

2-Oxo Driven Unconventional reactions: Microwave Assisted Approaches to Tetrahydrofuro[3,2-*d*]oxazoles and Furanones

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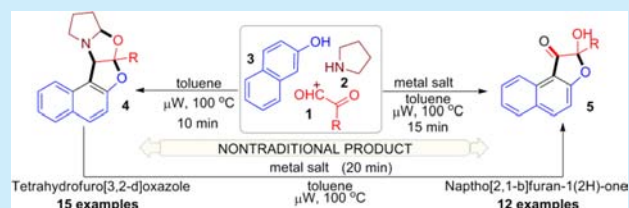
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S Supporting Information

ABSTRACT: A highly efficient, novel, microwave-assisted, metal-free, diastereoselective synthesis of tetrahydrofuro[3,2-*d*]oxazole is disclosed. The synthesis of naphthoxazoles is achieved for the first time without the aid of an external catalyst. On the contrary, our reactions generated naphthofuranones when treated in the presence of metals in microwave/thermal conditions. The unusual behavior of our reactions has further been explored in the generation of furanones from tetrahydrofuro[3,2-*d*]oxazole through the use of metals.



In several cases, the aldehyde group of 2-Oxoaldehydes (OA) has shown a difference in reactivity in comparison to normal aldehydes. This unusual behavior of OA is possibly due to the existence of an electron-withdrawing ketone group that promotes the reactivity of the aldehyde.¹ Even though reactions through an aldehyde group of OA with different nucleophiles are well understood in diverse ways, the direct role of the α -carbonyl group toward cyclization reactions with various nucleophiles in the presence of a secondary amine is not well explored. Our continued interest to unravel the unusual behavior of OA has helped to explore a few novel concepts that can find applications in diverse directions. Recently, we established an unprecedented reactivity of OA toward various nucleophiles in the presence of a secondary amine as a catalyst.^{1c} In addition to the basic concept, we developed the mildest possible methods for α -ketoamides.^{1d} On the basis of recent findings regarding the iminium ion and literature precedent, we developed a novel, mild, metal-free method for tetrahydrofuro[3,2-*d*]oxazole. In addition, we successfully established the unusual behavior of the same reaction in the presence of a metal that resulted in generation of naphthofuranones under microwave/thermal conditions. On basis of the latter method, we established the first report for the direct conversion of tetrahydrofuro[3,2-*d*]oxazole to furanones through the use of metals (Scheme 1).

Fused oxazole in general and tetrahydrofuro[3,2-*d*]oxazole in particular represent a diverse set of natural products,² modified sugar derivatives, and important bioactive molecules. The synthesis of some rare sugars and antisense oligonucleotides has also been achieved by exploiting the tetrahydrofuro[3,2-*d*]oxazole motif as a versatile biomimetic synthetic precursor.³ In literature, these structures have been explored as prodrugs of caspase inhibitors with apoptotic-regulating activity (Figure 1).⁴ As a result, different groups worldwide are interested in the

Scheme 1. Summary of this Work

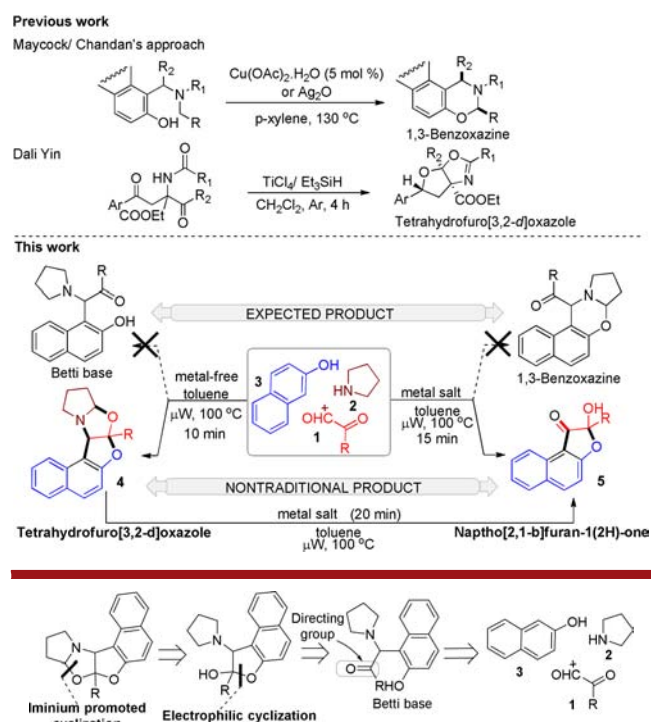


Figure 1. Retrosynthetic strategy for tetrahydrofuro[3,2-*d*]oxazoles.

synthesis of such a skeleton from simple starting materials in a sustainable and atom-economical fashion.⁵ Herein, we primarily

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report a novel synthetic strategy for tetrahydrofuro[3,2-*d*]oxazole **4** through a Betti base as an intermediate. A general approach for **4** is proposed, taking advantage of recent developments in chemistry regarding 2-oxoaldehydes, wherein the 2-oxo group can direct the reaction between 2-oxoaldehyde **1**, pyrrolidine **2**, and β -naphthol **3** in an unconventional way (Figure 1). Since β -naphthols **3** are better nucleophiles than simple phenols and pyrrolidines **2** were found to be the reagent of choice for iminium promoted chemistry, we primarily focused on their application toward the generation of **4**.

Maycock et al. and Chandan et al. described elegant methods employing a metal catalyzed cyclization approach to oxazines.⁶ Both of these methods used Betti bases as starting materials (previous work, Scheme 1). In our case, we successfully employed the precursor of the Betti base, intermediate **A**, in two diverse ways. In one approach, under metal-free conditions, we generated tetrahydrofuro[3,2-*d*]oxazoles **4**, which otherwise was supposed to give the Betti base as the final product.⁷ In contrast, under Maycock and Chandan conditions, we exclusively isolated furanones **5**, instead of 1,3-benzoxazines.⁶

We commenced our study with a reaction of phenylglyoxal **1a** (0.746 mmol), pyrrolidine **2** (0.895 mmol), and β -naphthol **3** (0.746 mmol) at room temperature (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions

entry	2 (equiv)	additive (mol %)	condition (μ w) (°C)	time (min)	yields (%) ^c	
					4a	5a
1	1	–	rt	180	52	25
2	1	–	100	180	44	25
3	1	–	50 W, 80	5	53	–
4	1	–	50 W, 100	5	60	–
5	1	–	50 W, 100	10	80	–
6	1	–	50 W, 120	10	75	–
7 ^a	1.2	–	50 W, 100	10	85	–
8	1.5	–	50 W, 100	10	85	–
9	1.2	–	100 W, 100	15	85	–
10	1.2	Cu(OAc) ₂ (10)	rt	180	–	65
11	1.2	"	80	60	–	86
12	1.2	"	50 W, 100	15	–	92
13 ^b	0.2	"	50 W, 100	15	–	92
14	0.2	"	100 W, 100	15	–	90

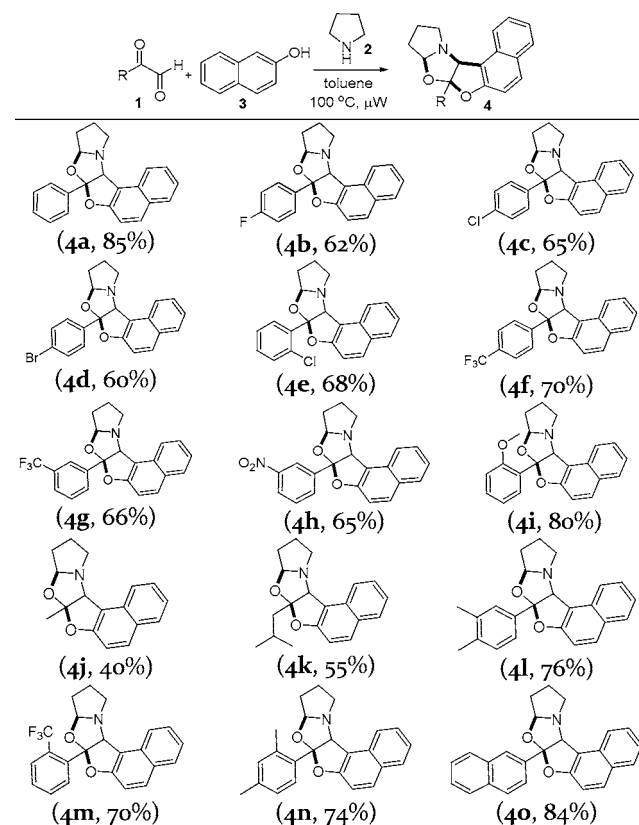
^a**1a** (0.746 mmol), **2** (0.895 mmol), and **3** (0.746 mmol) in toluene (1 mL) at 100 °C in μ W (50 W), 10 min for **4a**. ^b**1a** (0.746 mmol), **2** (0.149 mmol), β -naphthol **3** (0.746 mmol) and Cu(OAc)₂·H₂O (10 mol %) in toluene (1 mL) at 100 °C in μ W (50 W), 15 min for **5a**. ^cIsolated yields.

Surprisingly, we could isolate a mixture of two products **4a** (52%) and **5a** (25%) after 3 h. In order to attain better yields and product selectivity, the same reaction was conducted at 100 °C (entry 2). However, no improvement was seen in the nature of the reaction. Further different reactions were monitored under microwave radiation at different time intervals/temperatures with varied concentrations of pyrrolidine **2** (entries 3–9). We discovered **4a** could be achieved exclusively in 85% yield in 10 min when the reaction was conducted between

phenylglyoxal **1a** (0.746 mmol), β -naphthol **3** (0.746 mmol), and pyrrolidine **2** (0.895 mmol) at 100 °C under microwave conditions (entry 7). Yet, when the same reaction was conducted in the presence of copper(II) acetate (10 mol %) at room temperature, we obtained exclusively 2-hydroxy-2-phenylnaphtho[2,1-*b*]furan-1(2*H*)-one **5a** in 65% yield (entry 10). Later we performed a few reactions between **1a**, **2**, and **3** under microwave conditions (entries 11–14). To our delight, we isolated **5a** in 92% yield within 15 min under microwave conditions with 10 mol % copper catalyst (entry 12). The same reaction when tried with 20 mol % of pyrrolidine **2** at 50 W generated the desired product in comparable yields (entry 13). This perhaps was the best suitable set of conditions for generation of **5** for maximum yields.

In order to investigate the substrate scope of the former reaction with respect to various 2-oxoaldehydes **1**, we primarily focused on the synthesis of different tetrahydrofuro[3,2-*d*]oxazoles **4** (Scheme 2). In general, all the reactions tested

Scheme 2. Scope of the Tetrahydrofuro[3,2-*d*]oxazoles Synthesis^a



^aReaction condition: **1a** (0.746 mmol), **2** (0.895 mmol), and β -naphthol **3** (0.746 mmol) in toluene (1 mL) at 100 °C using a μ W (50 W) source for 10 min.

generated the desired product in good yields (entry **4a**–**4o**). However, reactions with 2-oxoaldehydes bearing electron-withdrawing groups at the ortho position, i.e., 2-Cl (**4e**) and 2-CF₃ (**4m**), para position, viz., –F (**4b**), –Cl (**4c**), –Br (**4d**), –CF₃ (**4f**), and meta position, for example –CF₃ (**4g**), –NO₂ (**4h**), produced slightly lower yields than those of unsubstituted **4a** and ones containing a donating group, **4i**, **4l**, and **4n**. In addition our reaction worked well with different aliphatic/naphthal 2-oxoaldehydes (**4j**, **4k**, and **4o**). In general, we

observed that naphthoxazoles **4** attained diastereoselectivity. However, the reaction with OA containing ortho/meta groups such as CF_3 (**4m**) and CH_3 (**4n** and **4l**) failed to conserve diastereoselectivity.

The structures of all tetrahydrofuro[3,2-*d*]oxazoles **4** were elucidated with the help of HRMS, ^1H , ^{13}C , and DEPT. The structure of compound **4a** was further confirmed by single crystal X-ray diffraction studies (Figure 2; for details see

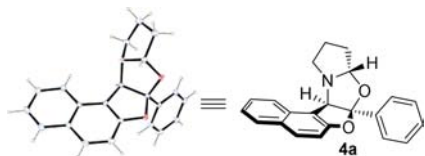
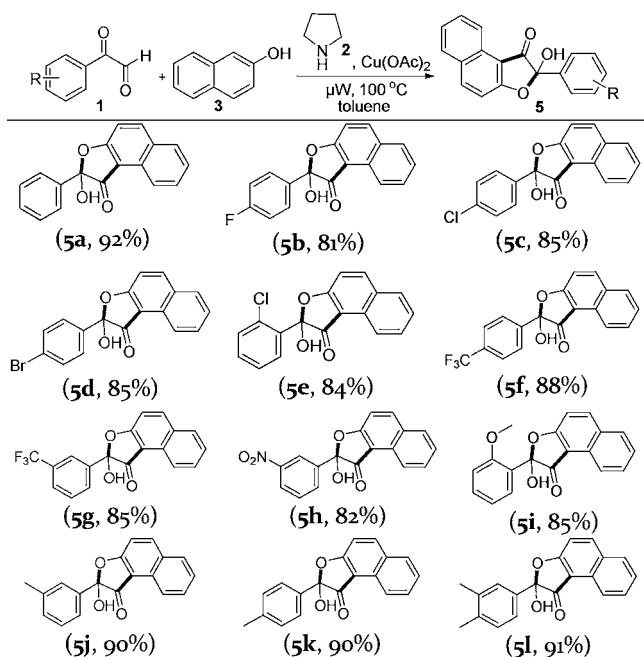


Figure 2. ORTEP diagrams of compound **4a**.

Supporting Information (SI)). Surprisingly, we could establish that compound **4a** had fixed stereochemistry (Figure 2). To authenticate the result, we performed chiral HPLC, wherein we successfully separated two isomers (see SI).

In continuation, different test reactions were performed with various 2-oxoaldehydes **1** as per optimized conditions mentioned in entry 13, Table 1 (Scheme 3). In general we observed that irrespective of the nature of substitution, all the tested reactions were efficiently transformed to **5** within 10 min (81–92%, **5a–5l**).

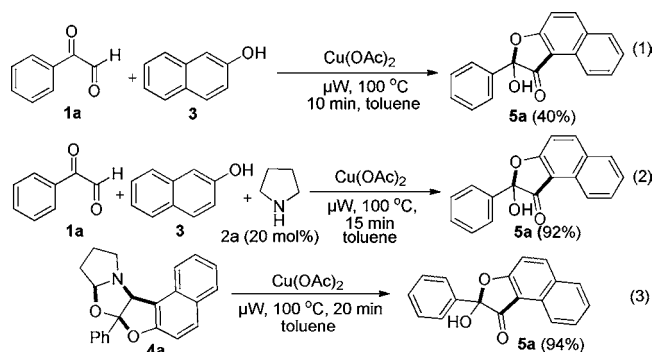
Scheme 3. Scope of the Furanones Synthesis Reaction^a



^aReaction conditions: **1** (0.746 mmol), **2** (0.149 mmol), **3** (0.746 mmol) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10 mol %) in toluene (1 mL) at 100 °C using a μW (50 W) source for 15 min.

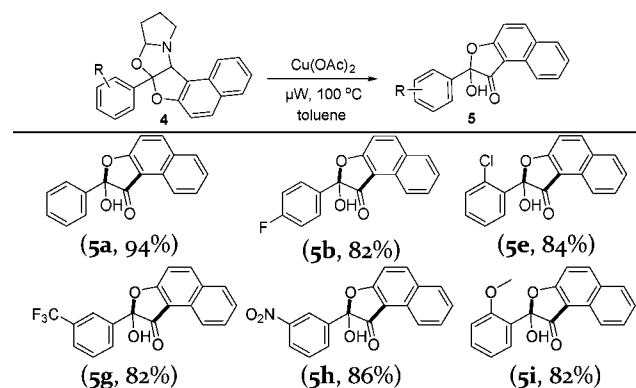
To gain insight into the mechanism of both of the reactions, we conducted few additional experiments (Scheme 4). As evident from experiment 1, although compound **5a** was isolated in low yields (40%) with a copper catalyst, the best results were obtained when treated with copper in the presence of 20 mol % of amine **2** (experiment 2). These observations

Scheme 4. Controlled Experiments



were indicative of generation of the desired product (**5a**) predominantly by the amine catalytic pathway. Also, compound **4a** on treatment with metal under microwave conditions gave **5a** in 94% yield (experiment 3). However, almost 20 min were required to complete the reaction. Since our latter reaction, as described in Scheme 3, generated the desired product in excellent yields with 20 mol % pyrrolidine in 10 min, we presume that generation of **5** in general is a metal and/amine catalyzed reaction. As an advantage, we established that compound **5** can be transformed to **4** through use of metal. In this regard, the scope of this transformation was further explored by changing the identity of tetrahydrofuro[3,2-*d*]oxazoles. As shown in Scheme 5, a variety of oxazoles **4** could be used in our transformation regardless of their substitution pattern or electronic nature.

Scheme 5. Scope of the Conversion of Tetrahydrofuro[3,2-*d*]oxazoles to Furanones^a



^aReaction conditions: **4** (1.0 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10 mol %) in toluene (1 mL) at 100 °C using a μW (50 W) source for 20 min.

Based on the previous literature reports^{6–8} and the above-mentioned results, we propose the mechanism of these reactions as depicted in Figure 3. The initial step for the synthesis of **4** and **5** involves reaction of 2-oxoaldehyde **1** and pyrrolidine **2** to form 2-oxoiminium ion (intermediate **A**). This intermediate behaves differently under metallic/nonmetallic conditions. In the metal-free pathway (path A), intermediate **A** isomerizes to **I** which can react with **3** in two possible ways. On one hand, intermediate **I** can undergo an ene reaction with **3** which later undergoes O-cyclization to **II**. On the other hand, intermediate **A** can undergo O-cyclization to a fused compound **III** that can later generate **II** by undergoing ene cyclization with **3**. However, The LC-ESI-MS analysis supported the former

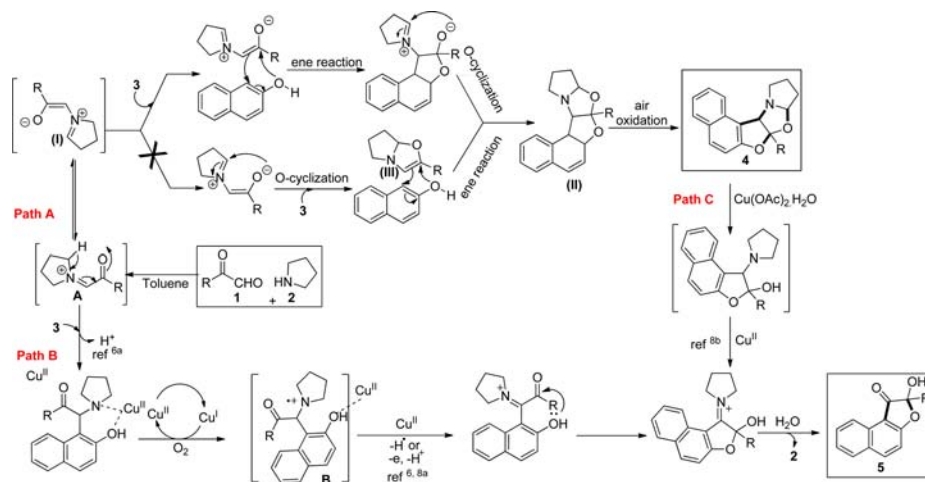


Figure 3. Proposed mechanism.

mechanism, as we failed to trap the mass of III (SI, p 6). Later, intermediate II on air oxidation generates desired tetracyclic compound 4. In the case of the metal catalyzed reaction (path B), intermediate A on reaction with 3 produces the Betti base, which generates intermediate ammoniumyl radical cation B through a single electron transfer (SET) to Cu^{II} . Radical B on successive loss of an H radical (or a combination of electron and H^+) led to an iminium salt^{6,8a} that is quite stabilized by the adjacent 2-oxo group. The iminium intermediate ultimately on cyclization undergoes hydrolysis to 5. The generation of 5 through the Betti base was well supported by LC-ESI-MS mass analysis (SI, p 6). In addition, generation of 5 from 4 (path C) can be predicted by involvement of Cu^{II} in the ring opening and deamination reaction.^{8b}

In conclusion, we have outlined a new strategy for the generation of tetrahydrofuro[3,2-*d*]oxazoles 4 and naphthofuranones 5 through 2-oxo directed nontraditional reactions. In general, all the reactions were performed without the aid of external additives or co-oxidants. The most imperative feature of naphthotetrahydrofuro[3,2-*d*]oxazoles synthesis can be the diastereoselectivity. Further detailed mechanistic studies and their application with other amines and phenols and biological activities will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01271.

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Notes

The authors declare no competing financial interest.

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