by the ortho substituents present in the boronic acids **2g**,**h**. Cross-coupling of the heterocyclic boronic acids **2k**,**l** met with failure (Table 3, entries 11 and 12).

In conclusion, we have developed an optimized protocol for the decoration of the 2(1*H*)-pyrazinone scaffold at position N1 via Cu(II)-mediated cross-coupling. The reactions were performed at 0 °C upon microwave irradiation under simultaneous cooling. Even though these cross-coupling reactions furnished only moderate yields under conventional conditions at room temperature, the new protocol was found to be highly beneficial in promoting the cross-couplings as well as in preventing the decomposition of the compounds observed during heating experiments. The choice of the base seems to play an important role. The investigation of the scope and limitations of this cross-coupling protocol is under current investigation.

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Supporting Information Available: Synthesis and characterization data (^1H, ^{13}C NMR, and HRMS) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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