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

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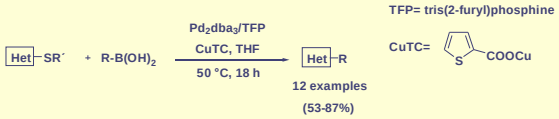
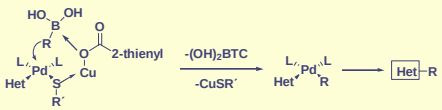
❶ Introduction

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 acid under neutral conditions[1].



A key feature of these protocols is the requirement of stoichiometric amounts of Cu(I) carboxylate as a metal cofactor[2].

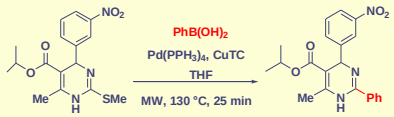
The Mechanism



Here we present a direct microwave-assisted Pd(0)-catalyzed/Cu(I)-mediated carbon-carbon cross-coupling of 3,4-dihydropyrimidine-2-thiones and 3,4-dihydropyrimidine-5-carboxylic acid thiol ester with boronic acids under Liebeskind-Srogl conditions.

[1] Liebeskind, L. S.; Srogl, J. *J.Am.Chem.Soc.* 2000, *122*, 11260; [2] Liebeskind, L. S.; Srogl, J. *Org. Lett.* 2002, *4*, 979.

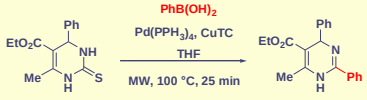
❷ Microwave-Assisted Liebeskind-Srogl Coupling



Applying controlled single-mode microwave heating, the reaction conditions were refined. The considerably shortened reaction times and high yields represent a clear improvement.

❸ Microwave-Assisted Boronic Acid-Thioamide Carbon-Carbon Coupling

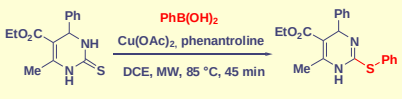
Pd(0)/Cu(I)



We attempted to directly couple dihydropyrimidine-2-thione with $PhB(OH)_2$ employing Pd(0)/Cu(I) Liebeskind-Srogl conditions. The reaction proceeded successfully in good isolated yield[3].

❹ Boronic Acid-Thioamide Carbon-Sulfur Coupling

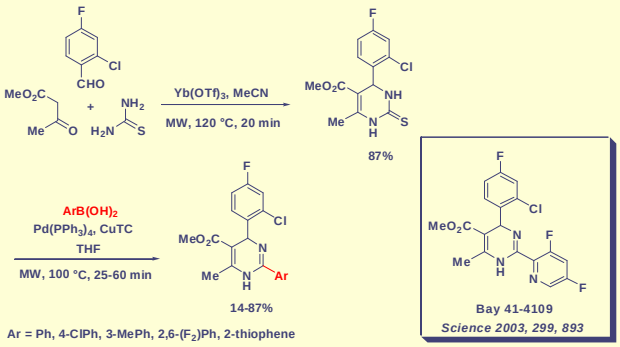
Cu(II)



For comparison, the corresponding carbon-sulfur cross-coupling of dihydropyrimidine-2-thiones with $PhB(OH)_2$ was attempted under stoichiometric Cu(II) conditions[3].

[3] Lengar, A.; Kappe, C. O. *Org.Lett.* 2004, *6*, 771.

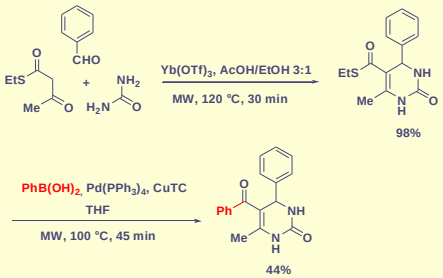
❺ Preparation of Dihydropyrimidine Libraries



In the context of our ongoing research we were intrigued by the possibility of applying a Liebeskind-Srogl type reaction toward an efficient synthesis of combinatorial libraries of 2-aryl-1,4-dihydropyrimidines. This heterocyclic scaffold displays a range of pharmacological properties. Bay 41-4109 and related 2-(hetero)aryl-substituted dihydropyrimidines are highly potent nonnucleoisidic inhibitors of hepatitis B virus replication that have in vitro and in vivo antiviral activity[4].

[4] Deres, K.; Schröder, C. H.; Paessens, A.; Goldmann, S.; Hacker, H.J.; Weber, O.; Kraemer, T.; Niewoehner, U.; Pleiss,U.; Stoltefuss, J.; Graef, E.; Koletzki, D.; Masantschek, R. N. A.; Reimann, A.; Jaeger, R.; Groß, R.; Beckermann, B.; Schlemmer, K.-H.; Haebich, D.; Rübsamen-Waigmann, H. *Science* 2003, *299*, 893.

❻ Modification at the C5 Position Using Liebeskind-Srogl couplings



The reaction of S-ethyl acetothioacetate, benzaldehyde and urea produced a new 3,4-dihydropyrimidine-5-carboxylic acid thiol ester in a high yield. This thiol ester can be applied for Liebeskind-Srogl couplings with different boronic acids. The scope and optimization of this reaction are currently under investigation.

❼ Conclusion

- thioether-boronic acid cross-coupling (Liebeskind-Srogl reaction) using microwave heating
- new C-C cross-coupling reaction involving thioamides and boronic acids
- microwave-assisted two-step synthesis of Bay 41-4109 analogs applying Biginelli multicomponent and Liebeskind-Srogl chemistry
- new possibility of the modification of dihydropyrimidine at the C5 position using Liebeskind-Srogl coupling under microwave conditions

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