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Short communication

Copper catalyzed tandem Chan–Lam type C—N and Staudinger-phosphite N—P coupling for the synthesis of N-arylphosphoramidates

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ABSTRACT

A copper(II)-catalyzed one-pot conversion of aryl/heteroaryl boronic acids to N-aryl phosphoramidates *via* a tandem Chan–Lam and Staudinger-phosphite coupling has been reported. The method is highly efficient, economical and safe involving *in-situ* generation of organic azides. The method was successfully extended to boronic esters and potassium organotrifluoroborate salts, however, the organoboranes with B–C(sp^3) were found to be unreactive under the reaction conditions. The current method has a wide substrates scope and offers the possibility of synthesizing phosphoramidates in good yield, and notably, the mild reaction conditions used allow for potentially sensitive functionalities to be used in the developed protocol are of great importance in drug discovery.

1. Introduction

Phosphoramidates are an important class of organic compounds with widespread application in different areas of chemistry. In the sphere of medicinal chemistry, phosphoramidates have recently been used for bioconjugation of proteins to afford pharmaceutically active peptide-based protease inhibitors [1]. The phosphoramidate moiety (O=)P–NH mimics the tetrahedral transition state during amide bond hydrolysis and thus serve as surrogates for amide bonds, which makes them useful synthetic targets to evaluate different proteases for the revelation of a variety of biological processes and as the targets for the treatment of ailments like HIV [2]. Oligodeoxynucleoside phosphoramidate analogs display broad-spectrum anticancer properties and act as potent inhibitors of human immunodeficiency virus-1 (HIV-1) [3]. Phosphoramidate motifs also form important pharmacophore of many drugs molecules *e.g.*, sofosbuvir (FDA approved drug) used for the treatment of hepatitis C virus (HCV), evofosfamide (TH-302) which is in clinical evaluation for cancer treatment (Fig. 1) [4]. In addition to pharmaceutical uses, a number of phosphoramidate analogs have been used as enantioselective chiral ligands for the metal-catalyzed reactions in organic synthesis [5].

Considering their increasing interest particularly in the pharmaceutical arena, the spectacular impetus has been paid for the development of new and more efficient synthetic methods for the synthesis of phosphoramidates. The traditional and the main route for their synthesis involves the use of amines and some strategies in this context used include, (I) the reaction of amines with suitable phosphoryl halide [6], (II) reaction of amines with phosphoryl chloride generated *in situ* by halogenation of H-phosphonate with carbon tetrachloride [7], and (III) oxidation of phosphite triesters with I_2 in the presence of alkyl amines and the reduction of nitroarenes with phosphite followed by phosphorylation with trimethyl phosphite [8]. Some recent extensions and applications include the oxidative coupling of amines and H-phosphonates using Cu(I) [9], Ir(III) [10], I_2 [11] and more recently, trichloroisocyanuric acid-catalyzed synthesis of phosphoramidates has been reported [12]. All these methods involve more or less pre-functionalization–defunctionalization strategy and rely upon the use of hazardous phosphoryl halides, excess use of reagents, harsh reaction conditions and prolonged reaction time.

An alternative route for the synthesis of compounds with (O=)P–NH moiety is offered by the Staudinger reaction between trivalent phosphorus species and organic azides [13]. This route has been much explored for the bioconjugation in the chemoselective protein functionalization such as phosphorylation and site-specific pegylation of proteins to produce peptides with phosphoramidate functionality which are having important pharmacological implications when presented on therapeutic polypeptides besides improving the aqueous solubility [14,15]. Recently Chan-Evans-Lam type reaction using stoichiometric Cu(II) salt was applied for arylation of phosphinamides and phosphonamides [16]. In our previous communication, we reported the synthesis of phosphoramidates from alkyl/aryl halides and successfully

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