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NIS-TBHP promoted oxidative coupling of C—N and C—O bonds: A metal-free approach to polysubstituted oxazoles

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ABSTRACT

A metal-free approach to polysubstituted oxazoles *via* the oxidative coupling of readily available benzylamines and 1,3-dicarbonyl derivatives in the presence of an external base has been developed. A variety of functional groups on both of the starting materials are tolerated using this method, affording the corresponding oxazoles in moderate to good yields. Iodination was proposed as the initiation step of the reaction and a plausible mechanism has been proposed to explain the reaction pathway.

Introduction

Oxazoles are one of the most widely found motifs in biologically active compounds, synthetic intermediates, and pharmaceuticals [1]. In particular, 2,5-disubstituted and 2,4,5-trisubstituted oxazoles are found in numerous natural products and pharmacologically active compounds such as the antimycobacterial natural product texaline [2], the antipancreatic cancer agent PC-046 [3], and the antidiabetic agent AD-5061 [4] (Fig. 1). Therefore, continuing efforts have been devoted to the development of concise and efficient methods for the construction of substituted oxazoles. There are three typical methods for the preparation of oxazoles: the cyclization of acyclic precursors [5], the coupling of prefunctionalized oxazoles with organometallic reagents [6], and the oxidation of oxazolines [7]. However, the development of single step reactions which proceed with operational simplicity for the synthesis of oxazoles from readily available starting materials is still of great demand.

A copper catalysed oxidative system was utilized by Wang's group [8] and Chen's group [9] for the preparation of polysubstituted oxazoles from benzylamines and β-diketone derivatives (Scheme 1a). Yuan and co-workers reported an alternative electrochemical procedure which does not require any transition metal catalyst or oxidant compared with the traditional thermo-chemical methods (Scheme 1b) [10]. Xie and co-workers reported a Bu_4NI/TBHP promoted system in which the hypoiodite or iodite anion plays an important role for the assembly of oxazoles (Scheme 1c) [11]. Herein, we report the NIS (*N*-iodosuccinimide)-TBHP (*tert*-butyl hydroperoxide) promoted oxidative reaction of benzylamines and 1,3-dicarbonyl derivatives in the presence of an external base for the synthesis of oxazoles (Scheme 1d).

The model coupling reaction of benzylamine **1a** and ethyl 3-oxo-3-phenylpropanoate **2a** was performed for the optimization study (Table 1). The combination of NIS, TBHP and Na_2CO_3 in DMA (dimethylacetamide) at 50 °C for 16 h afforded the highest yield (85%) of the desired product **3aa** (Entry 1). No reaction occurred in the absence of NIS (Entry 2). The yield dropped to 32% without the addition of TBHP (Entry 3). An external base Na_2CO_3 increased the yield from 72% to 85% (Entry 4). When the amount of NIS or TBHP was increased, the yield decreased (Entries 5–6). The addition of iodine instead of NIS gave product **3aa** in only 62% yield (Entry 7). When tetrabutylammonium iodide replaced NIS in this reaction, the yield dropped to 36% (Entry 8). Besides TBHP, DTBP (di-*tert*-butyl peroxide) was also tested as an oxidant, but the yield decreased dramatically to 25% (Entry 9). Other external bases such as Li_2CO_3 and K_2CO_3 gave lower yields than Na_2CO_3 (Entries 10–11). Screening of other solvents such as DMSO (dimethyl sulfoxide), DCE (dichloroethane), MeCN (acetonitrile), THF (tetrahydrofuran) and EtOAc (ethyl acetate) indicated that

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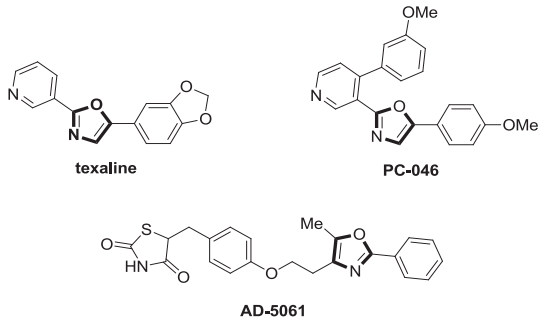
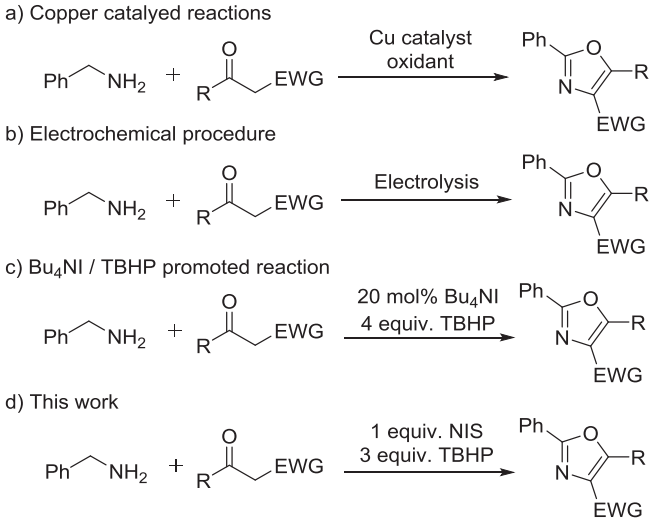


Fig 1. Bioactive oxazole derivatives.



Scheme 1. Selected annulation approaches to multisubstituted oxazoles.

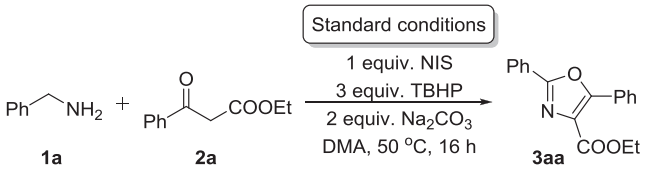
the best solvent was DMA (Entries 12–16). Finally, the reaction temperature was optimized and the results showed running the reaction at 50 °C gave the highest yield of product **3aa** (Entries 17–18).

With the optimal reaction conditions in hand, we extended the substrate scope with respect to the benzylamine (Scheme 2). (4-Ethoxyphenyl)methanamine and naphthalen-1-ylmethanamine gave the desired products **3ab** in 77% yield and **3ac** in 70% yield, respectively. A steric effect was observed with *para*-substituted product **3ad** (73%), *meta*-substituted product **3ae** (64%) and *ortho*-substituted product **3af** (62%). Inductive electron-withdrawing groups such as fluoro, chloro and bromo were tolerated in this reaction (**3ag** 76%, **3ah** 69% and **3ai** 81%). Conjugative electron-withdrawing groups such as cyano and methyl carboxylate also gave the corresponding products **3aj** in 55% yield and **3ak** in 54% yield, respectively. In addition to the phenyl ring, thiophene- and furan-containing products could also be obtained in 74–87% yield (**3al**, **3am** and **3an**).

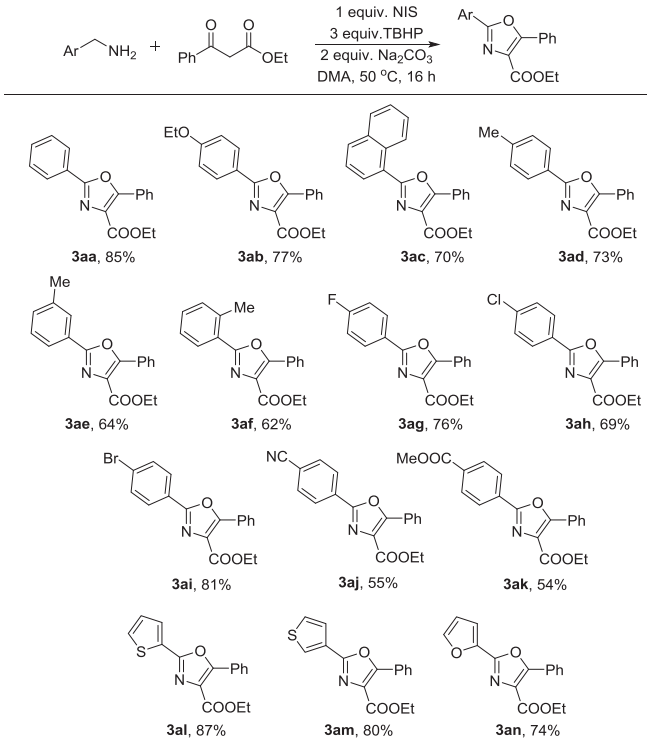
Next 1,3-dicarbonyl derivatives with different aryl and alkyl substituents were investigated as shown in Scheme 3. 1,3-Dicarbonyl derivatives with electron-withdrawing groups such as -CF_3, -Br, -Cl, and -F on the phenyl ring gave the desired products in 48–68% yield. Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-3-oxopropanoate with an electron-donating group gave the expected product **3bg** in 47% yield. Other β-ketoesters with heterocycles such as tetrahydrofuran, *N*-methyl pyrrole, pyridine, thiophene and furan were also suitable substrates. Furthermore, 1,3-dicarbonyl derivatives such as ethyl 3-oxobutanoate, ethyl 4,4-dimethyl-3-oxopentanoate and pentane-2,4-dione were compatible and gave the corresponding products in 64–80% yield.

A control experiment was performed to determine the possible reaction pathway. Ethyl 3-oxo-3-phenylpropanoate (**2a**) was converted to ethyl 2-iodo-3-oxo-3-phenylpropanoate (**4a**) in 95% yield in the presence of 1.1 equiv. NIS.[12] When intermediate **4a** was subjected to the reaction conditions (without the addition of NIS), the desired product **3aa** was isolated in 83% yield (Scheme 4). These results suggested that the first step of this transformation

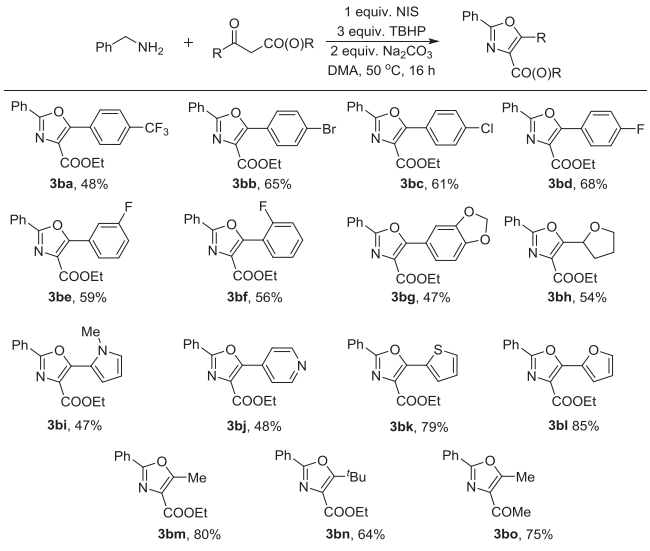
Table 1
Optimization of the reaction conditions.[a] [a] Reagents and conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), NIS (0.2 mmol), TBHP (0.6 mmol), Na_2CO_3 (0.4 mmol), DMA (2 mL), 50 °C, 16 h. Isolated yield.



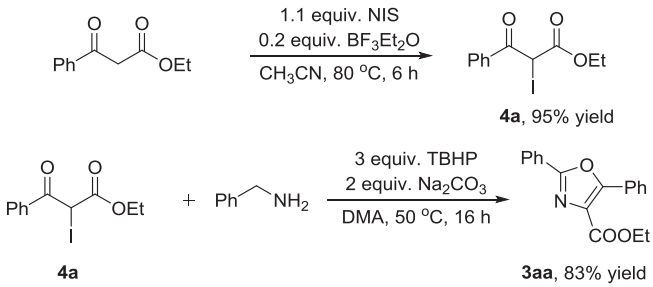
Entry	Deviation from the standard conditions	Yield **3aa** (%)
1	No change	85
2	Without NIS	0
3	Without TBHP	32
4	Without Na_2CO_3	72
5	2 equiv. NIS	53
6	5 equiv. TBHP	69
7	I_2 instead of NIS	62
8	Bu_4NI instead of NIS	36
9	DTBP instead of TBHP	25
10	Li_2CO_3 instead of Na_2CO_3	68
11	K_2CO_3 instead of Na_2CO_3	27
12	DMSO instead of DMA	61
13	DCE instead of DMA	37
14	MeCN instead of DMA	54
15	THF instead of DMA	0
16	EtOAc instead of DMA	45
17	30 °C instead of 50 °C	56
18	70 °C instead of 50 °C	75



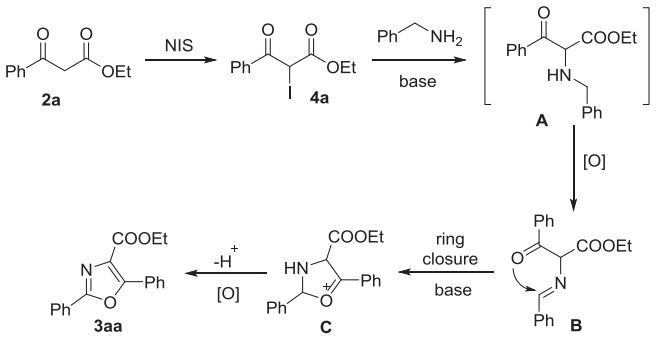
Scheme 2. Scope of the amines for the synthesis of oxazoles.



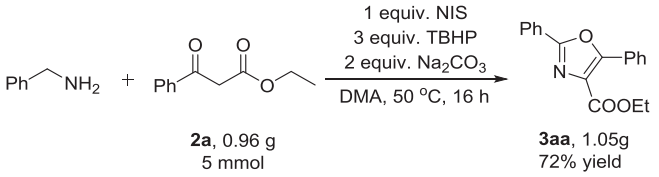
Scheme 3. Scope of the 1,3-dicarbonyls for the synthesis of oxazoles.



Scheme 4. Control experiment.



Scheme 5. Plausible mechanism.



Scheme 6. Gram-scale synthesis.

could be the iodination process. Based on the above results and previous reports,[13] a plausible mechanism has been proposed in Scheme 5. Firstly, the NIS-mediated iodination process forms **4a**, which undergoes coupling with benzylamine in the presence of base to generate intermediate **A**. Further oxidation gives imine intermediate **B**. In the presence of base, cyclization generates intermediate **C**, which undergoes deprotonation and dehydrogenative aromatization to give the final product **3aa**.

A gram-scale reaction was performed to demonstrate the practicality of our protocol. The reaction of benzylamine with ethyl 3-oxo-3-phenylpropanoate (**2a**) on a 5 mmol scale using the optimized conditions provided the oxazole product **3aa** in 72% yield (Scheme 6).

In summary, we have developed a metal-free approach to 2,4,5-trisubstituted oxazoles *via* NIS-TBHP promoted oxidative coupling in the presence of an external base using readily available starting materials. This facile and efficient protocol tolerates a variety of functional groups on the 1,3-dicarbonyl derivatives. Further investigations and the application of this methodology to other useful heterocycles are currently ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151846. These data include MOL files and InChiKeys of the most important compounds described in this article.

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