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Efficient One-Pot Synthesis of Dihydroquinolinones in Water at Room Temperature

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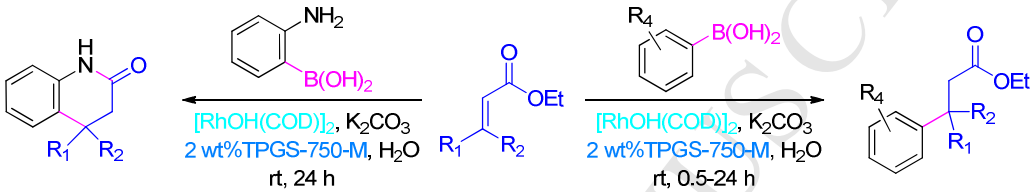
Abstract:



A mild and robust one-pot protocol for the Rh-catalyzed 1,4-addition of 2-aminoboronic acid to α,β-unsaturated esters for the efficient synthesis of dihydroquinolinones has been developed. Furthermore the addition of a variety of substituted boronic acids to diverse α,β-unsaturated esters has been investigated. The reactions proceed in water containing catalytic amounts of the commercially available designer surfactant TPGS-750-M (via the formation of nanomicelles). This mild and easy to perform process proceeds at room temperature and tolerates a wide range of functionalities.

Keywords: Rh-catalyzed 1,4-addition; Dihyroquinolinone; Micelles; Green Chemistry

1. Introduction

The dihydroquinolinone (dihydroquinolin-2-one) core structure can not only be found in a large number of natural products but also in important drug candidates. Examples shown in Figure 1 include drugs like cilostazol (**1**) (a PDE3 phosphodiesterase inhibitor for the treatment of peripheral vascular disease) and aripiprazole (**2**) (an anti-psychotic used for the treatment of schizophrenia). Natural products like the insecticidal antibiotic Yaequinolone A1 (**3**), isolated from the fungal strain *Penicillium sp.* FKI-2140,[1] and the alkaloid Trigolutesin A (**4**), isolated from *Trigonostemon lutescens*,[2] also contain the dihydroquinolinone core.

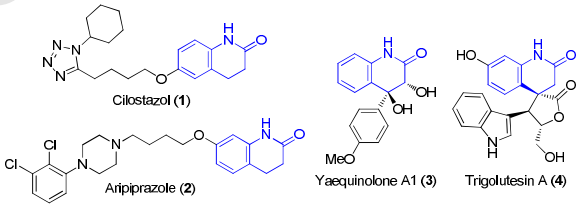


Figure 1. Drugs and natural products containing the dihydroquinolinone core.

Methods which allow efficient access to substituted dihydroquinolinones are therefore of significant interest, in particular if such a process allows high functional group tolerance. In addition to the classical Friedel-Crafts cyclization approaches,[3] several other methods for the synthesis of dihydroquinolinones have been published over the last few years, e.g. triflic acid-mediated cyclization of N-benzylcinnamanilides[4] or hypervalent iodine oxidative cyclization of aryl-methoxyamides[5] and various metal catalyzed reactions.[6-8]Alternatively, free radical cyclization of allylsulfonyl substituted N-aryl amide derivatives[9] and radical cyclization of butenyl arylhydroxamate[10] were recently disclosed. However, most of the reported reactions are either multi-step or require reaction conditions which are not suited for the synthesis of dihydroquinolinones containing sensitive functional groups. Similar limitations are described for a one-pot rhodium catalyzed 1,4-addition of