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Break-and-Build Strategy for the Synthesis of 2-Benzoylbenzoxazoles from *o*-Aminophenols and Acetophenones

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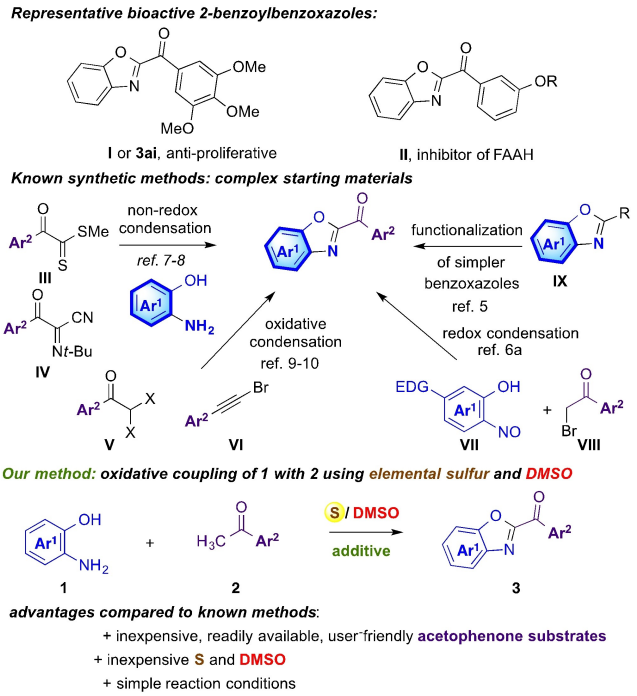
Abstract: Although compounds with a 2-benzoylbenzoxazole motif are biologically relevant, there are only a few methods for synthesizing them, most of which relied on multistep process or required substrates bearing activating groups. Herein, we report an efficient method for the synthesis of such compounds by direct reactions of *o*-aminophenols with acetophenones promoted by sulfur in DMSO. The reaction was found to proceed via a Willgerodt rearrangement-type benzoxazolation of acetophenones followed by a benzylic oxidation to reinstall the carbonyl function. This method has a broad substrate scope and good tolerance for sensitive functional groups.

Keywords: sulfur; 2-benzoylbenzoxazole; DMSO

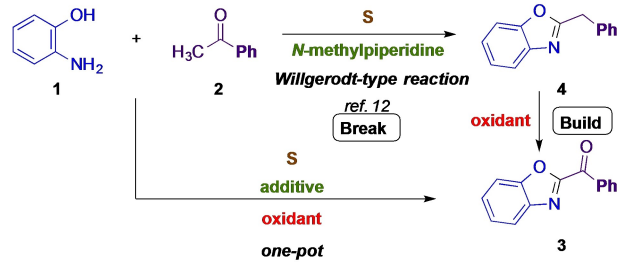
Benzoxazole derivatives are prevalent in biologically and pharmacologically important molecules as well as in functional materials.[1] A subgroup of this family is 2-benzoylbenzoxazoles, which are well-known for their significant biological activities such as antiproliferative activity (compound **I**),[2] inhibition of fatty acid amide hydrolase FAAH[3] (compound **II**) (Scheme 1). Consequently, several methods have been developed for the synthesis of 2-benzoylbenzoxazoles,[4] most of them were based on functionalization of simpler benzoxazole cores **IX**[5] or using complex starting materials which required multistep syntheses.[6]

The intuitive approach based on the construction of the benzoxazole ring by condensation of *o*-aminophenols **1** were described with phenylglyoxalic derivatives such as dithioester **III**[7] or imidoyl cyanide **IV**[8] via non redox condensation. Alternatively, when oxidation conditions were applied, condensation of **1** with derivatives of lower oxidation states such as α,α-dihaloacetophenones **V**[9] or 2-bromophenylacetylenes **VI**[10] were known. In this context, a direct use of acetophenones **2**, which are inexpensive and readily available in a wide range of structure, in a selective oxidative condensation with *o*-aminophenols **1** would provide a convenient and cost-effective approach to a library of 2-benzoylbenzoxazoles for drug discovery study.

We have recently reported a Willgerodt rearrangement-type benzoazolation of acetophenones **2** with *o*-aminophenols **1** promoted by sulfur[11] and *N*-methylpiperidine (Scheme 2).[12] In this reaction leading to **4aa**, while the methyl group of acetophenone **2a** was oxidized and benzoxazolized with 2-aminophenol **1a**, the carbonyl group was reduced to a methylene group. Since this methylene group is surrounded by the phenyl group and the newly installed benzoxazole moiety, this new situation could open up opportunities for oxidation of **4aa** into a carbonyl in **3aa**. Such operation was previously performed on separated 2-benzylbenzoxazole derivatives using relatively complex reaction conditions involving strong oxidizing agents in the presence of transition metal catalysts.[5m] We reason that a direct transformation from **1a** and **2a** to **3a** could be performed in one-pot in the presence of a suitable oxidant in the reaction medium. As DMSO is well known as an excellent solvent and a mild and



Scheme 1. 2-Benzoylbenzoxazoles: Bioactivity and Syntheses.



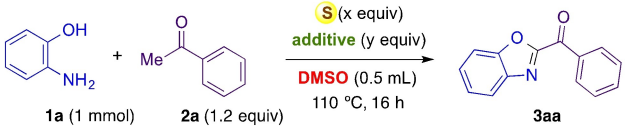
Scheme 2. Break-and Build Strategy for the Synthesis of **3**.

selective oxidizing agent, especially in the presence of sulfur,[13] we focused our attention to develop this strategy.

For this purpose, we first performed the benzoxazolation of acetophenone **2a** with 2-aminophenol **1a** under the standard conditions (80 °C, 16 h) using sulfur (3 equiv.), *N*-methylpiperidine (NMP) (1 equiv.) in the presence of DMSO (3 equiv.) (Table 1, entry 1).

To our delight, this initial test resulted in a 80% conversion of 2-aminophenol **1a** into a nearly 1:1 mixture of **4aa**:**3aa**. Oxidation of the methylene moiety was significantly accelerated by heating at higher temperature (110 °C, entry 2). At this stage, we realized that DMSO could act as oxidant to regenerate sulfur from H_2S byproduct of the first step of Willgerodt-type benzoxazolation, the amount of sulfur could be lowered to stoichiometric amount, i.e. 1 equiv. (entry 3).

Table 1. Screening of the Reaction Conditions.



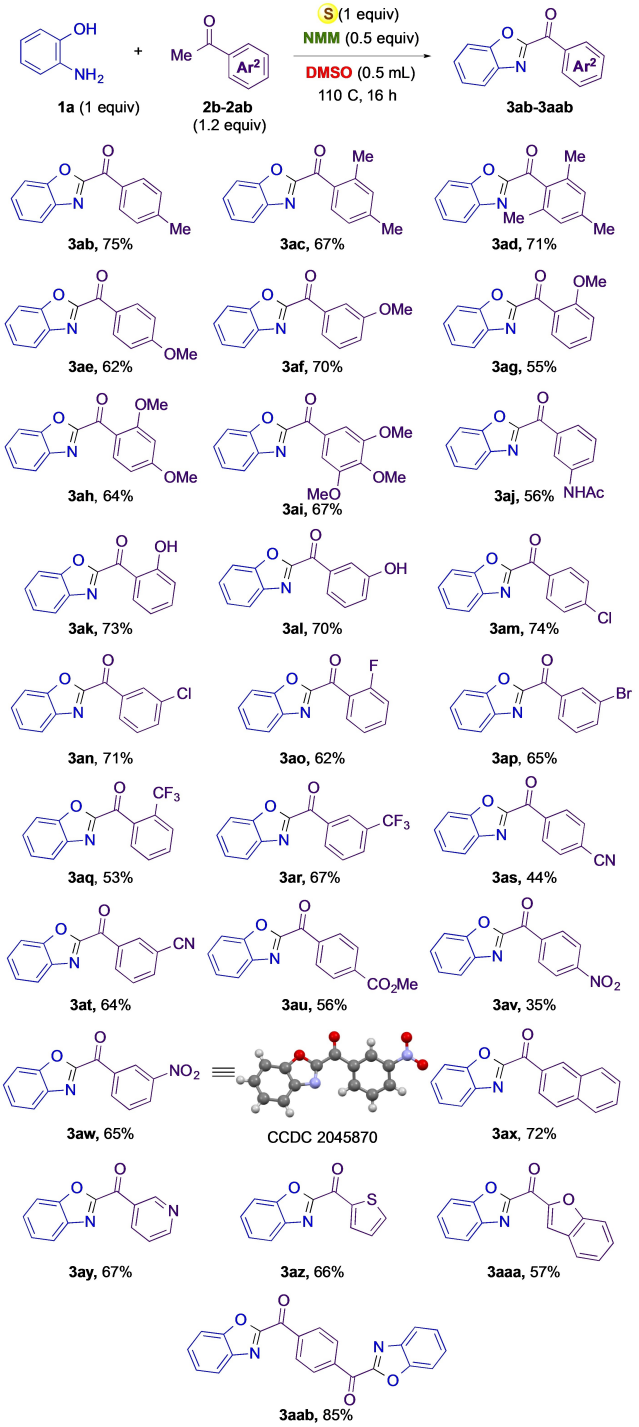
1a (1 mmol) **2a** (1.2 equiv) **3aa**

Entry[a]	x	additive	y	yield (%)[b]
1[c]	3	*N*-methylpiperidine	1	30
2	3	*N*-methylpiperidine	1	65
3	1	*N*-methylpiperidine	1	68
4	1	*N*-methylpiperidine	0.5	72
5	0.5	*N*-methylpiperidine	0.5	54
6	1	pyridine	0.5	70
7	1	*N*-methylmorpholine	0.5	77
8	1	DIPEA	0.5	71
9	1	tri-*n*-propylamine	0.5	70
10	1	DABCO	0.5	73
11	1	–	0	52
12	0	*N*-methylmorpholine	0.5	0
13[e]	1	*N*-methylmorpholine	0.5	36
14[f]	1	*N*-methylmorpholine	0.5	0[d]

[a] Reaction conditions: *o*-aminophenol **1a** (1 mmol), acetophenone **2a**, sulfur (x mmol, 32 mg.mmol^{-1}), additive (y mmol), DMSO (0.5 mL), 110 °C, 16 h unless otherwise noted.
[b] isolated yield unless otherwise noted.
[c] Reaction temperature 80 °C.
[d] Determined by ^{1}H NMR of the crude mixture.
[e] DMSO (0.3 mL) was used.
[f] DMF (0.5 mL) was used in place of DMSO.

Moreover, we noticed that the amount of NMP, which acted as a basic sulfur activator, could be further reduced to 0.5 equiv. without lowering the reactivity (entries 4–5). Interestingly, other nitrogen bases such as pyridine, *N*-methylmorpholine (NMM), diisopropylethylamine (DIPEA), tri-*n*-propylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) (entries 6–10) could be used in place of NMP. It is noteworthy that the expected product **3aa** could be formed even in the absence of a base, despite in lower yield (entry 11). The reaction in the absence of sulfur resulted in recovery of unchanged starting materials, which confirmed clearly the crucial role of this element in promoting the cascade transformation (entry 12). Finally, lowering the DMSO amount (entry 13) of replacing DMSO by another polar aprotic solvent such as DMF (entry 14) prevented partially or totally the formation of **3aa**, which confirmed the importance of DMSO in this oxidative condensation.

With this set of optimized reaction conditions, we next studied the scope and limitations of our strategy. In general, starting from 2-aminophenol **1a** and acetophenones **2** bearing a wide range of substituents of different electronic nature or positions, the reactions led to the expected 2-benzoylbenzoxazole products **3** in reasonable yields (Scheme 3). Acetophenones bear-



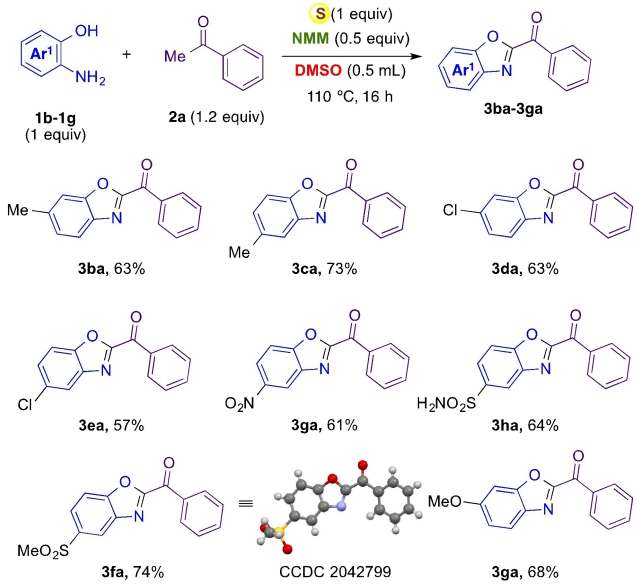
Scheme 3. Scope of Methyl Aryl Ketones **2**.

ing electron donating groups such as methyl, methoxy, acetamido displayed good reactivity, provide the expected benzoxazoles **3 ab**–**3 aj** in moderate to good yields. We emphasized that the product **3 ai** (compound **I** in Scheme 1) was previous demonstrated to be biologically active.[2] Interestingly, the reaction conditions could be applied to acetophenones bearing unprotected hydroxy groups in good to excellent yields. It should be noted that **3 al** could serve as a direct precursor to provide a wide range of bioactive derivative via acylation of its hydroxy group (compound **II** in Scheme 1). Acetophenones bearing halogen groups in different positions such as *p*-Cl, *m*-Cl, *o*-F and *m*-Br (**2 m**–**2 p**) displayed good reactivities and gave the products **3 am**–**3 ap** in good yields. Gratifyingly, acetophenones substrates having an electron withdrawing group such as CF_3, CN, CO_2Me or NO_2, showed also to be competent substrates. The structure of nitro **3 aw** was unambiguously confirmed by X-ray diffraction analysis.

Although CN and NO_2 groups were known to react with H_2S,[14] which is a possible intermediate/by-product of this transformation, via nucleophilic addition and reduction, respectively, the expected benzoxazole products **3 as**, **3 at**, **3 av** and **3 ax** were obtained in reasonable yields. In case of *p*-nitroacetophenone **2 v**, the superiority of NMM compared to other basic additive such as NMP and pyridine or without base in assisting the benzoxazolation process was clearly demonstrated as NMM was the only base that could afford the expected benzoxazole **3 av**, despite in low yield.

2-Acetonapthone as well as heterocyclic substrates derived from pyridine, thiophene and benzofuran gave moderate to good yields of the corresponding benzoxazole products **3 ax**–**3 aaa**. The twofold reaction could be performed when *p*-diacetylbenzene (0.6 equiv.) was used.

The reaction conditions could also be applied successfully to substituted 2-aminophenols (Scheme 4). Benzoxazoles bearing a methyl group **3 ba**



Scheme 4. Scope of *o*-Aminophenols **1**.

and **3ca** were obtained in yields of 63% and 73%, respectively. Chloro substituents were also compatible with the reaction conditions: the oxidative coupling products **3da** and **3ea** were formed in moderate yields (63% and 57%, respectively). The presence of an electron withdrawing groups such as sulfone, sulfonamide or nitro on the phenyl ring of 2-aminophenol could reduce the nucleophilicity of the hydroxy group, they had little effect on the yields. In the case of 4-nitro-2-aminophenol **1g**, thanks to low solubility in methanol of product **3ga**, it was easily isolated from the reaction mixture by a simple trituration/filtration operation with methanol. The structure of sulfone **3fa** obtained in 61% yield was confirmed by X-ray diffraction analysis. *o*-Aminophenol substrate bearing an electron donating group MeO **1g** showed also good reactivity under our conditions, leading to benzoxazole **3ga** in good yield.

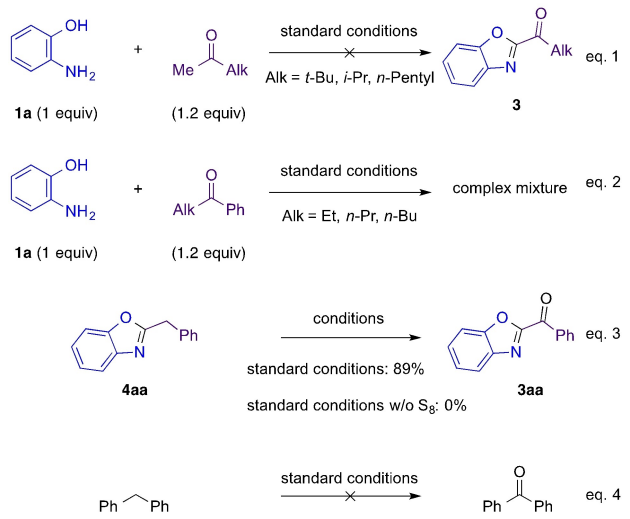
Our reaction conditions were however not applicable to aliphatic methyl ketones such as pinacolone, 3-methyl-2-butanone of 2-heptanone (Scheme 5, eq. 1). In these cases, the reactions mixtures were found to be complex, possibly because both step of benzoxazolation of methyl ketones and methylene oxidation occurred more difficultly in the absence of an aryl group on the methyl ketone substrates. Indeed, the presence of the products issued from the first step could be detected in the crude mixtures, the subsequent oxidation of their methylene moiety failed. The reaction conditions applied to homologous of acetophenones such as propiophenone, butyrophenone or valerophenone led to complex mixtures since the intermediates of Willgerodt rearrangement of the longer chains underwent uncontrollable oxidation by DMSO (Scheme 5, eq. 2).

In order to support the proposed reaction mechanism, the primary Willgerodt-type product **4aa** was prepared separately and allowed to react with DMSO (0.5 equiv.) (Scheme 5, eq. 3). The product **3aa** was formed in high yield under the standard conditions. On the other hand, performing the similar reaction in the absence of sulfur resulted in recovery of **4aa**. This confirmed unambiguously that the oxygen atom of 2-benzoylbenzoxazole **3aa** product comes from DMSO.

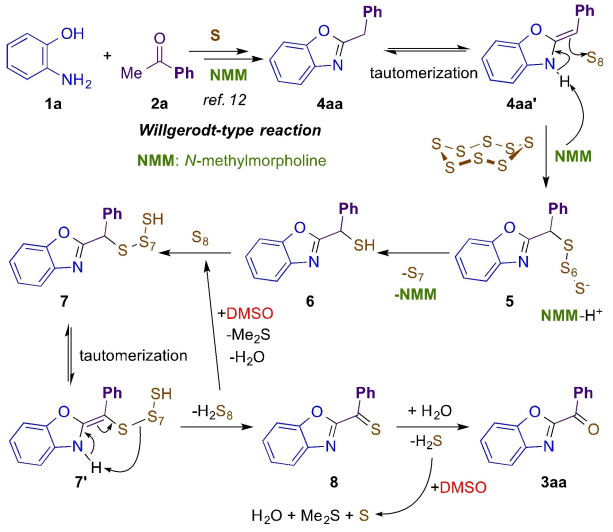
Additionally, we found that diphenylmethane could not be oxidized into benzophenone and remained unchanged under these oxidizing conditions (eq. 4). These results suggested the important role of both aryl and 2-benzoxazolyl substituents as well as the participation of sulfur to the oxidation of methylene moiety.

On the basis of these results and our previous works,[13] a plausible mechanism is proposed in Scheme 6. The reaction commenced with a Willgerodt-type reaction as described previously to provide benzoxazole **4aa**.

An easily tautomerization **4aa**⇌**4aa'** facilitated by the presence of both benzoxazole and phenyl moieties would favor the formation of polysulfide salt **5**. Sulfur extrusion from **5** followed by a sulfur-promoted oxidation of thiol **6** to thione **8** would proceed via polysulfide **7** and its tautomer **7'**. Hydrolysis of thione **8** would lead to **3aa**.[15] Since the oxygen atom of a carbonyl function of a ketone was known to be exchanged rapidly with water, it is not conclusive to use labelled water to confirm if the ketone oxygen atom **3aa** was issued from water or not via the hydrolysis step **8**→**3aa**.[16] Water involving in this step is generated from the recycling of sulfur by oxidation of hydrogen (poly)sulfide with DMSO.[17] At the present stage, we cannot exclude the pathway involving direct functionalization of the methyl group of acetophenone **1a** without the intermediacy of a Willgerodt-type reaction.



Scheme 5. Control Experiments.



Scheme 6. Proposed Reaction Mechanism.

In conclusion, we have reported an efficient method for a direct access to 2-benzoylbenzoxazoles from 2-aminophenols and acetophenones via a cascade of sulfur-promoted Willgerodt type benzoxazolation and methylene oxidation in DMSO. The reactions conditions are compatible with many functional groups and heterocycles. The method is highlighted by the fact that both starting materials *o*-aminophenols and acetophenones are inexpensive and readily available in a wide range of structures. Moreover, since sulfur and DMSO were used as oxidant in the presence of substoichiometric amount of *N*-methylmorpholine as an additive, our method is inarguably the cheapest and most convenient method to provide a library of 2-benzoylbenzoxazoles.

Experimental Section

A mixture of 2-aminophenol **1** (1 mmol), acetophenone (1.2 mmol), elemental sulfur (32 mg, 1 mmol), *N*-methylmorpholine (56 mg, 0.5 mmol), and DMSO (0.5 mL) was heated under an argon atmosphere in a 7-mL test tube at 110 °C for 16 h. The product was purified by column chromatography on silica gel (heptane:EtOAc 1:0 to 5:1 or dichloromethane: heptane 2:1 to 1:0). For experimental details, full characterization, and copies of NMR spectra of all compounds, see Supporting Information.

CCDC 2045870 and 2042799 contain the supplementary crystallographic data for **3aw** and **3fa**, respectively in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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