Rapid Palladium-Catalyzed C3-Arylation of 2(1*H*)-Pyrazinones: Effect of Simultaneous Cooling on Microwave-Assisted Reactions on Solid Support

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Abstract: An unprecedented microwave-assisted palladium-catalyzed reaction on polymer support with simultaneous cooling has been developed. It has also been illustrated that under simultaneous cooling, certain decomposition and side reactions during the reaction, because of heating, can be minimized.

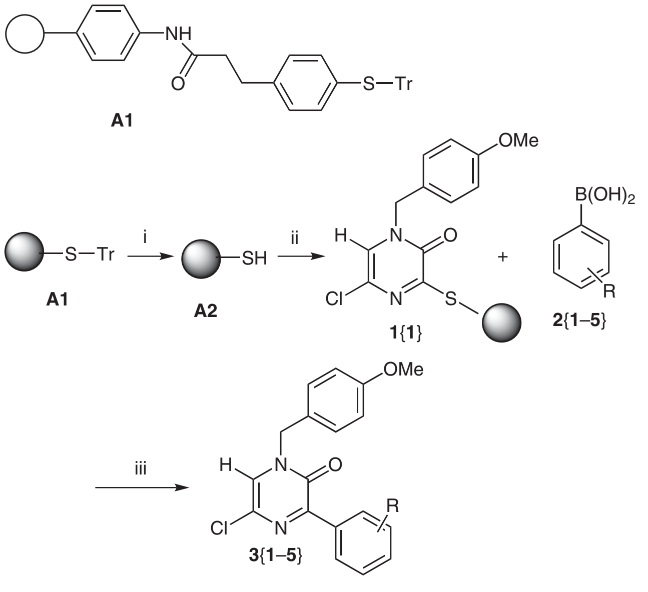
Key words: 2(1*H*)-pyrazinones, palladium catalysis, solid support, microwave, simultaneous cooling

Progress in chemical biology and medicinal chemistry relies extensively on the availability of combinatorial libraries of novel small molecules. Metal-catalyzed coupling reactions have been extensively used for the design of such libraries and have attracted much attention from both industry and academia.[1] Although it has ample been demonstrated that controlled microwave irradiation has revolutionized the art and progress of metal-catalyzed cross-coupling reactions,[2] in some cases the irradiation at high temperature has a deleterious effect on the compounds present in the reaction mixture, resulting in relatively low yields. We have previously demonstrated that simultaneous cooling during microwave irradiation could exert a beneficial effect on the stability of the compounds present in the reaction mixture resulting in increased yields.[3] However, to our knowledge, it has never been demonstrated that this cooling technique could also be used for solid-phase organic synthesis (SPOS). In continuation of our ongoing work concerning the synthesis and decoration of the 2(1*H*)-pyrazinone scaffold[4] we stipulated to pursue this technique for SPOS. In this communication, the effect of simultaneous cooling on microwave-assisted SPOS is for the first time addressed, through the study of the C3-arylation of 2(1*H*)-pyrazinones.

We have recently described the C-3 arylation of 2(1*H*)-pyrazones for the development of potent sodium-channel blockers and cell-adhesion inhibitors using the Liebeskind–Srogl coupling protocol.[5] The pyrazinone scaffold, which is coupled with the solid support via a thiophenyl linker, could be simultaneously arylated and cleaved from the resin (traceless linking) upon treatment with a suitable aryl boronic acid in the presence of copper(I) thiophene-2-carboxylate (CuTC) and palladium(0) under conventional heating at 50 °C for two days (Scheme 1). The 1-(4-methoxybenzyl)-3,5-dichloropyrazin-2(1*H*)-one (**1{1}**) was coupled with the commercially available thiophenol resin **A2** as described previously.[5] A set of commercially available boronic acids **2{1–5}** was reacted at room temperature in the presence of CuTC and $Pd(PPh_3)_4$ in dry THF according to the Liebeskind–Srogl protocol.[6] The reaction proceeded slowly and reached completion after seven days, resulting in moderate yields ranging from 32–41% (Table 1).

There was no improvement of yield when the reaction time was prolonged. Moreover, when the washed and dried resin beads, after the initial seven days of reaction, were re-subjected to stirring at the same temperature with a second number of equivalents of the required reagents, no additional amount of arylated pyrazinone could be isolated.

To improve the yields and to accelerate the reaction, the temperature was elevated to 35 °C. Although this resulted in a reduced reaction time of five days, no increase of the



{**1**} R = H, {**2**} R = 3-CF$_3$, {**3**} R = 3-OEt, {**4**} R = 4-OMe, {**5**} R = 4-*t*-Bu

Scheme 1 *Reagents and conditions*: (i) TFA–TES (95:5), r.t., 1 h; (ii) pyrazinone (4 equiv), Hünig's base (10 equiv), THF, r.t., 12 h; (iii) $(RC_6H_4)B(OH)_2$ (2 equiv), CuTC (2 equiv), $Pd(PPh_3)_4$ (6 mol%), THF (see Table 1).

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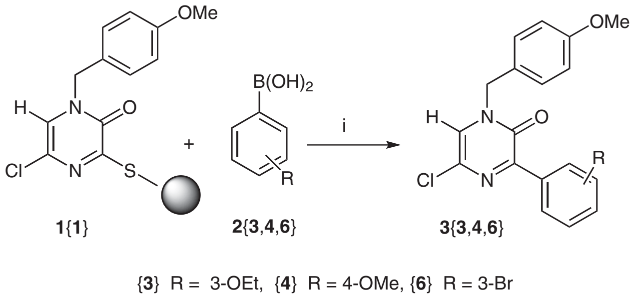
Table 1 Optimization of Parameters under Conventional Conditions

Product formed[a]	Yield (%)[b], time (d)[c]			
	r.t.	ΔT (35 °C)	ΔT (65 °C)	ΔT (80 °C)
3{1}	33, 7	31, 5	39, 2	23, 2
3{2}	37, 7	31, 5	36, 2	25, 2
3{3}	32, 7	33, 5	35, 2	21, 2
3{4}	41, 7	37, 5	38, 2	–
3{5}	36, 7	29, 5	37, 2	–

[a] All reactions were performed on a 0.176 mmol scale.

[b] Isolated yields based on the loading of trityl-protected resin **A1**; no improvement of the yield was observed upon subjecting the isolated and washed resin beads a second time to reaction with another number of equivalents of reagents.

[c] Time required for obtaining the maximum yield.



Scheme 2 *Reagents and conditions*: (i) $(RC_6H_4)B(OH)_2$ (2 equiv), CuTC (2 equiv), Pd(0) source (6 mol%; see Table 2), THF, ΔT (65 °C), 2 d.

Table 2 Screening of the Influence of Catalyst[a]

Entry	R	Catalyst	Product	Yield (%)[b]
1	3-EtO	$Pd(PPh_3)_4$	**3{3}**	35
2	4-MeO	$Pd(PPh_3)_4$	**3{4}**	38
3	3-Br	$Pd(PPh_3)_4$	**3{6}**	35
4	3-EtO	Pd_2dba_3	**3{3}**	27
5	4-MeO	Pd_2dba_3	**3{4}**	22
6	3-Br	Pd_2dba_3	**3{6}**	31
7	3-EtO	$Pd(OAc)_2$	**3{3}**	13
8	4-MeO	$Pd(OAc)_2$	**3{4}**	traces[c]
9	3-Br	$Pd(OAc)_2$	**3{6}**	23

[a] All reactions were performed on a 0.176 mmol scale.

[b] Isolated yields based on the loading of trityl-protected resin **A1**.

[c] Detected by CI-MS.

yields was obtained (Table 1). When the reaction was performed at 65 °C it reached completion in two days with a slight improvement of the yield. However, no further improvement of the yields was observed upon prolonging the reaction time or upon re-subjecting the washed and dried resin beads a second time to reaction with fresh reagents. Increasing the temperature to 80 °C resulted in strongly decreased yields. Furthermore, fall in the yields was observed when switching from THF to dioxane, MeCN, DMF, DMA, or CH_2Cl_2. Alternative catalysts as $Pd_2(dba)_3{\cdot}CHCl_3$ and $Pd(OAc)_2$ were investigated, however, the best results were obtained using 5 mol% $Pd(PPh_3)_4$ (Scheme 2, Table 2).

We then turned our attention to the investigation of this solid-support protocol applying microwave irradiation. When the reactions were performed at a ceiling temperature of 35 °C or even 50 °C using a maximum power of 250 W, no product formation was observed even after long irradiation time of two hours. As we observed that the power input was rather low, we decided to perform the next experiments that were run at 65 °C with simultaneous air cooling. This time the desired compounds could be isolated in moderate yields ranging from 27–33% (Table 3). Although these microwave-assisted reactions are much faster compared to those runs under conventional heating conditions at 65 °C (Table 1), inferior yield were obtained. When the resin was washed and dried properly after completion of the reaction and re-subjected to reaction with freshly added reagents, no additional C3-arylated pyazinone could be isolated. As the same observation was made for the reactions run under conventional heating, this clearly suggests a certain decomposition of the resin-bound pyrazinone during irradiation. Therefore we surmised that microwave irradiation at relatively low temperature with simultaneous forced liquid cooling could solve the problem.[3] This should allow to maintain the power input at the maximum level of 300 W during the

Table 3 Optimization of Microwave-Irradiation Conditions[a]

Product formed	Yield (%)[b,c]			
	MW and air cooling[d]	MW and liquid cooling[e]	MW and liquid cooling[f]	MW and liquid cooling[g]
3{1}	27	29	30	58
3{2}	33	31	33	53
3{3}	29	31	32	60
3{4}	31	35	35	63
3{5}	28	31	34	54

[a] All reactions were performed on a 0.176 mmol scale with boronic acid (3 equiv), $Pd(PPh_3)$ (5 mol%), and CuTC (2 equiv) in dry THF (5 mL) under microwave irradiation.

[b] Isolated yields based on the loading of trityl-protected resin **A1**; the compounds were purified by column chromatography on silica gel.

[c] No improvement of the yields was observed upon subjecting the isolated and washed resin beads a second time to reaction with another number of equivalents of reagents.

[d] Conditions: 65 °C, 250 W, 30 min.

[e] Conditions: 35 °C, 300 W, 1 h.

[f] Conditions: 35 °C, 300 W, 2 h.

[g] Conditions: 35 °C, 300 W, 1 + 1 h. (The resin was washed and dried properly after 1 h and subjected a second time to reaction with freshly added reagents.)

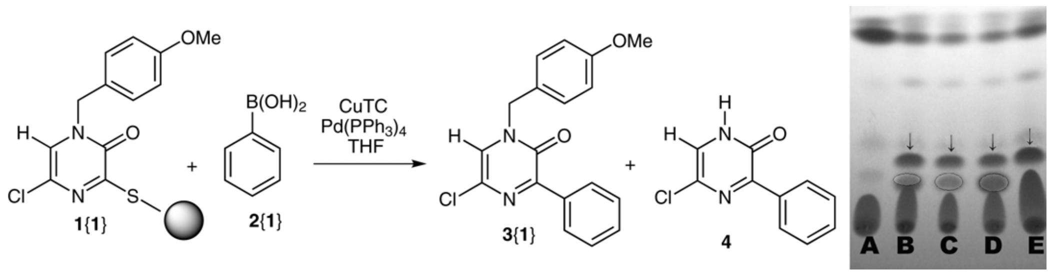


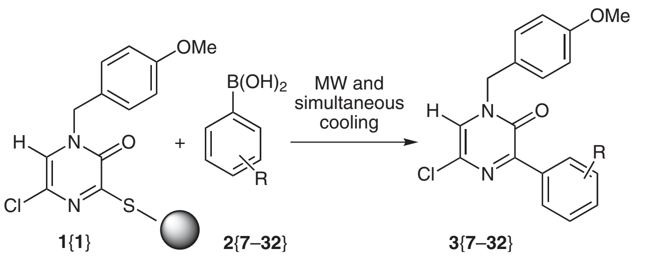
Figure 1 TLC (EtOAc–hexane, 15:85) profile of reactions run under different conditions. The spots marked by an arrow represent the desired product **3**, with the circled ones representing side product **4**. **A**: boronic acid **2** (3 equiv), Pd(PPh$_3$)$_4$ (5 mol%), CuTC (2 equiv) in anhyd THF (5 mL) without resin-bound pyrazinone under conventional heating at 65 °C for 2 d; **B**: resin-bound pyrazinone **1** (0.176 mmol), boronic acid **2** (3 equiv), Pd(PPh$_3$)$_4$, (5 mol%), CuTC (2 equiv) in anhyd THF (5 mL) under conventional condition at r.t. for 7 d; **C**: as for **B** under conventional heating at 65 °C for 2 d; **D**: as for **B** upon microwave irradiation with simultaneous air cooling at 65 °C with a maximum power of 250 W for 30 min; **E**: as for **B** upon microwave irradiation with simultaneous liquid cooling at 35 °C continuously at 300 W power for 1 h.

full run of the reaction, while keeping the bulk of material at a relatively low temperature.[7] When the reactions were run with simultaneous liquid cooling[8] at 0 °C, 10 °C, or 20 °C for one hour, no arylated pyrazinone was formed. At 30 °C only traces of the desired compounds were detected.

However, increasing the temperature to 35 °C resulted in the requested arylation after one hour of irradiation, although still with comparable moderate yields as for the microwave-assisted reactions that were run at 65 °C with air cooling (Table 3). Prolonging the irradiation time to two hours did not result in a significant increase of the yields. Interestingly TLC analysis revealed that reactions run with simultaneous liquid cooling did not show side-product formation (Figure 1). Isolation of this side compound from the reaction mixture obtained upon microwave irradiation with air cooling, yielded 11% of the N1-deprotected pyrazinone **4**, although the reason for its formation is not quite clear. We also observed that, even after a relatively long irradiation time of two hours, the color of the resin did not turn into black, as was observed in all previous cases under conventional heating as well as upon microwave irradiation without simultaneous liquid cooling. Most probably upon prolonged heating the catalyst starts to decompose while the boronic acid might undergo protodeboronation, resulting in incomplete arylation of the resin-bound pyrazinone which is thermally decomposing on the resin. However, if microwave irradiation with simultaneous liquid cooling was used, no thermal decomposition of the unreacted pyrazinone bound to the solid support takes place. Consequently, when the reaction was worked up after one hour of irradiation with simultaneous liquid cooling, and the washed and dried resin beads were brought into reaction with fresh reagents for an additional hour of microwave irradiation with simultaneous cooling, the arylated compounds could be isolated in greatly increased yields ranging from 53–63% (Table 3).

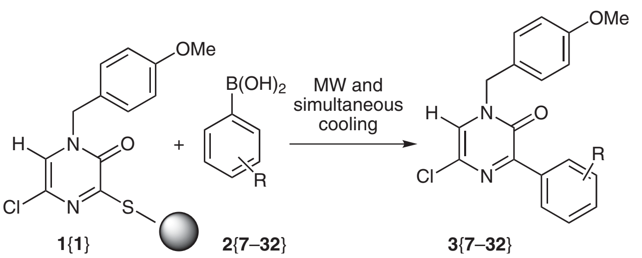
This represents an improvement of the yield with 17–25% and a reduction of the reaction time from two days to two hours, compared to the best conditions obtained under conventional heating (ΔT = 65 °C, Table 1). Clearly simultaneous liquid cooling prevents the decomposition of the resin-bound pyrazinone during prolonged irradiation.

Table 4 Scope and Limitations: Variation of the Boronic Acids[a]



Entry	R	Product	Yield (%)[b]
1	2-F	**3{7}**	58
2	3-F	**3{8}**	60
3	4-F	**3{9}**	59
4	2,4-F	**3{10}**	61
5	3,4-F	**3{11}**	54
6	2-Cl	**3{12}**	33
7	3-Cl	**3{13}**	56
8	4-Cl	**3{14}**	51
9	2,4-Cl	**3{15}**	Traces[c]
10	3,4-Cl	**3{16}**	54
11	2-Me	**3{17}**	21
12	3-Me	**3{18}**	59
13	4-Me	**3{19}**	62
14	3,4-Me	**3{20}**	57
15	3,5-Me	**3{21}**	59
16	3-NO$_2$	**3{22}**	0[d]
17	4-CN	**3{23}**	0[d]
18	2-CO$_2$Et	**3{24}**	26
19	4-CO$_2$Et	**3{25}**	61
20	2-CHO	**3{26}**	0[d]

Table 4 Scope and Limitations: Variation of the Boronic Acids[a] (continued)



Entry	R	Product	Yield (%)[b]
21	4-CHO	**3{27}**	59
22	4-OH	**3{28}**	51
23	4-CO_2H	**3{29}**	0[d]
24	4-COMe	**3{30}**	56
25	4-$NHMe_2$	**3{31}**	0[d]
26	4-$CONH_2$	**3{32}**	0[d]

[a] All reactions were performed on a 0.176 mmol scale with boronic acid (3 equiv), $Pd(PPh_3)$ (5 mol%), and CuTC (2 equiv) in dry THF (5 mL) under microwave irradiation with simultaneous cooling at 35 °C for 1 + 1 h; the resin was washed and dried properly after 1 h and re-subjected for the second time to reaction with freshly added reagents.

[b] Isolated yields based on the loading of trityl-protected resin **A1**; the compounds were purified by column chromatography on silica gel.

[c] Detected by CI-MS.

[d] After filtration of the reaction mixture, no pyrazinone-related product was detected in the filtrate.

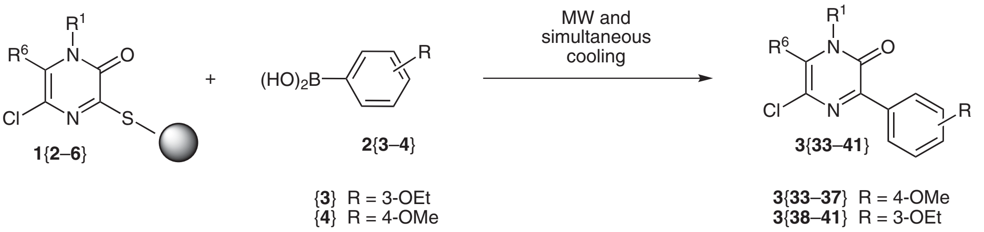
The scope and limitations of the new protocol were investigated by varying the boronic acids (Table 4). The arylation does not work well with bulky substituents in the *ortho* position of the boronic acid (entries 6, 9, 11, 18, and 20). Also a strong electron-withdrawing group as cyano in the *para* position seems to be deleterious for the reaction (entry 17).

Finally we investigated the applicability of the procedure for differently substituted 2(1*H*)-pyrazinones at the N1- and C6-position (Table 5). Applying the same conditions of microwave irradiation with simultaneous liquid cooling at 35 °C, excellent yields for all different substrates were obtained (entries 1–9).

In conclusion, we have demonstrated that the technique of microwave irradiation with simultaneous forced liquid cooling is applicable to solid-phase organic synthesis. The C3-position of the 2(1*H*)-pyrazinone scaffold could be efficiently arylated using the Liebeskind–Srogl protocol.[9] It was demonstrated that the use of microwave irradiation with simultaneous liquid cooling resulted in significantly increased yields together with dramatically shortened reaction times compared to the conventional protocols. Cooling prevents the resin-bound pyrazinone from decomposition during irradiation. The scope of this technique for SPOS is under current investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 5 Scope and Limitations: Variation of the Pyrazinone Part[a]



Entry	R^1	R^6	3{7–15}	Yield (%)[b]
1	$CH_2C_6H_{11}$	H	**3{33}**	54
2	$(CH_2)_3Ph$	H	**3{34}**	60
3	Bn	Me	**3{35}**	62
4	Me	Me	**3{36}**	63
5	C_6H_{11}	H	**3{37}**	57
6	$CH_2C_6H_{11}$	H	**3{38}**	52
7	$(CH_2)_3Ph$	H	**3{39}**	59
8	Bn	Me	**3{40}**	61
9	Me	Me	**3{41}**	60

[a] All reactions were performed on a 0.176 mmol scale with boronic acid (3 equiv), $Pd(PPh_3)$ (5 mol%), and CuTC (2 equiv) in dry THF (5 mL) under microwave irradiation with simultaneous cooling at 35 °C for 1 + 1 h; the resin was washed and dried properly after 1 h and re-subjected for the second time to reaction with freshly added reagents.

[b] Isolated yields based on the loading of trityl-protected resin **A1**; the compounds were purified by column chromatography on silica gel.

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(7) See power profile in Supporting Information.

(8) All microwave-irradiation experiments were carried out in a dedicated CEM-Discover-Coolmate monomode microwave apparatus (CEM Corporation P.O. Box 200 Matthews, NC 28106), operating at a frequency of 2.45 GHz with continuous irradiation power from 0–300 W. Reaction mixtures were efficiently stirred with a magnetic stirrer. The reactions were carried out in an open 10 mL double-walled glass vial which was cooled to 0–35 °C using a microwave transparent cooling liquid. The temperature of the cooling liquid was between 15 °C and 18 °C. Irradiation and cooling were started simultaneously, starting with the reaction mixture at r.t. The temperature was measured with a fiber-optic probe device inserted into the reaction vessel; a schematic representation of the setup can be found at http://cemsynthesis.com

(9) Experimental details and characterization data (^{1}H NMR, ^{13}C NMR, and HRMS) of all new compounds are available in the Supporting Information.