Tetrahedron 71 (2015) 3351–3358

Contents lists available at ScienceDirect

Tetrahedron

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

Oxidative photochemical cyclization of ethyl 3-(indol-3-yl)-3-oxo-2-phenylpropanoate derivatives: synthesis of benzo[*a*]carbazoles

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ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form 18 March 2015
Accepted 27 March 2015
Available online 2 April 2015

Keywords:
Photocyclization
Benzo[*a*]carbazole
Ethyl 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanoates
Ullmann–Hurtley reaction

ABSTRACT

6-Ethoxycarbonyl-5-hydroxy-benzo[*a*]carbazoles were prepared from ethyl 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanoates in two steps: the first step involved α-arylation of the indicated starting materials via Ullmann–Hurtley reaction; in the key second step, the thus formed coupling products underwent oxidative photocyclization to afford the benzo[*a*]carbazole ring. The present photocyclization features the use of $CuBr_2$ to prompt the transformations, which could not be realized under the conventional conditions.

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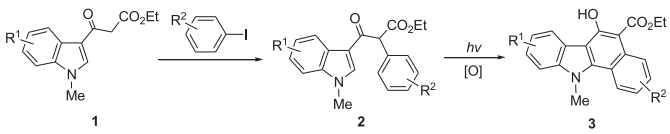
1. Introduction

Benzo-annulated carbazole ring systems are attractive synthetic targets due to their important pharmacological properties[1] as well as their wide-ranging usefulness in material science.[2] In this regard, many methodologies based on various cyclization and cycloaddition reactions have been developed to gain access to these structural moieties in diverse substitution patterns.[3,4] As a continuation of our interest in the synthesis of benzocarbazoles,[5] herein we wish to report a new synthetic route towards benzo[*a*]carbazoles, which is outlined in Scheme 1.



Scheme 1. Designed synthetic route to benzo[*a*]carbazole ring system.

Our synthesis of benzo[*a*]carbazoles **3** was designed to start from the readily available compound **1**,[6,7] which was expected to be converted to **3** in two steps: the first step involves the α-arylation of compound **1** to afford **2**; the latter serves as the precursor for the second key oxidative photocyclization step. We employed the Ullmann–Hurtley reaction to realize the α-arylation of **1**.

2. Results and discussion

Copper-catalyzed Ullmann type reactions have recently emerged to prominence although they have already been known for over a century.[8] The development of new efficient catalytic systems has greatly expanded the scope and practical usage of this methodology in the coupling of C(aryl)–C, C(aryl) –N, C(aryl) –O and C(aryl) –S bonds. In this context, many studies have been reported recently on applying the Ullmann–Hurtley reaction to the α-arylation of carbonyl compounds.[9,10] On the basis of these studies, we chose the most commonly used CuI as catalyst, and examined some typical reaction conditions for their efficacy on the reaction of **1** with aryl iodides. Our results indicated that using 2-picolinic acid (PA) as ligand and dioxane as solvent, the expected coupling took place most effectively.[11] As such, variously substituted compounds **2** were prepared as illustrated in Scheme 2. However, there are several compounds, which were unable to be obtained by the indicated procedure (Fig. 1).

Following the preparation of compounds **2**, attempt was then made to explore conditions for the next key photochemical cyclization step. Oxidative photochemical cyclization of conjugated arylolefins and related compounds constitutes a powerful means for the synthesis of polycyclic aromatic compounds.[12] In general, the reactions are carried out in the presence of an oxidant, with iodine and oxygen being most commonly used, to fulfill the aromatization

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http://dx.doi.org/10.1016/j.tet.2015.03.107
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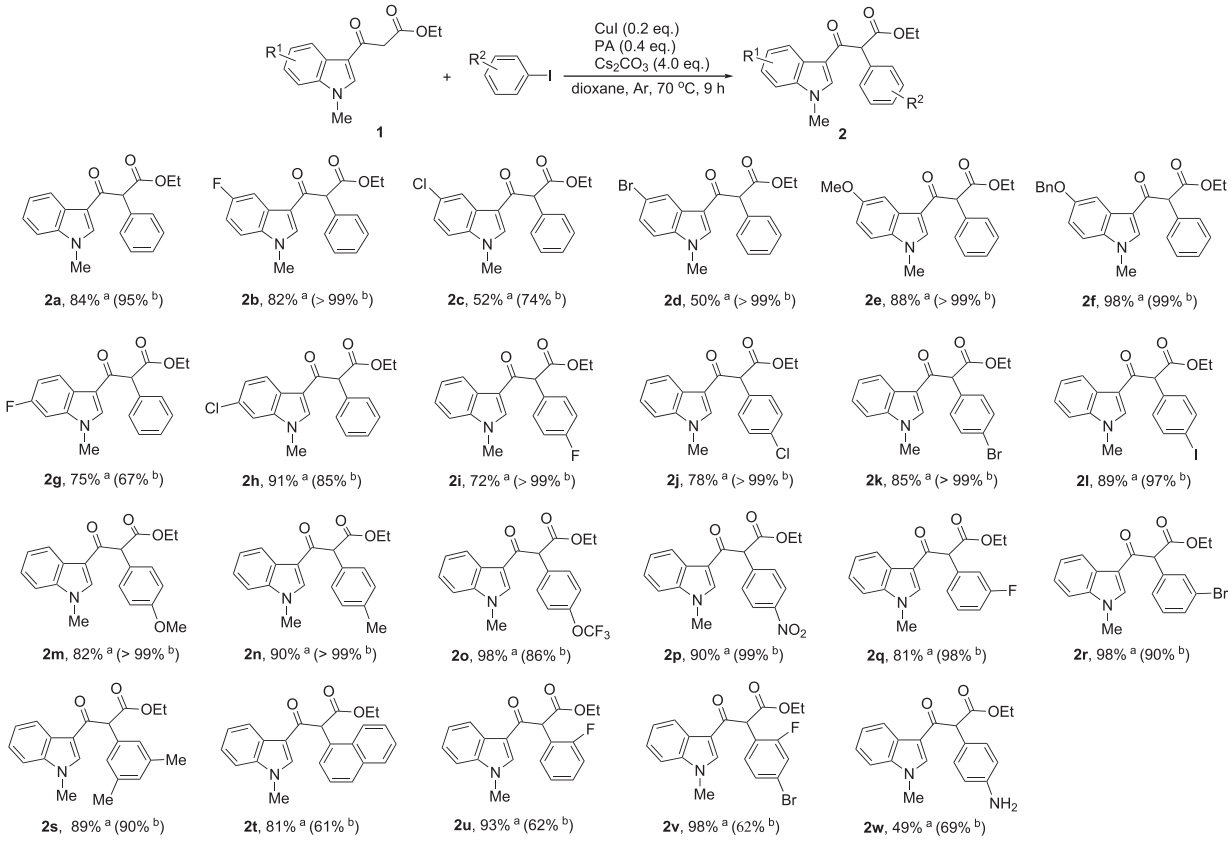

Footnote: [a] Isolated yield based on the consumed reactant. [b] conversion of **2**. The reaction was carried out on 1.0 mmol scale.

Scheme 2. Synthesis of compounds **2** via Ullmann–Hurtley reaction.

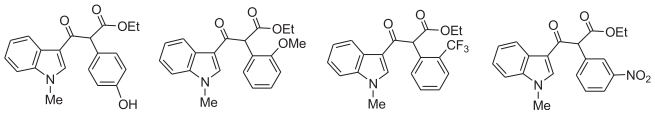

Fig. 1. Compounds inaccessible with the standard protocol.

after the cyclization step. The reactions realized in this way, referred to as the Mallory reaction, are widely employed to prepare polycyclic aromatic hydrocarbons, and their applications to the synthesis of fused heterocyclic compounds are also well documented.[13,14] For example, Snieckus et al.[15] and others[16] have applied this photocyclization protocol to the synthesis of benzocarbazoles. Protti et al. recently reported a synthetic route to benzo[*a*]carbazoles via domino elimination/photocyclization of 2-aryl-3-(1-tosylalkyl)indoles.[4l] Despite these investigations, however, the use of this methodology to the cyclization of 1,3-diaryl substituted carbonyl compounds like **2** has not been reported. We hoped that through this synthetic study, the scope of this methodology could be further expanded.

To achieve this goal, we firstly chose **2a** as the model compound, and subjected it to the standard Mallory reaction conditions[12d] with a medium-pressure (500W) mercury lamp as the light source (Table 1, entry 1). However, the desired reaction did not take place, with only **2a** being recovered after longtime irradiation. Using $PhI(OAc)_2$ as oxidant[17] in place of iodine could not effect the reaction either (Table 1, entry 2). We assumed that for the reaction to take place, a catalyst might be required to prompt **2a** to tautomerize to its enolate form. So the irradiation was next conducted in the presence of 2.0 equiv of $BF_3 \cdot OEt_2$. However, The desired reaction did not happen by this treatment (Table 1, entry 3).

Despite this initial failure, we continued with our exploration by employing copper salts to prompt the reaction. We expected that copper could play a dual role during the reaction (Scheme 3): Firstly, it would facilitate the tautomerization by binding with the carbonyl group; secondly, copper(II) could act as oxidant for the oxidative aromatization, Indeed, when 1.0 equiv of $CuBr_2$ was used as oxidant, compound **3a** was generated in moderate yield in THF after irradiation for 10 h (Table 1, entry 5). The yield and conversion were remarkably increased by (1) using a mixed solvent of THF and toluene (4:1), (2) raising the amount of $CuBr_2$ to 1.5 equiv, and (3) extending the irradiation time to 24 h (Table 1, entry 10). Control dark experiment indicated that the reaction actually involves a photo-induced cyclization process (Table 1, entry 12). The reaction also took place in the presence of $CuPF_6$ (Table 1, entry 4), but other copper salts such as $CuCl_2$, $Cu(OAc)_2$, CuBr and CuTc (Copper(I) thiophene-2-carboxylate) were ineffective. Besides copper salts, several other commonly used transition metal oxidants were also tested, and these results are also listed in Table 1 (entries 13–16).

The optimized conditions (Table 1, entry 10), were then applied to the aforementioned compounds **2b**–**2w** to examine the scope of this methodology. The results are shown in Table 2. It turned out that substituents at both the indole phenyl ring and α-benzene ring exerted a big influence on the conversion and yield of **3**. The most prominent features of the substituent effect are: (1) the presence of a fluoro atom can greatly facilitate the cyclization process, but when it was at the *ortho*-position of α-phenyl ring, the fluoro atom was eliminated during the reaction (Table 2, entries 21 and 22), with **3a** being formed exclusively; (2) the bromine and iodine atoms were eliminated wherever they were located (Table 2, entries 4,11,12,18 and 22). Control experiment showed that for these

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