Palladium-catalyzed copper(I)-mediated cross-coupling of arylboronic acids and 2(1*H*)-pyrazinones facilitated by microwave irradiation with simultaneous cooling†

Brajendra Kumar Singh,[a,b] Vaibhav Pravinchandra Mehta,[a] Virinder Singh Parmar[b] and Erik Van der Eycken*[a]

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The application of a palladium-catalyzed Cu(I)-mediated Liebeskind–Srogl protocol for the decoration of the 2(1*H*)-pyrazinone scaffold resulted in significantly improved yields and rates when performed under microwave irradiation with simultaneous cooling.

Introduction

In the pursuit of lead compounds that bind to therapeutically relevant targets, several classes of pyrazinones have been investigated. Much attention has been devoted to C3-arylated pyrazinones. Some of them have been described as potent sodium channel blockers.[1] and others act as cell-adhesion inhibitors for the treatment or prevention of inflammatory diseases (Fig. 1).[2] Moreover, C3-arylated 2(1*H*)-pyrazinones are suitable precursors for the synthesis of functionalizable external β-turn mimics[3] and substance P antagonist analogues.[4] We have previously described an efficient procedure for the C3-arylation of the 3-chloro-2(1*H*)-pyrazinone scaffold applying a microwave-assisted Suzuki cross-coupling reaction of the reactive imidoyl chloride moiety.[5] In the context of generating small libraries of C3-arylated compounds, we started to investigate solid phase organic synthesis (SPOS) applying a thiophenyl linker, which could simultaneously be cleaved and substituted (traceless linking) resulting in C3-arylation of the pyrazinone scaffold, applying Liebeskind–Srogl cross-coupling conditions with suitable aryl boronic acids (Scheme 1).[6]

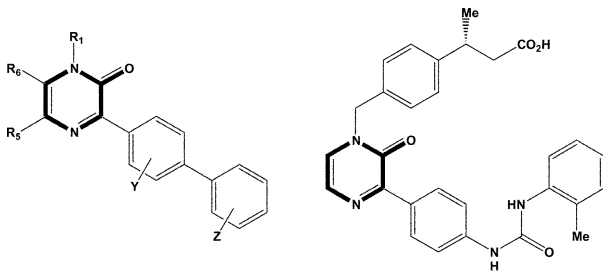
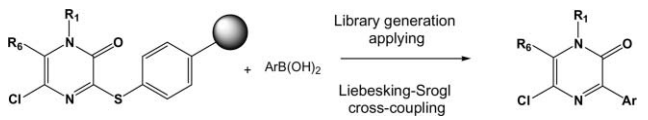


Fig. 1 Some biologically-active C3-arylated 2(1*H*)-pyrazinones.

As a proof of concept we examined this reaction in solution phase, mimicking the sulfur linker with a thiophenol substituent.



Scheme 1 Traceless linking concept using the Liebeskind–Srogl protocol.

However, we found that these reactions were rather sluggish at room temperature, affording the arylated compounds in rather moderate yields. During our investigations we discovered that both the rate as well as the yield of these cross-coupling reactions could be greatly improved when performed under microwave irradiation in combination with simultaneous cooling. Here, we would like to disclose the results of our investigations.

Results and discussion

The cross-coupling reaction according to Liebeskind–Srogl is a typical palladium-catalyzed, copper (I)-mediated, base-free coupling of a boronic acid with a π-deficient heteroaromatic thioether.[6] Normally, copper (I) thiophene-2-carboxylate (CuTC) is used in a slight excess. To evaluate the decoration of the C3-position of the 2(1*H*)-pyrazinone scaffold, we examined the cross-coupling of pyrazinone **1**{**1**} with various commercially-available boronic acids **2**{**1**–**5**}, applying this protocol. The *p*-methoxybenzyl (PMB) group in **1**{**1**} serves as a protective group for the N1-position of the pyrazinone scaffold.[7] We first investigated the reaction under conventional conditions (Table 1).

In a typical run, a mixture of pyrazinone **1**{**1**} (0.21 mmol), boronic acid **2**{**1**–**5**} (3 equiv.), $Pd(PPh_3)_4$ (5 mol%) and CuTC (2.0 equiv.) in THF was stirred at room temperature (rt). However, the reaction required several days, delivering the desired compounds **3**{**1**–**5**} in rather moderate yields ranging from 63 to 77%, along with unidentified side compounds (Table 1). Although the reaction could be sped up upon conventional heating at 65 °C, reducing the reaction time to almost one day, this did not result in any improvement of the yield (Table 1). Therefore, we decided to investigate the reaction under microwave irradiation conditions.[8] A ceiling temperature of 65 °C was used, together with a maximum power input of 200 W, keeping other conditions the same as previous experiments. Although the reaction time could be reduced tremendously, to a mere 30 min, a severe drop of the yield was observed to 51–63%, as a noticeable array of unidentified

[a]*Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001, Heverlee/Leuven, Belgium. E-mail: Erik.VanderEycken@chem.kuleuven.be; Fax: +32 (0)16 327 990; Tel: +32 (0)16 327 406*
[b]*Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi, 110 007, India*

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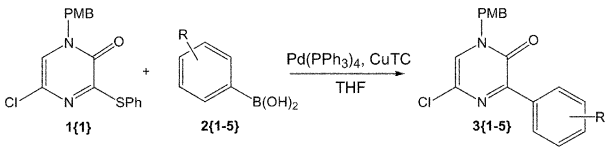
Table 1 Arylation of pyrazinone **1**{**1**} using Liebeskind–Srogl conditions[a]



2,3{1} R = 3-OEt; **2,3{2}** = 3-CF_3; **2,3{3}** R = 4-OPh; **2,3{4}** R = 4-OMe; **2,3{5}** R = H

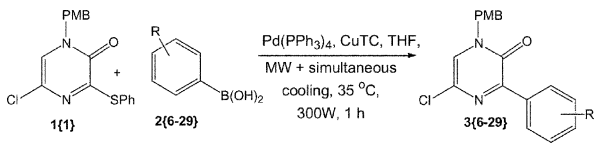
Boronic acid	Product formed	Rt yield (%); time/h	Δ*T* (65 °C) yield (%); time/h	MW[b] (65 °C, 30 min) yield (%)	MW + cooling[c] (35 °C, 1 h) yield (%)
2{**1**}	**3**{**1**}	77; 96	79; 22	62	88
2{**2**}	**3**{**2**}	70; 104	69; 27	54	83
2{**3**}	**3**{**3**}	63; 101	63; 25	51	80
2{**4**}	**3**{**4**}	74; 98	73; 26	63	90
2{**5**}	**3**{**5**}	74; 99	76; 27	61	90

[a] Reactions were run on a 0.21 mmol scale of pyrazinone **1**{**1**} with 3 equiv. of boronic acid **2**{**1**–**5**}, $Pd(PPh_3)_4$ (5 mol%) and CuTC (2.0 equiv.) in 3 mL of THF. [b] MW-Irradiation conditions at a maximum power level of 200 W. [c] Coolmate, MW-irradiation continuously at the maximum power of 300 W; the temperature was measured with a fiber-optic device inserted into the reaction vessel.

side compounds (TLC monitoring) was formed (Table 1). We have previously demonstrated that the analogous problems of copper (II) mediated cross-coupling reactions according to Chan and Lam[9] could be solved upon application of microwave irradiation with simultaneous cooling,[10] keeping the bulk of the material at a relatively low temperature by cooling the vial with a microwave-transparent cooling liquid. This should also allow the maintenance of the maximum power input of 300 W during the full run of the irradiation. We, therefore, decided to investigate the reaction upon microwave irradiation at a lower temperature with simultaneous cooling. To ensure a correct temperature measurement, a fiber optic sensor was used. However, when the reactions were run at 0, 10, 20 or 30 °C, they did not reach completion, even after irradiation for 3 × 1 h continuously at 300 W.[11] Interestingly, no side-product formation could be detected in the reaction mixture, as indicated by CI-MS. Increasing the amount of boronic acid to 8 equiv. did not alter the outcome of these reactions. Satisfactorily, we found that when the temperature was raised to 35 °C, the reaction was completed in 1 h, resulting in increased yields ranging from 80 to 90% (Table 1). Clearly, keeping the bulk of the material at a relatively low temperature of 35 °C (compared to 65 °C under microwave irradiation without simultaneous cooling), has a beneficial influence on the yield of the reaction. The reaction could not reach completion when performed under microwave irradiation at 35 °C, without simultaneous cooling. Clearly a continuous power input of 300 W is necessary to reach full conversion (see the temperature–power profile shown in the Experimental section).

Thus, having an efficient protocol at hand, we decided to investigate the scope and limitations of this microwave-assisted coupling procedure by varying the boronic acids (Table 2). The reactions proceeded well with halide-substituted boronic acids (entries 1–4, 6, 7, 9 and 11), although when a relatively large substituent is in the *ortho* position, the coupling seems to be inhibited (entries 5, 8 and 10). Analogous observations were made with a methyl substituent (entries 12–15) as well as with the electron-withdrawing ethoxycarbonyl group (entries 23–24). However, with an *ortho* fluoro substituent the reaction worked well (entries 1 and 3). Heterocyclic boronic acids, with the exception of 5-methylthiophene-2-boronic acid, did not work (entries 18–20). Good results were also obtained with 1- and 2-naphthalene boronic acid (entries 21 and 22).

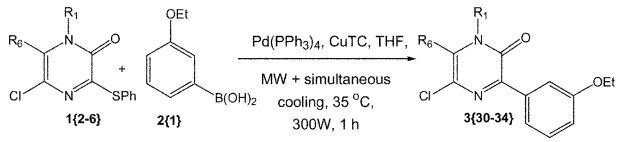
Table 2 Evaluation of the scope and limitations of the optimized procedure applying different boronic acids **2**{**6**–**29**}[a]



Entry	**3**{**6**–**29**}	R	Yield[b] (%)
1	**3**{**6**}	2-F	75
2	**3**{**7**}	3-F	76
3	**3**{**8**}	2,4-F	80
4	**3**{**9**}	3,4-F	75
5	**3**{**10**}	2-Cl	31[c,d,e]
6	**3**{**11**}	3-Cl	81
7	**3**{**12**}	4-Cl	73
8	**3**{**13**}	2,4-Cl	Traces[c,d,e]
9	**3**{**14**}	3,4-Cl	89
10	**3**{**15**}	2-Br	Traces[c,d,e]
11	**3**{**16**}	3-Br	84
12	**3**{**17**}	2-Me	28[c,d,e]
13	**3**{**18**}	3-Me	81
14	**3**{**19**}	4-Me	85
15	**3**{**20**}	3,4-Me	80
16	**3**{**21**}	4-*tert.*-Butyl	96
17	**3**{**22**}	4-CN	Traces[c,d,e]
18	**3**{**23**}	5-Methylthiophene-2-	64
19	**3**{**24**}	4-Pyridyl	Traces[c,d,e]
20	**3**{**25**}	2-Benzofuryl	Traces[c,d,e]
21	**3**{**26**}	1-Naphthyl	90
22	**3**{**27**}	2-Naphthyl	88
23	**3**{**28**}	2-COOEt	26[c,d,e]
24	**3**{**29**}	4-COOEt	90

[a] Reactions were run on a 0.21 mmol scale of pyrazinone **1**{**1**} with 3 equiv. of boronic acid, $Pd(PPh_3)_4$ (5 mol%) and CuTC (2.0 equiv.) in 3 mL of THF at 35 °C under MW-irradiation with simultaneous cooling, 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] Isolated yields. [c] Starting material was recovered. [d] Detected by CI–MS. [e] Reaction did not work under conventional heating conditions.

Table 3 Evaluation of the scope and limitations of the optimized procedure applying different 2(1*H*)-pyrazinones **1**{**2**–**6**}[a]



Entry	R_1	R_6	**3**{**30**–**34**}	Yield[b] (%)
1	C_6H_{11}	H	**3**{**30**}	90
2	$CH_2C_6H_{11}$	H	**3**{**31**}	89
3	$(CH_2)_3Ph$	H	**3**{**32**}	92
4	CH_2Ph	Me	**3**{**33**}	91
5	Me	Me	**3**{**34**}	94

[a] Reactions were run on a 0.21 mmol scale of pyrazinone **1**{**2**–**6**} with 3 equiv. of boronic acid, $Pd(PPh_3)_4$ (5 mol%) and CuTC (2.0 equiv.) in 3 mL of THF at 35 °C under MW-irradiation with simultaneous cooling, 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] Isolated yields.

Finally, we investigated the applicability of the procedure for differently substituted 2(1*H*)-pyrazinones at the N1- and C6-position (Table 3). Applying the same procedure of microwave irradiation with simultaneous cooling at 35 °C, excellent yields for all different substrates were obtained (entries 1–5).

Conclusions

In conclusion, an optimized protocol was developed for the C3-arylation of 2(1*H*)-pyrazinones, applying Liebeskind–Srogl conditions under microwave irradiation with simultaneous cooling at 35 °C. The procedure works well for boronic acids bearing no relatively large *ortho* substituent. When the reactions were performed under microwave irradiation at elevated temperature (65 °C), only moderate yields were observed. Although the couplings could be performed under conventional conditions, this required rather long reaction times and resulted in noticeably lower yields. We can conclude that the reactions clearly benefit from simultaneous cooling during microwave irradiation, most probably due to the high and sustained power input next to cooling the bulk of the material after reaction.

Experimental

General remarks

^{1}H NMR spectra were recorded on Bruker Avance 300 MHz and 400 MHz instruments, using $CDCl_3$. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150–250 °C as required. High-resolution EI-mass spectra were performed with a resolution of 10 000. The low-resolution spectra were obtained with a HP5989A MS instrument. For thin-layer chromatography, analytical TLC plates (Alugram SIL G/UV$_{254}$ and 70–230 mesh silica gel (E.M. Merck)) were used. The $Pd(PPh_3)_4$, CuTC and boronic acids were purchased from Acros Organics (Janssen Pharmaceutical, Geel) and were used without further purification. All starting pyrazinones were prepared according to a known literature procedure.[12] All compounds were fully characterised by comparison of their spectral data and melting points. Melting points of the compounds are uncorrected.

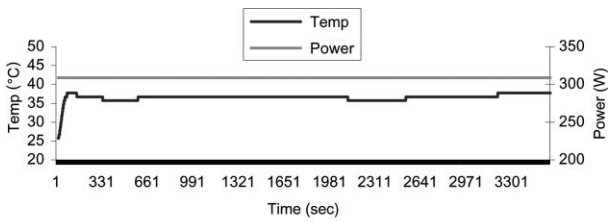
Microwave irradiation experiments

The reactions were carried out in an open 10-mL double-walled glass vial which was cooled to 35 °C using a microwave-transparent cooling liquid.[11b] The temperature of the cooling liquid was between 10 and 15 °C. Irradiation and cooling were started simultaneously, starting with the reaction mixture at rt. The temperature was measured with a fiber optic device inserted into the reaction vessel (a schematic representation of the set-up can be found at http://cemsynthesis.com/).

General procedure of Liebeskind cross-couping of pyrazinone 1 with boronic acids

Liebeskind conditions. To a suspension of pyrazinone {**1**} (0.076 g, 0.21 mmol) in THF (3 mL) were added boronic acid (0.63 mmol, 3 equiv.), $Pd(PPh_3)_4$ (5 mol%) and CuTC (2.0 equiv.). The reaction mixture was heated at 65 °C for the time indicated (Table 1). 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 (95 : 5)] to furnish the products **3**{**1**–**5**}.

Upon microwave irradiation with simultaneous cooling[11] at 35 °C. To a suspension of pyrazinone **1**{**1**–**6**} (0.076 g, 0.21 mmol) in THF (3 mL) were added boronic acid (0.63 mmol, 3 equiv.), $Pd(PPh_3)_4$ (5 mol%) and CuTC (2.0 equiv.). The mixture was irradiated continuously at 35 °C at the maximum power of 300 W for 1 h. After completion of the reaction, the solvent was removed under reduced pressure. The crude product was then absorbed on silica gel and the residue was purified by column chromatography over silica gel using *n*-hexane–CH_2Cl_2 (95 : 5) as the eluent, to give the C-3-arylated pyrazinones **3**{**1**–**34**}.



Temperature–power profile: microwave irradiation with simultaneous cooling at 35 °C for the formation of **3**{**1**}

5-Chloro-3-(3-ethoxyphenyl)-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (3{1}). It was obtained as a yellow oil in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.95 (m, 2H), 7.34–7.25 (m, 3H), 7.14 (s, 1H), 7.00–6.98 (m, 1H), 6.89–6.87 (d, 2H, J = 8.36 Hz), 5.03 (s, 2H), 4.11–4.06 (q, 2H, J = 6.9 Hz), 3.76 (s, 3H), 1.42–139 (t, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 160.13, 158.78, 154.50, 151.9, 136.19, 130.46, 129.18, 126.41, 125.32, 121.93, 117.70, 114.81, 114.72, 63.66, 55.44, 52.45, 14.92. HRMS (EI): calcd for $C_{20}H_{19}O_3N_2Cl$: 370.1084, found: 370.1071.

5-Chloro-3-(3-trifluoromethylphenyl)-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (3{2}). It was obtained as a yellow solid m.p. 107–108 °C in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.63–8.60 (m, 1H), 7.71–7.68 (m, 1H), 7.58–7.53 (m, 1H), 7.32–7.30 (d, 2H, J = 8.2 Hz), 7.23 (s, 1H), 6.93–6.90 (d, 2H, J = 9.1 Hz), 5.08 (s, 2H), 3.8 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 160.18, 154.25, 150.18, 135.50, 132.40, 121.97, 130.35, 129.03, 128.55, 126.98, 126.46, 126.08, 114.72, 114.23, 55.31, 52.49. HRMS (EI): calcd for $C_{19}H_{14}O_2N_2F_3Cl$: 394.0696, found: 394.0684.

5-Chloro-3-(4-phenoxyphenyl)-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (3{3}). It was obtained as a yellow oil in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43–8.40 (s, 1H), 7.39–7.25 (m, 4H), 7.17–7.01 (m, 6H), 6.92–6.89 (d, 2H, J = 9.12 Hz), 5.06 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 160.19, 159.86, 156.45, 154.59, 151.60, 131.41, 130.49, 129.88, 129.21, 126.66, 126.50, 124.61, 124.07, 119.74, 117.88, 114.78, 55.50, 52.51. HRMS (EI): calcd for $C_{24}H_{19}O_3N_2Cl$: 418.1084, found: 418.1081.

5-Chloro-3-(4-methoxyphenyl)-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (3{4}). It was obtained as a yellow solid m.p. 96–97 °C in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44–8.41 (d, 2H, J = 9.1 Hz), 7.30–7.27 (d, 2H, J = 8.2 Hz), 7.1 (s, 1H), 6.95–6.88 (m, 4H), 5.03 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 161.78, 160.01, 154.53, 151.60, 131.26, 130.37, 127.75, 126.53, 124.07, 114.62, 113.56, 55.41, 52.36. HRMS (EI): calcd for $C_{19}H_{17}O_3N_2Cl$: 356.0928, found: 356.0938.

5-Chloro-3-phenyl-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (3{5}). It was obtained as a yellow solid m.p. 113–114 °C in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36–8.33 (m, 2H), 7.44–7.42 (m, 3H), 7.31–7.28 (d, 2H, J = 8.2 Hz), 7.16 (s, 1H), 6.91–6.88 (d, 2H, J = 9.12 Hz), 5.04 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 160.10, 154.50, 152.24, 134.94, 130.74, 130.46, 129.37, 128.21, 126.56, 126.35, 125.22, 114.68, 55.41, 52.48. HRMS (EI): calcd for $C_{18}H_{15}O_2N_2Cl$: 326.0822, found: 326.0817.

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