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\(^1\).

The Mechanism

A key feature of these protocols is the requirement of stoichiometric amounts of Cu(1) carboxylate as a metal cofactor\(^1\).

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.

Microwave-Assisted Boronic Acid-Thioamide Carbon-Carbon Coupling

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\(^2\).

Boronic Acid-Thioamide Carbon-Sulfur Coupling

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

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 nonnucleosidic inhibitors of hepatitis B virus replication that have in vitro and in vivo antiviral activity\(^3\).

Modification at the C5 Position Using Liebeskind-Srogl couplings

The reaction of 5-ethyl acetathioacetate, 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.

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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