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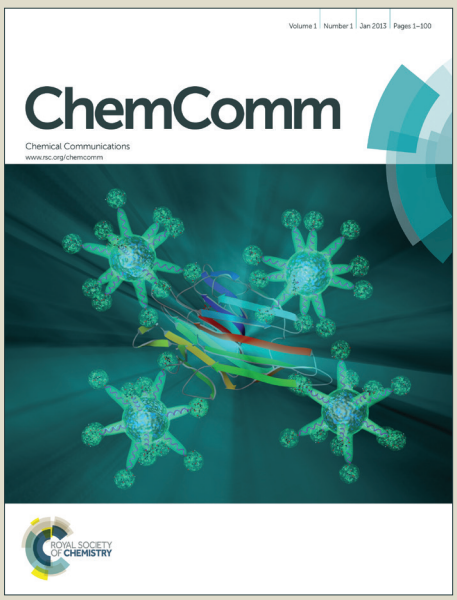





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# A one-pot hypoiodite catalysed oxidative cycloetherification approach to benzoxazoles.

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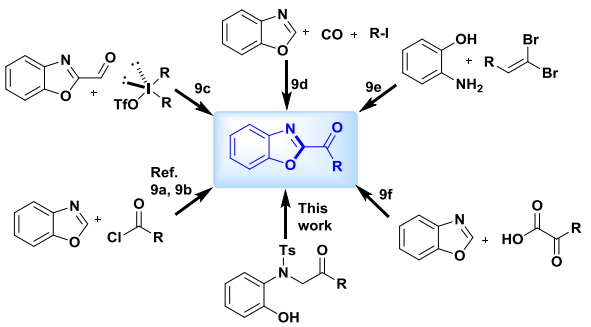
**A practical one-pot hypoiodite catalysed oxidative cyclization approach to synthesize α-ketobenzoxazole derivatives was successfully developed. This operationally simple protocol utilizes easily-accessible starting materials and has a broad substrate scope with excellent yields.**

Over the past few decades, hypervalent iodine compounds have been receiving widespread attention in organic synthesis due to their mild, effective, safe, and environmentally friendly characteristics.[1] Recently, Ishihara and co-workers described the intramolecular α-oxyacylation of carbonyl compounds catalysed by chiral quaternary ammonium iodide.[2] After exploring the catalytic utilization of in situ generated hypoiodite species from hypervalent iodine in combination with co-oxidants, this metal-free approach emerged as a promising alternative to oxidative C-H functionalization.[3] By extending the novel catalytic system, several other groups have made remarkable progress in C-O,[4] C-N,[5] and C-C[6] bond formation reactions. Despite these advances, this protocol has been largely unexplored in the development of useful heterocycles of significant interest and desirability.

Benzoxazole derivatives are an important structural motifs present in natural products and functional materials, and they represent privileged scaffolds in drug discovery.[7] In particular, the structural variants of α-ketobenzoxazoles exhibit significant biological activity with FAAH inhibitors, cysteine protease inhibitors and channel activating protease inhibitors.[8] Furthermore, they are versatile synthetic intermediates with a carbonyl group that can easily be functionalized for further synthetic applications. To the best of our knowledge, the available methods[9] (Scheme 1) to access such compounds include the traditional Friedel-Craft type acylation of benoxazoles, NHC catalysed C-H arylation of aldehydes, palladium catalysed carbonylative C-H functionalization, ruthenium catalysed 1,2-dibromoethens with 2-aminophenols, and palladium catalysed decarboxylative acylation of benoxazoles. These methods have some limitations such as strict reaction conditions, expensive metal catalysts and narrow substrate scope. Owing to their significant interest in chemistry and biology, we report a one-pot hypoiodite catalysed approach to α-ketobenzoxazole derivatives.

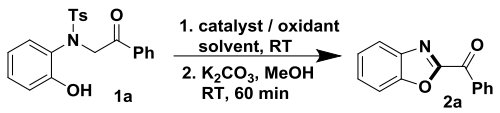



Scheme 1. Previous approaches to α-keto benoxazoles

The starting material, *N*-(2-hydroxyphenyl)-4-methyl-*N*-(phenacyl)benzenesulfonamide (**1a**) was initially synthesized via a base mediated N-Alkylation of 2-(tosylamino)phenol with phenacyl bromide.[10] Under initial conditions, 1mmol of **1a**, 10 mol% n-tetrabutyl ammoniumiodide (TBAI) and 2 equivalents of $H_2O_2$ in EtOAc at room temperature followed by 1equivalent $K_2CO_3$ in methanol. The desired product **2a,** was formed at 62% yield (Table 1, entry 1). To improve the reaction yield, various oxidants (entries 2-4) and catalyst (entries 5-9) were

investigated and among them TBHP and TBAI was found to be the most effective. The absence of either the catalyst or oxidant failed to proceed the reaction (entries 10-11). Solvent studies revealed that THF provided superior yield (entries 12-17). Optimization was further investigated using different quantities of catalyst (entries 18-19) and oxidant (entry 20). Entry 12 was chosen as the optimum reaction condition for this transformation.

Table 1 optimization of reaction conditions [a]

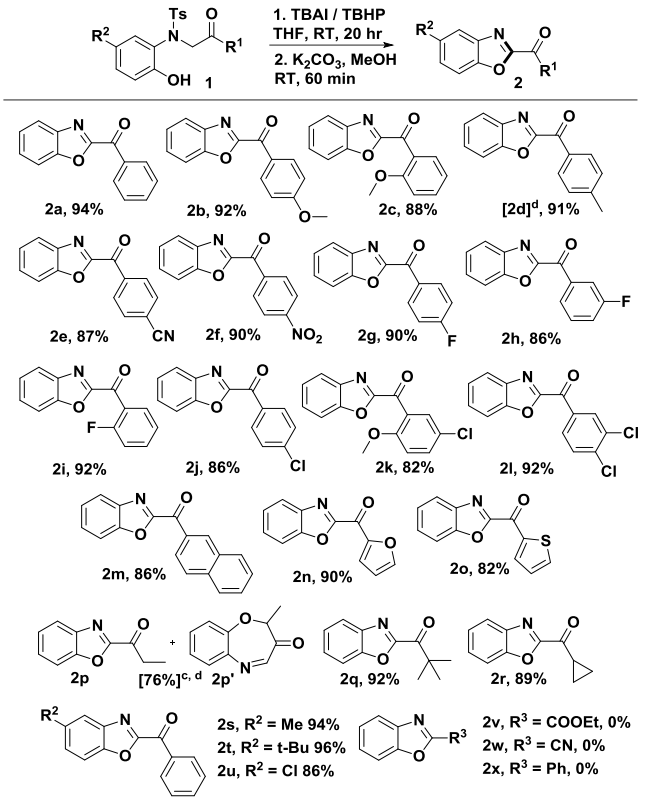



| Entry | Catalyst | Oxidant | Solvent | Time/h | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | TBAI | $H_2O_2$[c] | EtOAc | 20 | 66 |
| 2 | TBAI | TBHP[d] | EtOAc | 20 | 88 |
| 3 | TBAI | DTBP | EtOAC | 20 | 56 |
| 4 | TBAI | Oxone | EtOAc | 30 | nr |
| 5 | TBABr | TBHP | EtOAc | 20 | nr |
| 6 | TBACl | TBHP | EtOAC | 20 | nr |
| 7 | KI | TBHP | EtOAc | 20 | 22 |
| 8 | $I_2$ | TBHP | EtOAc | 20 | traces |
| 9 | NIS | TBHP | EtOAc | 20 | nr |
| 10 | - | TBHP | EtOAc | 20 | nr |
| 11 | TBAI | - | EtOAc | 20 | nr |
| **12** | **TBAI** | **TBHP** | **THF** | **20** | **94** |
| 13 | TBAI | TBHP | ACN | 20 | 78 |
| 14 | TBAI | TBHP | DCE | 20 | 79 |
| 15 | TBAI | TBHP | Toluene | 20 | 52 |
| 16 | TBAI | TBHP | EtOH | 20 | 60 |
| 17 | TBAI | TBHP | MeOH | 20 | 39 |
| 18[e] | TBAI | TBHP | THF | 20 | 84 |
| 19[f] | TBAI | TBHP | THF | 20 | 92 |
| 20[g] | TBAI | TBHP | THF | 20 | 68 |

[a]Reaction conditions: step I: **1a** (1 mmol), catalyst (10 mol%), oxidant (2 equiv), solvent (5 ml). step II : $K_2CO_3$ (1 equiv), MeOH (3 ml), RT, 60 min. [b] isolated yield, [c] 30% solution in water, [d] 70% solution in water, [e] 5mol% of TBAI was used, [f] 20 mol% TBAI was used, [g] 1.0 equiv of TBHP was used.

With the chosen optimized reaction condition, a systematic investigation of substrate scope was pursued and the results were assembled in Table 2. A variety of arenes at $R^1$ containing electron donating groups (**2a-2d**) and electron withdrawing groups (**2e-2f**) were examined, and successfully converted to their corresponding benzoxazoles in excellent yields. The various aryl halides at $R^1$ (**2g-2l**) were also well tolerated under standard reaction conditions. Notably, the $R^1$ was naphthyl (**2m**) or hetroaryl (**2n-2o**), the reactions went smoothly and the desired products isolated in high yields. The reaction conditions were also suitable for alkyl and cycloalkyl at $R^1$ (**2p-2s**), providing good to excellent yields. Of particular note, when $R^1$ was ethyl, (**2p**) the seven membered cyclized product (**2p'**) was also observed in trace quantities. The $R^2$ was replaced with various groups, such as methyl, t-butyl and chloro, (**2s-2u**), and

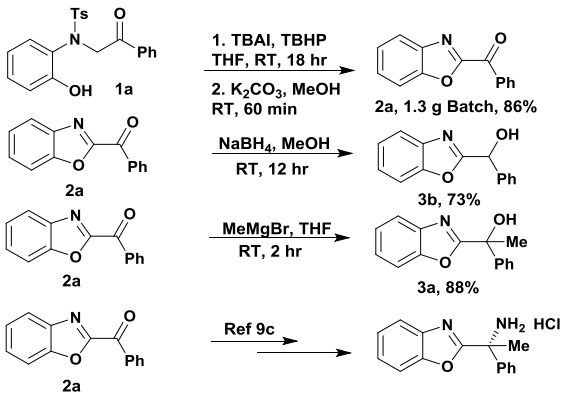
Table 2 Substrate scope of α-keto benzoxazoles [a,b]




[a] Reaction conditions: **1** (1mmol), TBAI (10 mol%) and TBHP (70% in water, 2 equiv) in THF (5ml) at RT for 20 h, followed by $K_2CO_3$ (1.0 equiv) and MeOH (2 ml) at RT for 60 min. [b] Isolated yields [c] Compounds **2p** & **2p'** obtained as inseparable mixture. [d] Compounds are impure.

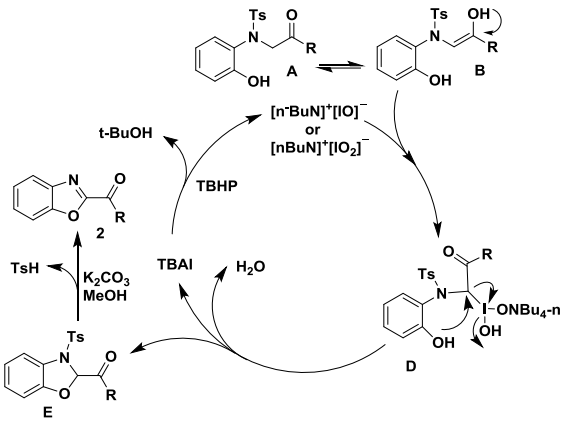
the reactions proceeded quite smoothly, providing the expected products. Compound **2t** was unambiguously confirmed by X-ray analysis.[11] Attempted replacement of $R^3$ with ester, cyano or phenyl (**2v-2x**) did not give the expected product. The reasons could be the poor enolizing capacity of the ester (**2v**) at standard reaction conditions and the absence of enolizing group in **2w** and **2x.**

To demonstrate the practicability of this protocol, a gram scale synthesis of **2a** was carried out with high yields. In addition, synthetic applications manipulating the carbonyl




Scheme 2. Synthetic utility of the protocol.

groups were also shown in Scheme 2.




Scheme 3. Proposed catalytic pathway.

Based on previous literature[2a, 4e] and the observed results, a possible reaction pathway is delineated in Scheme 3. Initially, compound **A** undergoes enolization and is in equilibrium with its enol form, intermediate **B**. The in situ generated hypoiodite species **C** from TBAI and TBHP will activate the enol-carbon of intermediate **B** to form **D**. The subsequent intramolecular nucleophilic attack of phenolic OH gives the intermediate **E** and regenerates the catalyst for the next cycle.[12] Finally, intermediate **E** undergoes detosylation in the presence of base to give the final product **2**.

In conclusion, we have demonstrated a practical one-pot approach to prepare α-ketobenzoxazoles under mild and transition metal-free conditions. Moreover, the key features of this work include an inexpensive catalytic system, exceptional functional group tolerance, easily accessible starting materials, and scalability. Evaluation of biological studies on synthesized compounds and further investigations to extend the strategy on various useful heterocycles are now under investigation.

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## Notes and references

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10 A series of starting materials (**1a**-**1u**) synthesized in moderate to good yields (41-71%). For experimental procedures, please see SI.

11 CCDC 991635 (**2t**) contains the supplementary crystallographic data for this paper.

12 The intermediate "**E**" can isolable in the absence of base (see SI).