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Tunable Carbon–Carbon and Carbon–Sulfur Cross-Coupling of Boronic Acids with 3,4-Dihydropyrimidine-2-thiones

Alenka Lengar and C. Oliver Kappe*

Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

oliver.kappe@uni-graz.at

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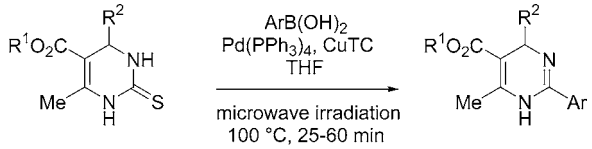
ABSTRACT



Direct microwave-assisted Pd(0)-catalyzed/Cu(I)-mediated carbon–carbon cross-coupling of 3,4-dihydropyrimidine-2-thiones and boronic acids under Liebeskind–Srogl conditions leads to 2-aryl-1,4-dihydropyrimidines in moderate to high yield. In contrast, Cu(II)-mediated reaction of the same substrates leads to carbon–sulfur cross-coupling.

Transition metal-catalyzed carbon−carbon cross-coupling procedures have revolutionized the art and practice of organic synthesis in the last two decades.[1] The generally mild reaction conditions, high functional group tolerance, and broad availability of starting materials have contributed to the growing success of, e.g., Pd-catalyzed carbon−carbon bond formation methods. Among the many different cross-coupling procedures known today, protocols involving boronic acids as coupling partners have gained momentum in recent years.[2] The large number of arylboronic acids that are commercially available makes this type of coupling chemistry highly attractive in the context of high-throughput synthesis and scaffold decoration. In addition, boronic acids are air and moisture stable and of relatively low toxicity, and the boron-derived byproducts can easily be removed from the reaction mixture. Apart from the well-known Suzuki−Miyaura biaryl cross-coupling,[3] a number of related transition metal-catalyzed C−C,[4] C−O,[5] C−S,[6] and C−N[7] coupling protocols have recently been reported in the literature, underpinning the versatility and importance of boronic acids as building blocks in organic synthesis.[2]

Recently, Liebeskind and Srogl developed a novel carbon−carbon cross-coupling protocol, involving the Pd(0)-catalyzed, Cu(I)-mediated coupling of thioether-type species with boronic acids under neutral conditions (Scheme 1).[8,9] A key feature of these protocols is the requirement of stoichiometric amounts of a Cu(I) carboxylate (e.g., Cu(I) thiophene-2-

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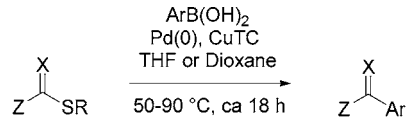
Scheme 1. Thioorganics-Boronic Acid Cross-Coupling Reactions



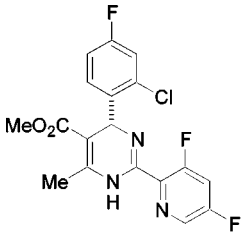
X = O, Z = C (thiol esters)
X = N, Z = C (heteroaromatics)
X = Z = N (isothioureas)

R = Me (alkyl, aryl)

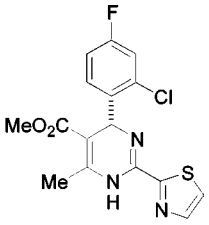
CuTC: Cu(I) thiophene-2-carboxylate

carboxylate, CuTC) as a metal cofactor. Due to the higher thiophilicity of the soft Cu(I) metal, selective sulfide coupling under Liebeskind−Srogl conditions can be performed even in the presence of, e.g., a Suzuki-active bromide.[10]

In the context of our ongoing research devoted to the generation of biologically active dihydropyrimidine scaffolds,[11] we were intrigued by the possibility of applying a thioether-boronic acid coupling strategy toward an efficient synthesis of combinatorial libraries of 2-aryl-1,4-dihydropyrimidines. This basic heterocyclic scaffold displays a range of interesting pharmacological properties. A recent highlight in this context has been the disclosure of Bay 41−4109, Bay 39−5493, and related 2-(hetero)aryl-substituted dihydropyrimidines, which are highly potent nonnucleosidic inhibitors of hepatitis B virus replication that have in vitro and in vivo antiviral activity.[12]



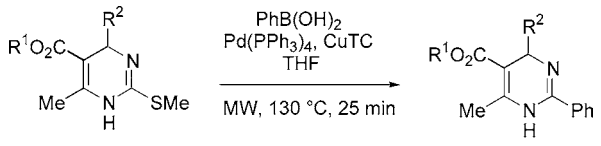
Bay 41-4109



Bay 39-5493

As a starting point in our studies we have investigated the coupling of 2-methylthio-1,4-dihydropyrimidine-5-carboxylates **1a**,**b**[13] with phenylboronic acid under standard Liebeskind−Srogl conditions (Scheme 2).[8] Refluxing a solution of the heterocycle-SMe ether **1a** with phenylboronic acid (1.25 equiv), $Pd(PPh_3)_4$ (5 mol %), and 2 equiv of CuTC in THF (Ar atmosphere) for 18 h provided the desired coupling product **2a** in 18% isolated yield. In our hands, the use of the sometimes more effective catalytic system Pd_2dba_3/tris(2-furyl)phosphine (TFP)[8−10] did not improve the yield. It has to be noted that all previously reported studies on thioether-boronic acid cross-coupling reactions have been limited to the use of either heteroaromatics or fully N-protected/substituted isothiourea systems. In fact, Liebeskind and co-workers note[8c] that couplings involving isothioureas, where, e.g., Z = NH−Boc (see Scheme 1), are troublesome and difficult to optimize, providing only low yields of the desired amidine products. Despite the disappointingly low yields in our initial experiments, we decided to increase the efficiency of the Liebeskind−Srogl-type couplings **1** → **2** further, utilizing microwave dielectric heating conditions.

Scheme 2. Microwave-Assisted Liebeskind−Srogl Couplings



1a,b

2a (82 %)
2b (86 %)

a: R^1 = Et, R^2 = Ph; **b**: R^1 = *i*-Pr, R^2 = 3-NO_2Ph

In the past few years, the utilization of controlled microwave heating in transition metal-catalyzed transformations has attracted considerable interest.[14] Many Pd-, Cu-, or Mo-catalyzed reactions that typically need hours or days to reach completion with conventional heating can sometimes be brought to full conversion in only minutes utilizing microwave heating.[14]

Applying controlled single-mode microwave heating (MW) in sealed vessels, the reaction conditions were refined with respect to the solvent, the type and concentration of the Pd(0) catalyst, the number of equivalents of the CuTC cofactor, the amount of boronic acid, and the reaction temperature and irradiation time. One of the best substrate/catalyst concentrations utilized 1.2−1.5 equiv of phenylboronic acid, 3−5 mol % $Pd(PPh_3)$, and 3.0 equiv of CuTC in THF. The cleanest conversions **1a**,**b** → **2a**,**b** (monitored by HPLC) were achieved by exposing the reaction mixtures to 130 °C for 25 min. Higher reaction temperatures resulted in more byproduct formation, while shorter reaction times led to incomplete conversions. 1,4-Dihydropyrimidines **2a** and **2b** were isolated in 82 and 86% yields, respectively, and identified by spectroscopic analysis and comparison of spectroscopic and analytical data with literature values.[15]

The above results clearly indicate the potential for enhancing sluggish Liebeskind−Srogl-type couplings (Scheme 1) by controlled microwave irradiation. Since most published examples require 16−18 h of heating under conventional reflux conditions,[8−10] the considerably shortened reaction

(9) For related, non-boronic acid couplings, see: (a) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (b) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033. (c) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803.

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(11) For reviews, see: (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (b) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 622.

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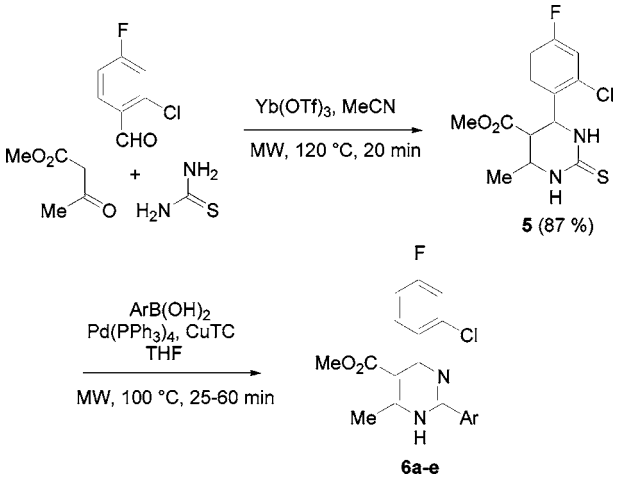
times and high yields utilizing microwave heating represent a clear improvement.

On the basis of the successful coupling of thioethers **1a**,**b** with phenylboronic acid described above, we next considered a further simplification in our strategy toward synthesizing Bay 41−4109 analogues. Dihydropyrimidine-2-thiones of type **3** (DHPMs) are readily available by Biginelli three-component condensation of aldehydes, CH-acidic carbonyl compounds, and thioureas (see also Table 1).[11,16] In the first series of test reactions, we therefore attempted to directly couple the model substrate DHPM **3a** with phenylboronic acid, employing the Pd(0)-catalyzed, Cu(I)-facilitated Liebeskind−Srogl conditions. To our great delight and surprise, this transformation proceeded without incident and furnished 1,4-dihydropyrimidine **2a** in good yields.

Table 1. Preparation of 2-Aryl-1,4-dihydropyrimidines **6** via Carbon−Carbon Coupling of DHPM **5** with Arylboronic Acids[a]



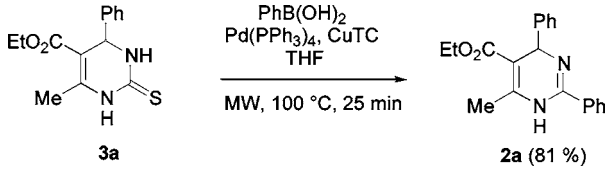
entry	$ArB(OH)_2$, Ar =	$Pd(PPh_3)_4$	time (min)	yield (%)[b]
6a	Ph	3 mol %	30	61
6b	4-ClPh	3 mol %	25	71
6c	3-MePh	5 mol %	30	82
6d	2,6-(F_2)Ph	8 mol %	60	26
6e	2-thiophene	6 mol %	50	14

[a] Reaction conditions: 1.5 equiv of $ArB(OH)_2$, 3 equiv of CuTC, THF, Ar, 100 °C controlled microwave irradiation/sealed vessel. For further details, see Supporting Information. [b] Isolated yield after flash chromatography.

Further refinement of the reaction conditions explored above (Scheme 2) demonstrated that here a reaction temperature of 100 °C (25 min) proved to be optimal. An 82% yield of **2a** was isolated from a run that utilized 1.5 equiv of phenylboronic acid, 3 mol % $Pd(PPh_3)_4$, and 3 equiv of CuTC cofactor in THF.[17] The use of Pd_2dba_3/tris(2-furyl)-phosphine (TFP)[8−10] or Pd_2dba_3/tBu$_3$P·HBF$_4$[18] did not provide a further improvement, and $Pd(OAc)_2$ (5 mol %) was significantly less effective (60% isolated product yield).

Importantly, the presence of the Cu(I) cofactor, Cu(I) thiophene-2-carboxylate (CuTC) was essential. In the absence of CuTC, product **2a** was not observed in any significant amount in the reaction mixture. Although the mechanism of the transformation **3a** → **2a** has not been investigated further, this result serves as an indication of the mechanistic similarities between the traditional Liebeskind−Srogl thioether-boronic acid couplings (Schemes 1 and 2) and the process depicted in Scheme 3. We also note that an inert atmosphere, preventing the oxidation of the Cu(I) cofactor,[8−10] was required in order to achieve high yields.

Scheme 3. Microwave-Assisted Boronic Acid-Thioamide Couplings



To the best of our knowledge, there is no literature precedent for a direct *carbon−carbon* cross-coupling of boronic acids with thioamides (or thioureas) as shown in Scheme 3. On the contrary, one may intuitively expect the corresponding 2-phenylthio-1,4-dihydropyrimidine derivative **4** (carbon−sulfur coupling) as the product from this transformation. There are several reports of related thiol/thioamide-boronic acid coupling protocols in the literature, albeit reported to be stoichiometric in Cu(II).[6,7a,19] Careful investigation of the $^1H/^{13}C$ NMR and MS data, in addition to comparison with authentic material obtained by the conventional Liebeskind−Srogl coupling (Scheme 2), unequivocally confirmed the identity of the coupling product **2a**.

For comparison purposes, the corresponding carbon−sulfur cross-coupling of DHPM **3a** with phenylboronic acid was attempted under stoichiometric Cu(II) conditions. Indeed, following a protocol recently described for 6-mercaptopurine,[7a] 2-phenylthio-1,4-dihydropyrimidine **4** was obtained in 72% isolated yield. Rapid optimization of conditions by a systematic stepwise variation of time and temperature utilizing controlled microwave irradiation led to the same compound in similar yields (79%) but considerably shorter reaction times (Scheme 4).

Having a protocol for the efficient and rapid microwave-assisted coupling of dihydropyrimidine-2-thiones **3a** with phenylboronic acid at hand,[20] we next proceeded to synthesize analogues of Bay 41−4109. The required DHPM-2-thione **5** was readily synthesized in high yield by microwave-assisted Biginelli condensation of the corresponding aldehyde,

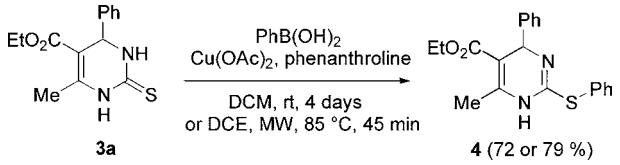
(16) For the rapid synthesis of combinatorial libraries of these heterocycles employing microwave-assisted solution-phase methods, see: Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.

(17) When the same reaction was run in an oil bath under conventional reflux conditions (ca 65 °C, reflux temperature, 18 h), the desired product **2a** was also formed but in significantly lower yield (ca. 40−50%).

(18) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(19) For a review of Cu-Mediated C−O, C−N, and C−S bond-forming reactions of the Ullmann type, see: ref 2c.

Scheme 4. Carbon−Sulfur Boronic Acid-Thioamide Coupling



CH-acidic carbonyl, and thiourea building blocks (Table 1).[16,21] Reaction of thione **5** with a small collection of diverse boronic acids using the Pd(0)/Cu(I) coupling conditions described in Table 1 resulted in the formation of the desired 2-aryl-1,4-dihydropyrimidine analogues **6a**−**e** in 14−82% yield. Although the isolated yields for 2-(hetero)aryl-dihydropyrimidines **6d** and **6e** (close analogues of Bay 41−4109 and Bay 39−5493) are low, it is clear that this two-step synthetic approach using readily available building blocks can be used for the synthesis of compound libraries after further optimization of the Liebeskind−Srogl-type coupling conditions.

In conclusion, we have demonstrated that thioether-boronic acid cross-coupling chemistry (Liebeskind−Srogl couplings) can be efficiently carried out by controlled microwave irradiation conditions. We have also discovered an unprecedented novel carbon−carbon cross-coupling reaction involving thioamides and boronic acids. Initial studies suggest a mechanistic similarity between the Pd(0)/Cu(I) Liebeskind−Srogl coupling protocols involving thioethers and boronic acid and this new method where "unprotected" thioamides are employed. Future studies will investigate the scope and limitations of this cross-coupling method.

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Supporting Information Available: Full experimental details and spectral data (NMR, MS) for all transformations and compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) **Typical Procedure for Carbon−Carbon Cross-Coupling of DHPM 3a with PhB(OH)$_2$.** To a microwave reaction vessel were added DHPM **3a** (69.1 mg, 0.25 mmol), PhB(OH)$_2$ (45.7 mg, 0.375 mmol), Cu(I) thiophene-2-carboxylate (CuTC) (142.9 mg, 0.75 mmol), and Pd(PPh$_3$)$_4$ (8.7 mg, 3.0 mol %). The vessel was flushed with Ar and sealed. Through the septum was added anhydrous THF (5 mL). The reaction vessel was irradiated at 100 °C for 25 min (Emrys Synthesiser, Personal Chemistry AB, Uppsala, Sweden). After cooling, the mixture was transferred to a round-bottom flask and adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 3:1) to yield dihydropyrimidine **2a**: ^{1}H NMR (CDCl$_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 2.5 (s, 3H), 4.12 (q, J = 7.5 Hz, 2H), 5.8 (s, 1H), 7.24−7.32 (m, 3H), 7.40−7.43 (m, 3H), 7.46 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 14.2, 29.7. 57.3, 59.9, 126.7, 127.1, 127.5, 128.5, 128.8, 131.2, 133.6, 145.0; IR (KBr) 1700, 1160, 1500 cm^{-1}; MS (pos. APCI): m/z 321 (M + 1).

(21) Dondoni, A.; Massi, A.; Sabatini, S. *Tetrahedron Lett.* **2002**, *43*, 5913.