Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient synthesis of phosphoramidates from halides in aqueous ethanol

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ARTICLE INFO

Article history:
Received 30 March 2016
Revised 30 April 2016
Accepted 2 May 2016
Available online xxxx

Keywords:
Phosphoramidates
Menthol
Aqueous ethanol

ABSTRACT

An environment friendly and efficient synthesis of primary phosphoramidates has been developed from benzyl/allyl/alkyl/propargyl halides in aqueous ethanol as a green reaction medium via in-situ formation of azide. The method is simple, metal free and high yielding at room temperature with wide substrate scope and functional group compatibility. The optimized protocol can be used for synthesis of phosphoramidate intermediates used as prodrug moieties to improve therapeutic potential of the parent drug.

Introduction

Phosphoramidates have gained considerable interest from last few decades as they have various applications in different area of medicinal chemistry. They have been used in enantioselective Lewis base activated catalytic conversion such as Aldol and allylation reactions.[1] In addition to catalytic applications, *N*-arylphosphoramidates have been used as precursors for the synthesis of various heterocycles such as azetidines, aziridines, quinazolinediones, and imines.[2,3] Beside this, they are also used to synthesize phosphate esters in nucleotides chemistry.[4] In analytical chemistry, phosphoramidates improve ionization efficiency and suppress matrix related ion effects in MALDI-TOF mass spectrometry.[5] McGuigan and Swords (1992) reported that phosphoramidates can be used as prodrug moieties to improve therapeutic potential of the parent drug.[6] Phosphoramidates serve as surrogates for amide bond in the synthesis of peptide based protease inhibitors[7] as well as represents some key structure in a number of biologically active natural products like agrocin 84,[8] phosmidosine,[9] and GS-6620.[10] They also form important pharmacophore of many biologically potent compounds e.g., sofosbuvir (FDA approved drug) used for the treatment of hepatitis C virus (HCV),[11] evofosfamide (TH-302) which is in clinical trials for cancer treatment (Fig. 1).[12] Recently, phosphoramidates have also been used in the field of plant hormone as abscisic acid agonists that play role in plant growth regulators.[13]

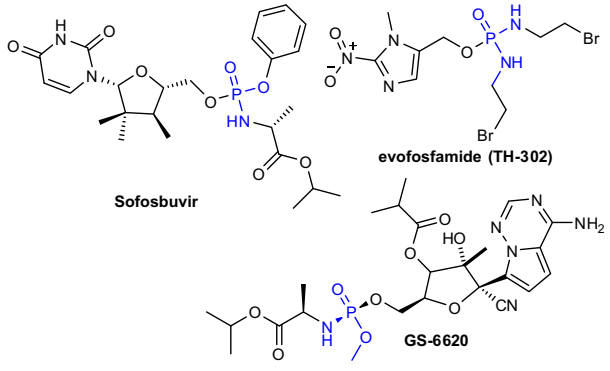

Figure 1. Some representative bioactive phosphoramidates.

Owing to their great utility and potential applications in different area of chemistry particularly in pharmaceutical arena, spectacular interest has been paid for the development of new and efficient method for the synthesis of phosphoramidates. A number of classical strategies employed for the synthesis of phosphoramidates, including (i) the reaction of amines with suitable phosphoryl halide,[10] (ii) reaction of amines with phosphoryl chloride generated in situ by halogenation of H-phosphonate with carbon tetrachloride,[14] and (iii) iodine catalyzed oxidation of phosphite triesters in the presence of excess butyl amine (250 equiv).[15] In addition to above, phosphoramidates were also synthesized through oxidative coupling of amines and H-phosphonates using Cu(I), Ir(III), and I_2 recently[16] (Scheme 1).

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http://dx.doi.org/10.1016/j.tetlet.2016.05.003
0040-4039/