Tetrahedron Letters 53 (2012) 4156–4160

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of dihydrobenzoimidazo[2,1-*a*]isoquinolines

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ARTICLE INFO

Article history:
Received 19 April 2012
Revised 23 May 2012
Accepted 29 May 2012
Available online 1 June 2012

Keywords:
Dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines
Metalation
Hydroamination
One-pot tandem reaction

ABSTRACT

A one-pot protocol toward several substituted 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines **1** starting with 2-allylbenzaldehydes **2** was described. The process was carried out the one-pot condensation/hydroamination reaction of substituted 2-allylbenzaldehydes **2** with 1,2-diaminobenzenes **3** in refluxing toluene in good yields. Skeleton **2** was prepared via one-pot ortho-metalative $PhBCl_2$-mediated double alkylation of hydroxybenzaldehyde **4** with LDA in moderate yields.

Introduction

Dihydroimidazoisoquinoline and its derivatives are very important compounds due to their pharmacological and biological activities.[1] For example, skeleton **A** is a potent phosphodiesterase (PDE10A) inhibitor with excellent selectivity compared to other enzymes,[2,3] and skeleton **B** has been identified as a platelet-activating factor (PAF) antagonist (Fig. 1). Functionalized benzimidazo[2,1-*a*]isoquinolines **C** are prevalent scaffolds that serve as crucial building blocks for numerous syntheses.[4–6] There are a number of processes available to generate skeleton **C**, but generally, they are described as in Figure 2: (1) $Pd(OAc)_2$-catalysed intermolecular tandem cyclization of 2-bromoarylaldehydes with terminal alkynes and 1,2-diaminobenzene under the microwave-accelerated irradiation condition,[5a] (2) CuI-catalysed the intramolecular cyclocondensation reaction of 2-bromoarylamidines with 1,2-diaminobenzene in refluxing MeCN,[5b] (3) the nucleophilic substitution of 3-fluoro-4-nitrophenol with tetrahydroisoquinoline followed by the intramolecular cyclodehydration of the resulting N-oxides with PCl_3.[5c]

While a great number of benzimidazo[2,1-*a*]isoquinolines and their derivatives with this specific substitution pattern have been developed, new methods for their preparation are needed.[6] Because the procedures are almost transition metal-mediated cyclization or microwave enhanced irradiation condition, we want to explore a one-pot method for preparing tetracyclic skeleton **1** by the treatment of 2-allylbenzaldehyde **2** with 1,2-diaminobenzene **3** via tandem condensation, followed by an intramolecular metal-free hydroamination of the corresponding benzimidazole. Metal-mediated hydroamination of alkenes with amines which had been developed, was done well.[7,8] However, there have been few investigations of the metal-free hydroamination approach.

In comparison with two excellent one-pot methods (Ohno and Yanada),[5a,6d] two major differences for preparing skeleton **1** are starting the benzaldehydes with the ortho-alkynyl group and the metal-promoted reaction condition. In previous studies, we have explored one efficient synthetic application of 2-allylbenzaldehyde to generate the tricyclic structure of 1-indanonyl oxepanes and benzodioxpanes via one-pot and facile $PhBCl_2$-mediated double alkylation of hydroxybenzaldehyde analogues with LDA in moderate yields (see Scheme 1).[9] Furthermore, we utilized the one-pot and convenient protocol to prepare the tetracyclic skeleton of 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines **1**.

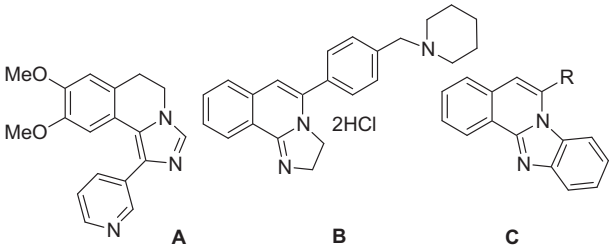

Figure 1. Structures of dihydroimidazoisoquinolines.

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http://dx.doi.org/10.1016/j.tetlet.2012.05.132

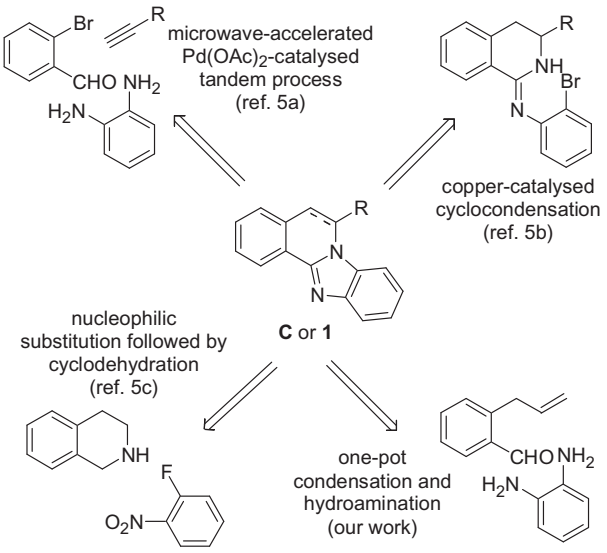
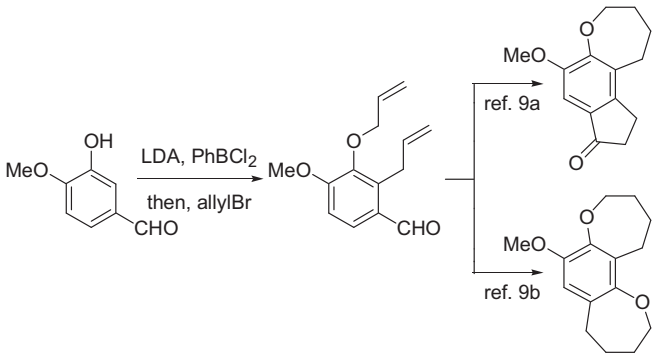
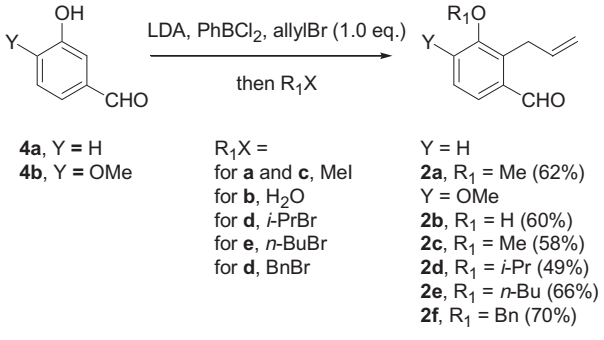


Figure 2. Synthetic strategies toward skeleton **1**.



Scheme 1. $PhBCl_2$-mediated syntheses of 1-indanonyl oxepane and benzodioxpanes.

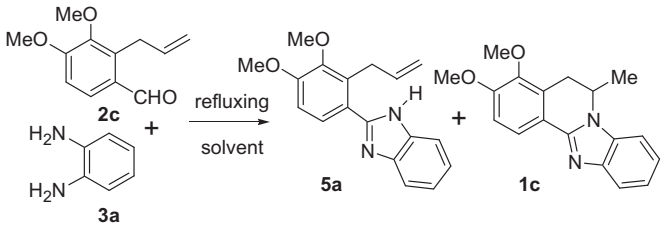


Scheme 2. Synthesis of 2-allylbenzaldehyde **2**.

Results and discussion

As the starting materials, substituted 2-allylbenzaldehydes **2a**–**2f** were prepared from commercially available 3-hydroxybenzaldehyde (**4a**) and isovanillin (**4b**) in one step, according to the known procedure with the sequence of C-allylation followed by the *O*-alkylation.[9b] As shown in Scheme 2, the treatment of **4a** or **4b** with $PhBCl_2$ and LDA afforded the dianion intermediate under the metalation condition. After the ordinal addition of allyl bromide and alkyl halide (R_1X), **2a**–**2f** were yielded with 49–70% yields.

Table 1
Reaction of compound **2c** with **3a**



Entry	Solvent (mL), temp, time (h)	**5a**/**1c**, yield[a,b] (%)
1	Toluene (5), reflux, 2	67/22
2	Toluene (1), reflux, 2	40/46
3	Toluene (1), reflux, 3	~8/75
4	Toluene (1), reflux, 4	—/88
5	DMF (1), reflux, 4	Trace/80
6	Declain (1), reflux, 4	Trace/76
7	DME (1), reflux, 4	Trace/70
8	CH_2Cl_2 (10), reflux, 6	89/—

[a] The reactions were run on a 0.5 mmol scale with **2c**.
[b] The products were >95% pure as determined by ^1H NMR analysis.

To initiate the synthetic work of skeleton **1**, one-pot condensation/hydroamination reaction of **2c** (R_1 = Me, Y = OMe) with 1,2-diaminobenzene **3a** in different solvent was examined. After screening four kinds of boiling solvents (toluene, DMF, decalin or DME), we found that **1c** was isolated with the similar yields (88%, 80%, 76% or 70%) by the reaction of **2c** (0.5 mmol) with **3a** (0.55 mmol) for 4 h. Some experimental conditions and results were shown in Table 1. Therefore, this reaction must be controlled in nearly solvent-free condition (1 mL of toluene); otherwise, benzimidazole **5a** was isolated as the major component among the product mixture (entry 1).[10] Toluene was chosen as the reaction solvent due to it possessing the appropriate boiling point and better operation convenience for the nearly solvent-free condition among these solvents. When CH_2Cl_2 was chosen as the solvent under this reaction condition, only **5a** was isolated (entry 8). Based on the above mentioned phenomenon, we envisioned that the nearly solvent-free condition should be the key factor affecting the distribution of hydroamination product. Compounds **1a**–**1r** were obtained by the domino condensation/hydroamination reaction of six substituted 2-allylbenzaldehydes **2** with three 1,2-diaminobenzenes **3** in refluxing toluene for 4 h; they are summarized in Table 2.[11]

According to the facile one-pot procedure, skeleton **1** with different functionalized group was also synthesized with 70–88% yields. In comparison with the isolated yields of products with different substituents, it was found that the skeleton **1** with hydroxyl group (entries 2, 8 and 14) or isopropyl group (entries 4, 10 and 16) was slightly poorer than the other analogues. Attempts to extend this one-pot reaction to 2-aminophenol or 2-aminobenzenethiol were unsuccessful. Only benzooxazole or benzothiazole skeleton was isolated. The formation of eighteen cycloadducts was confirmed through spectral analysis. For example, the ^1H NMR spectrum of **1c** exhibited a doublet of doublet δ 3.38 (J = 1.6, and 16.0 Hz) and 3.21 (J = 6.4 and 16.0 Hz) for the CH_2 protons. The methyl proton exhibited a singlet at δ 1.28 (J = 6.4 Hz) and the CH proton appeared a multiplet at the range of δ 4.89 and 4.82.[12] Finally, **1c** was confirmed by high resolution mass spectrometry, which showed a peak at m/z 295.1439 [M^++1]. Further, five compounds **1c**, **1i**, **1m**, **1n** and **1o** were determined by the single-crystal X-ray crystallography. Structure **1c** was shown in Figure 3.[13]