Tetrahedron xxx (2014) 1–9

Contents lists available at ScienceDirect

Tetrahedron

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

Hypervalent iodine-mediated synthesis of benzoxazoles and benzimidazoles via an oxidative rearrangement

Xiaohui Zhang [a,b], Ruofeng Huang [a,b], Jérôme Marrot [c], Vincent Coeffard [c,*], Yan Xiong [a,b,*]

[a] School of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400044, China
[b] State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China
[c] Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles-St-Quentin-en-Yvelines, 45 Avenue des États-Unis, 78035 Versailles Cedex, France

ARTICLE INFO

Article history:
Received 30 September 2014
Received in revised form 25 November 2014
Accepted 26 November 2014
Available online xxx

Keywords:
Hypervalent iodine
Benzoxazole
Benzimidazole
Rearrangement
Bioactive compound

ABSTRACT

A Beckmann-type rearrangement of *o*-hydroxy and *o*-aminoaryl N–H ketimines has been developed to prepare benzoxazoles and *N*-Ts benzimidazoles, respectively. The ketimine derivatives were easily prepared by condensation of ammonia with the corresponding ketones and (diacetoxyiodo)benzene was found to act as an efficient oxidant to trigger the [1,2]-aryl migration towards the formation of the desired heterocycles. Depending on the substitution pattern, the results revealed another mechanistic pathway through which benzisoxazoles or 1*H*-indazoles could be formed. The Beckmann-type rearrangement strategy was applied to the synthesis of benzimidazole-containing biorelevant targets such as chlormidazole and clemizole.

1. Introduction

With the preparation of the first organic hypervalent iodine species, iodobenzene dichloride ($PhICl_2$) in 1886, C. Willgerodt paved the way to what has recently evolved as a thriving field of chemistry.[1] Hypervalent iodine compounds have been developed as oxidants but they can be used as electrophilic reagents as well. These properties, combined with a non-toxic profile and an ease of handling, make hypervalent iodine reagents attractive alternatives to toxic transition metals in a wide range of organic transformations.[2] A profusion of publications that ensued from the discovery of (diacetoxyiodo)benzene (DAIB),[3] 2-iodoxybenzoic acid (IBX)[4] or Dess-Martin periodinane (DMP)[5] relied on the oxidation of various functional groups (i.e., alcohols, amine, thiols)[6] and applications in total synthesis of natural products.[7] Besides such reactivities, breakthroughs in this area have been driven by the implementation of new synthetic methodologies.[8] The electrophilic nature of the iodine atom in hypervalent iodine species associated with the leaving group ability of iodophenyl moiety have been harnessed by several research groups in synthetically interesting new directions. Within this context, oxidative rearrangement processes have been described in literature.[9] Despite great advances in this field, hypervalent iodine-mediated Beckmann rearrangement remains an unexplored territory to prepare benzoxazoles and benzimidazoles. These heterocycles are common structural units in many marketed pharmaceuticals and drug candidates.[10,11] For instance, Tafamidis is a drug marketed for the treatment of transthyretin-associated familial amyloid polyneuropathy, which is a progressive neurodegenerative disease, while Flunoxaprofen was investigated as a non-steroidal anti-inflammatory drug (Fig. 1). The benzimidazole scaffold is found in Esomeprazole and Bendamustine, which are respectively used in the treatment of gastroesophageal reflux disease and lymphocytic

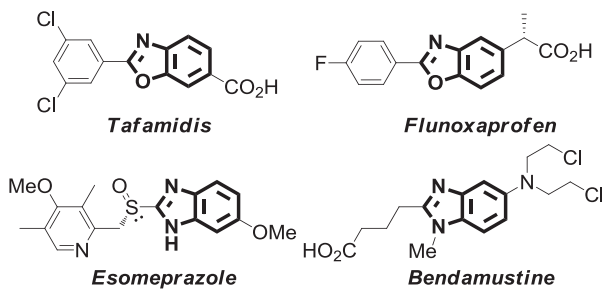


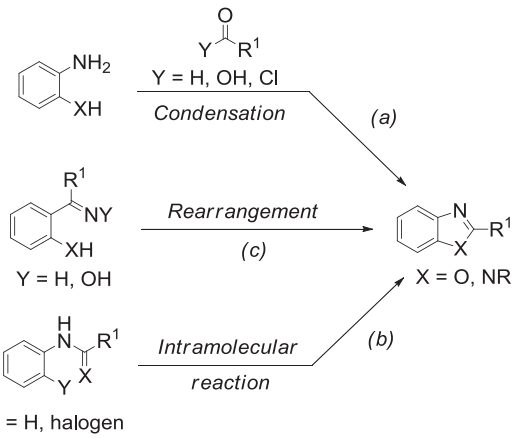
Fig. 1. Benzoxazole- and benzimidazole-containing drugs.

* Corresponding authors. Tel.: +33 139254410 (V.C.); tel.: +86 23 65111826 (Y.X.); e-mail addresses: vincent.coeffard@uvsq.fr (V. Coeffard), xiong@cqu.edu.cn (Y. Xiong).

http://dx.doi.org/10.1016/j.tet.2014.11.066
0040-4020/

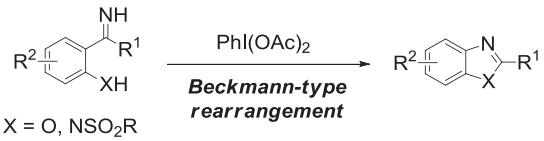
leukemia and lymphomas. Additionally, benzoxazoles and benzimidazoles are found in natural products,[12] polymers,[13] and various functional materials.[14]

The most common synthetic strategies towards the preparation of benzoxazole and benzimidazole structures lie in the condensation of *o*-aminophenols or *o*-phenylenediamines with an aldehyde or carboxylic acid derivatives (Scheme 1, route a)[15] and the intramolecular condensation of anilide or amidine derivatives under oxidative conditions (Scheme 1, route b).[16] Another strategy, which has received less attention by the academic community employs *o*-hydroxy or *o*-aminoaryl N–H ketimine derivatives (Scheme 1, route c). In the presence of various additives, these substrates undergo a Beckmann-type rearrangement to produce the corresponding benzoxazole or benzimidazole units.[17] Strong acids or harsh reaction conditions are often used to promote such rearrangements, while to the best of our knowledge, hypervalent iodine reagents have never been used to trigger the Beckmann-type rearrangement towards the formation of benzoxazole and benzimidazole motifs.



Scheme 1. Major synthetic routes towards benzoxazole and benzimidazole scaffolds.

Built upon the interesting features of hypervalent iodine reagents, we surmised that a hypervalent iodine-mediated Beckmann-type rearrangement could be the centerpiece of a strategy devoted to the synthesis of heterocyclic architectures from readily available substrates (Scheme 2). We describe herein a $PhI(OAc)_2$-mediated synthesis of benzoxazoles and benzimidazoles from the corresponding imines and the application of the methodology to the synthesis of biologically relevant targets.

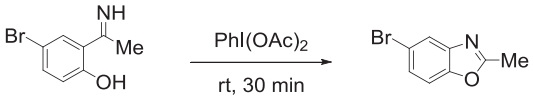


Scheme 2. Hypervalent-mediated preparation of benzoxazoles and benzimidazoles.

2. Results and discussion

We first investigated the reaction of bromo imine **1a**, readily prepared from the corresponding acetophenone derivative,[17c] in the presence of $PhI(OAc)_2$, in order to get the best reaction conditions (Table 1). The transformation of **1a** into the benzoxazole **2a** was performed at room temperature for 30 min as a model reaction. Our initial investigation concentrated on the study of the effect of the amount of $PhI(OAc)_2$ on the yield (entries 1–5). The best result was obtained by performing the reaction in MeOH with 1.5 equiv of $PhI(OAc)_2$.

Table 1
Optimization of the rearrangement of **1a** into **2a**[a]

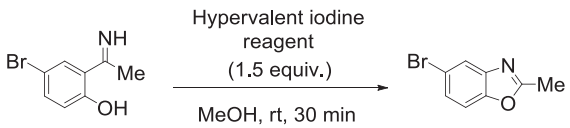


1a **2a**

Entry	$PhI(OAc)_2$ (equiv)	Solvent	Yield %[b]
1	1.1	MeOH	77%
2	1.3	MeOH	81%
3	1.5	MeOH	82%
4	1.7	MeOH	75%
5	2.0	MeOH	78%
6	1.5	EtOH	80%
7	1.5	*i*-PrOH	78%
8	1.5	MeOH:H_2O (1:1)	70%
9	1.5	Et_2O	43%
10	1.5	THF	50%
11	1.5	1,4-Dioxane	45%
12	1.5	CH_2Cl_2	55%
13	1.5	$CHCl_3$	54%
14	1.5	CH_3CN	66%
15	1.5	EtOAc	47%
16	1.5	Toluene	66%

[a] Reaction conditions: **1a** (1 mmol), $PhI(OAc)_2$ (see table), solvent (2 mL) for 30 min at room temperature.
[b] Isolated yield of **2a**.

Under these conditions, the benzoxazole **2a** was obtained in 82% yield. To study the effect of the medium, various solvents were tested. Alcoholic solvents gave high yields even in the presence of water (entries 6–8) while the use of ethereal or halogenated solvents led to a decrease in reactivity (entries 9–13). Acetonitrile, ethyl acetate and toluene enabled the formation of **2a** in yields ranging from 47 to 66% (entries 14–16). Therefore, methanol turned out to be the best solvent for the Beckmann-type rearrangement (entry 3). This result is in agreement with previous studies about Beckmann rearrangement, which showed that the rate of reaction was increased by using solvents with high dielectric constants.[18] Various hypervalent iodine reagents were then evaluated in order to study their influence on the reaction outcome (Scheme 3). The reaction of **1a** with $PhI(OAc)_2$ or PhIO afforded the benzoxazole **2a** in good yields while no reaction took place by mixing **1a** with the Koser's reagent [PhI(OH)(OTs)] or with $PhI(OTf)_2$. It is worthwhile noting that the use of a catalytic amount of iodobenzene in conjunction with *m*-chloroperbenzoic acid as a stoichiometric terminal oxidant did not allow the synthesis of **2a**. Under these conditions, only degradation products from **1a** were observed.



1a **2a**

$PhI(OAc)_2$, 82%
PhIO, 76%
PhI(OH)(OTs), no reaction
$PhI(OTf)_2$, no reaction

Scheme 3. Influence of the hypervalent iodine reagent.

The release of acetic acid (vide infra) during the course of the reaction prompted us to investigate the influence of acid and basic additives in the Beckmann-type rearrangement of **1a** in MeOH at room temperature for 30 min using 1.5 equiv of $PhI(OAc)_2$ (Table 2).

Treatment of **1a** with a mixture of $PhI(OAc)_2$ and different amounts of AcOH led to similar levels of yields for **2a** while the addition of trifluoroacetic acid in the reaction medium had