Tetrahedron 66 (2010) 986–994

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using ionic liquid-phase organic synthesis (IoLiPOS) methodology

Laetitia Duchet [a], Jean Christophe Legeay [a], Daniel Carrié [a], Ludovic Paquin [a], Jean Jacques Vanden Eynde [b], Jean Pierre Bazureau [a,*]

[a] Université de Rennes 1, Laboratoire Sciences Chimiques de Rennes, UMR CNRS 6226, Groupe Ingénierie Chimique & Molécules pour le Vivant (ICMV), Bât. 10A, Campus de Beaulieu, Avenue du Général Leclerc, CS 74205, 35042 Rennes Cedex, France
[b] Université de Mons, Département de Chimie Organique, 20 Place du Parc, 7000 Mons, Belgium

ARTICLE INFO

Article history:
Received 13 October 2009
Received in revised form
16 November 2009
Accepted 18 November 2009
Available online 24 November 2009

Keywords:
Ionic liquid
Liquid phase
1,2,4-Oxadiazole
Bioisostere
O-acylamidoxime
Amidoxime

ABSTRACT

New 3,5-disubstituted 1,2,4-oxadiazoles were synthesized in five steps by ionic liquid-phase organic synthesis (IoLiPOS) methodology. The strategy involved the preparation of amidoxime from the ionic liquid-phase bound arylnitrile. Addition of various carboxylic acid to the amidoxime produced the expected 3,5-disubstituted 1,2,4-oxadiazoles via the stable *O*-acyl amidoxime intermediate grafted on the ionic liquid-phase. The 1,2,4-oxadiazoles were easily cleaved by transesterification under mild reaction conditions in high purity with good overall yields. The structures of the intermediates in each step were verified by routine spectroscopic analysis (^{1}H, ^{13}C NMR, and HRMS).

1. Introduction

Nitrogen–oxygen heterocyclic derivatives are of synthetic interest because they represent an important class of natural and non-natural products, many of which exhibit biological activities. The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) relies on from the occurrence of 1,2,4-oxadiazoles in biologically active compounds and natural compounds.[1] This motif is often used as an amide or ester bioisostere.[2] Bioisosteric replacement of the amide moiety represents an area, that is, currently a center of focus because of its implications in peptide chemistry and the development of peptidomimetics.[3] The 1,2,4-oxadiazole scaffold is also found in several drugs and drug leads[4] including the metabrotropic glutamate subtype 5 (mGlu5) receptor antagonist[5] A (Fig. 1) and the potent S1P1 agonist[6] B. Compound D showed a promising profile as a lead compound[7] for the endogenous cannabinoïd CB2 receptor. Furthermore, derivatives C and E containing 1,2,4-oxadiazole ring systems have been identified, respectively, as β-II-tryptase inhibitor[8] and serotoninergic ($5\text{-}HT_3$).[9] Moreover, the 1,2,4-oxadiazole nucleus is the core structural unit of the muscarinic agonist[10] F.

There is a continual need for the development of new technologies that enable the rapid and efficient construction of biologically interesting molecules.[11] The application of automated methods to the synthesis of focused libraries to populate screening collections is an important field of research, particularly for the biopharmaceutical sector. The use of combinatorial chemistry techniques has become common place to generate compounds for the screening and optimization tools for library generation in drug discovery.[12] Liquid-phase combinatorial synthesis[13] offers several advantages: (i) the large excess of reagents typically used in solid-supported synthesis is normally not required, (ii) the purification is possible after each step, (iii) the reactions may be realized in homogeneous solution, (iv) characterization of immobilized intermediates is also straightforward because the soluble polymer support does not interfere with spectroscopic methods. In recent years, task-specific ionic liquids (TSILs)[14] and ionic liquid-phases (ILPs)[15] —a subclass of TSILs as alternative soluble supports for liquid-phase organic synthesis of small molecules[16]— are receiving growing attention due to their tuneable features for various targeted chemical tasks and the advantages as homogeneous supports. This concept initially developed in our laboratory[17] was successfully used to a wide range of applications[18] in solution-phase combinatorial synthesis.[19] In view of the emerging importance of TSILs as alternatives to classical soluble polymeric matrices in combinatorial chemistry, our aim in this study was to develop

* Corresponding author. Fax: +33 223 236 374.
E-mail address: jean-pierre.bazureau@univ-rennes1.fr (J.P. Bazureau).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.079

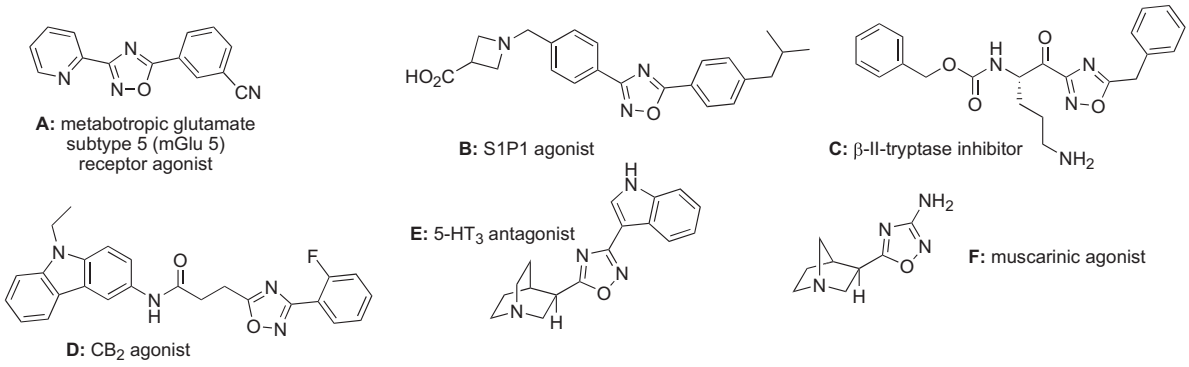


Figure 1. Selected biologically active 1,2,4-oxadiazoles.

a novel ionic liquid-phase strategy toward possible bioactive 3,5-disubstituted 1,2,4-oxadiazoles according to the 'ionic liquid-phase organic synthesis (IoLiPOS)' methodology.

2. Results and discussion

For the preparation of 1,2,4-oxadiazole scaffold, five general synthetic methods are used: (i) cyclization of the *O*-acyl amidoxime[20] formed from reaction of the amidoxime with an acyl chloride or a carboxylic acid, (ii) condensation of *N*-acylamidoximes, (iii) 1,3-dipolar cycloaddition of nitrile oxides to nitriles,[1] (iv) oxidation of 4,5-dihydro-1,2,4-oxadiazoles[21] and (v) electrocyclic ring closure of nitrenoids. For this study, the 1,2,4-oxadiazole can be built from an arylnitrile, hydroxylamine, and a carboxylic acid as building blocks. Thus, arylnitrile and hydroxylamine are converted into amidoxime (Fig. 2) and the *O*-acyl amidoxime is issued from condensation of amidoxime with a carboxylic acid.

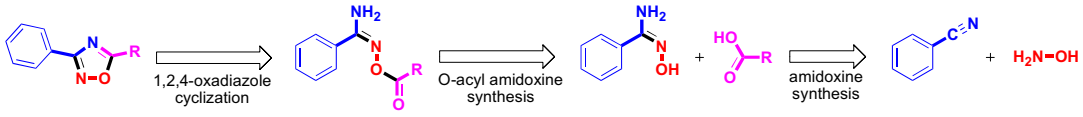
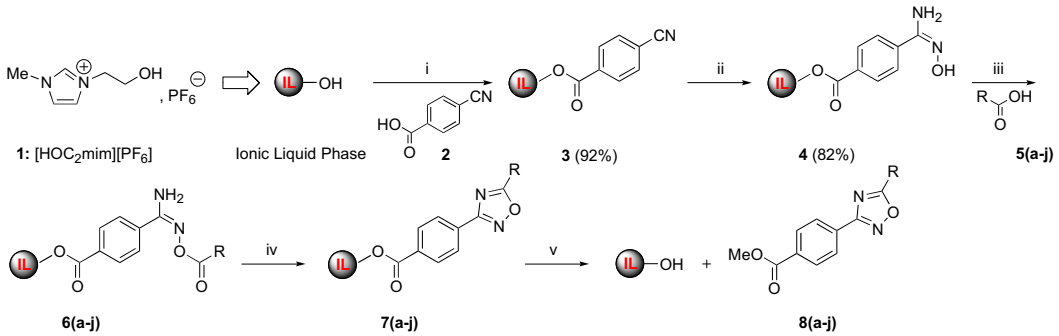


Figure 2. Retrosynthetic strategy toward 3,5-disubstituted 1,2,4-oxadiazole.

One of the common transformations in solid-phase organic synthesis (SPOS), in liquid-phase organic synthesis (LPOS) or in ionic liquid-phase organic synthesis (IoLiPOS) involves the construction of an ester linkage between solid, liquid or ionic liquid supported hydroxy or halogen functionality and carboxylic acid derivative. For this project, the carboxylic function will served as site of attachment to the ionic liquid-phase. As a suitable model reaction for ionic liquid-phase supported organic synthesis, we have chosen to use arylnitrile bound to the ionic liquid moiety (from commercial 4-cyanobenzoic acid) as novel task-specific ionic liquid. In this study, we have examined the chemical and physical properties of the 1-(2-hydroxyethyl)-3-methyl imidazolium hexafluorophosphate ([HOC_2mim][PF_6]) in IoLiPOS methodology. The starting ILP **1** used in Scheme 1, readily available from the reaction of 1-methylimidazole and 2-chloroethanol, presents a dynamic viscosity of 336 cPo at 25 °C and a solution like environment for bound molecules.

For the preparation of the starting ionic liquid-phase bound 4-cyanobenzoic acid **3**, the activation of the carboxylic group by carbodiimide still constitutes the most frequently used method. The esterification of 4-cyanobenzoic acid **2** with the ILP **1** in dry MeCN with 1.1 equiv of dicyclohexyl carbodiimide[22] (DCC) and 2% of 4-dimethylaminopyridine[23] (DMAP) as catalyst produced the functionalized ionic liquid phase **3** in 92% yield (Table 1). During the work-up, insoluble dicyclohexylurea (DCHU) was eliminated first by filtration to ensure the final purity of the new functionalized ionic liquid phase, then on a pad of Celite® to remove the residual traces of DCHU followed by evaporation of the solvent in vacuo. The crude ILP **3** was washed twice with AcOEt (1:5 w/v) and was further dried under high vacuum (10^{-2} Torr) at 25 °C for 24 h. The ILP **3** was characterized by mass spectrometry and proton NMR, confirming that in this esterification the major compound has a molecular ion corresponding to the appropriate product.

In the second step, the amidoxime **4** was obtained from the ILP bound arylnitrile **3** by treatment with hydroxylamine hydrochloride in the presence of potassium hydroxide in ethanol. As illustrated in Table 2, the reaction conditions investigated for the preparation of the amidoxime **4** are presented. Entry 1 shows with an equivalent mixture of KOH and hydroxylamine (1.5 equiv) gave



Scheme 1. Reagent and reaction conditions: (i) **2** 1.1 equiv, DCC 1.1 equiv, DMAP 2%, dry MeCN, 25 °C, 24 h. (ii) NH_2OH HCl 1.6 equiv, KOH 1.62 equiv, EtOH abs, 0 °C, 30 min, then **3** 1 equiv, reflux, 18 h. (iii) DCC 1.02 equiv, DMAP 6–8%, **5** 1.1 equiv, dry MeCN, 25 °C, 48 h. (iv) H_2O, reflux, 24 h. (v) MeONa 0.75 equiv, MeOH, reflux, 24 h.