TUNABLE CARBON–CARBON AND CARBON–SULFUR CROSS-COUPLING OF BORONIC ACIDS WITH 3,4-DIHYDRO-PYRIMIDINE-2-THIONES

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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 [1].

In the context of our ongoing research devoted to the generation of biologically active dihydropyrimidine scaffolds, 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 basic heterocyclic scaffold displays a range of interesting pharmacological properties. A recent highlight in this context has been the disclosure of Bay 41-4109 and related 2-(hetero)aryl-substituted dihydropyrimidines, which are highly potent non-nucleosidic inhibitors of hepatitis B virus replication that have in vitro and in vivo antiviral activity [2].

Here we present a rapid, microwave-assisted two-step synthesis of Bay 41-4109 analogs applying Biginelli multicomponent and Liebeskind-Srogl chemistry. 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 addition we also present a modification of Biginelli scaffold at the C5 position via Liebeskind-Srogl chemistry, starting from the corresponding dihydropyrimidine-5-carboxylic acid thiol esters.