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A one-pot hypoiodite catalysed oxidative cycloetherification approach to benzoxazoles†

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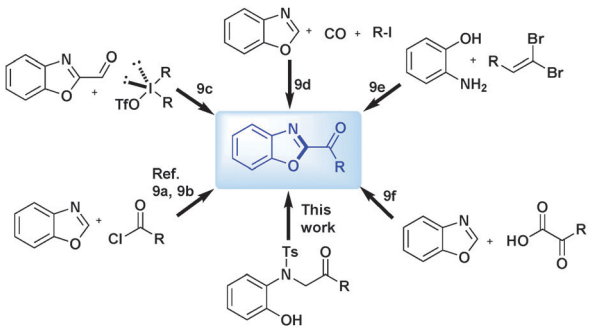
A practical one-pot hypoiodite catalysed oxidative cyclization approach to synthesize α-ketobenzoxazole derivatives was successfully developed. This operationally simple protocol utilizes easily-accessible starting materials and has a broad substrate scope with excellent yields.

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 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 activities such as 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, to access such compounds the available methods[9] (Scheme 1) include the traditional Friedel–Crafts type acylation of benzoxazoles, NHC catalysed C–H arylation of aldehydes, palladium catalysed carbonylative C–H functionalization, ruthenium catalysed 1,2-dibromoethenes with 2-aminophenols, and palladium catalysed decarboxylative acylation of benzoxazoles. These methods have some limitations such as strict reaction conditions, expensive metal catalysts and a narrow substrate scope. Owing to their significant role in chemistry and biology, we report a one-pot hypoiodite catalysed approach to α-ketobenzoxazole derivatives.



Scheme 1 Previous approaches to α-ketobenzoxazoles.

The starting material, *N*-(2-hydroxyphenyl)-4-methyl-*N*-(phenacyl)benzene sulfonamide (**1a**), was initially synthesized *via* a base mediated *N*-alkylation of 2-(tosylamino)phenol with phenacyl bromide.[10] Under initial conditions, 1 mmol of **1a**, 10 mol% *n*-tetrabutyl ammonium iodide (TBAI) and 2 equivalents of H_2O_2 in EtOAc were reacted at room temperature followed by 1 equivalent of K_2CO_3 in methanol. The desired product **2a** was formed in 62% yield (Table 1, entry 1). To improve the reaction yield, various oxidants (entries 2–4) and catalysts (entries 5–9) were investigated and among them TBHP and TBAI were found to be the most effective. The reaction failed to proceed in the absence of either the catalyst or the oxidant (entries 10 and 11). The solvent studies revealed that THF provided superior yield (entries 12–17). Optimization of the reaction conditions was further investigated using different quantities of catalysts (entries 18 and 19) and oxidants (entry 20). Entry 12 was chosen as the optimum reaction condition for this transformation.

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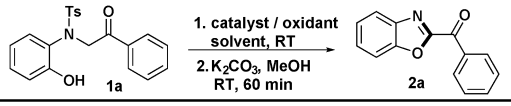
Table 1 Optimization of reaction conditions[a]



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

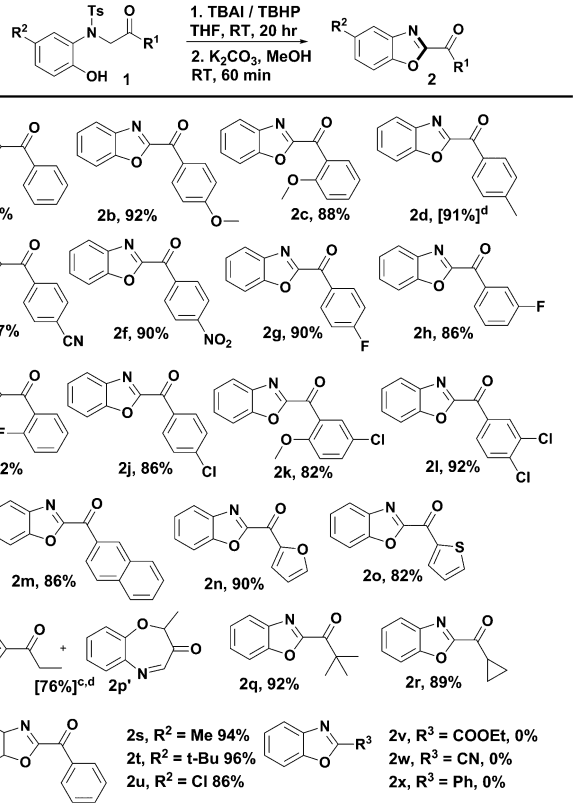
[a] Reaction conditions: step I: **1a** (1 mmol), catalyst (10 mol%), oxidant (2 equiv.), solvent (5 ml). Step II: K_2CO_3 (1 equiv.), MeOH (3 ml), RT, 60 min. [b] Isolated yield. [c] 30% solution in water. [d] 70% solution in water. [e] 5 mol% TBAI was used. [f] 20 mol% TBAI was used. [g] 1.0 equiv.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

With the chosen optimized reaction condition, a systematic investigation of the substrate scope was pursued and the results are collected in Table 2. A variety of arenes at R^1 containing electron donating groups (**2a–2d**) and electron withdrawing groups (**2e** and **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, if the R^1 was a naphthyl (**2m**) or heteroaryl (**2n** and **2o**) group, the reactions proceeded smoothly and the desired products were isolated in high yields. The reaction conditions were also suitable for alkyls and cycloalkyls 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 the reactions proceeded quite smoothly, providing the expected products. Compound **2s** was unambiguously confirmed by X-ray analysis.[11] Attempted replacement of R^3 with an ester, cyano or phenyl (**2v–2x**) group did not give the expected product. The reasons could be the poor enolizing capacity of the ester (**2v**) under standard reaction conditions and the absence of enolizing groups in **2w** and **2x**.

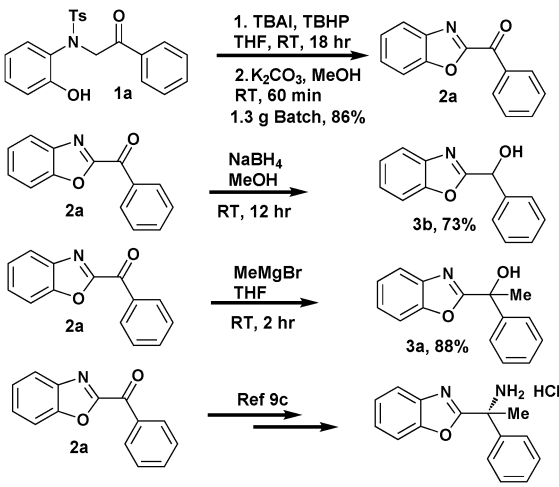
To demonstrate the practicability of this protocol, a gram scale synthesis of **2a** was carried out with high yields. In addition, synthetic applications manipulating the carbonyl groups are also shown in Scheme 2.

Based on previous literatures[2a,4e] and the observed results, a possible reaction pathway is delineated in Scheme 3. Initially,

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

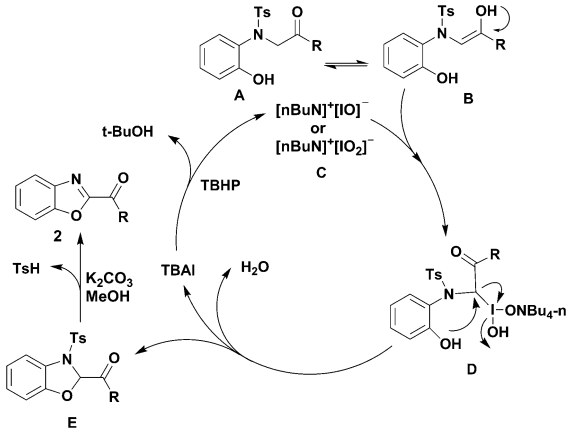


[a] Reaction conditions: **1** (1 mmol), TBAI (10 mol%) and TBHP (70% in water, 2 equiv.) in THF (5 ml) at RT for 20 h, followed by K_2CO_3 (1.0 equiv.) and MeOH (2 ml) at RT for 60 min. [b] Isolated yields. [c] Compounds **2p** & **2p′** are obtained as an inseparable mixture. [d] Compounds are impure.



Scheme 2 Synthetic utility of the protocol.

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**



Scheme 3 Proposed catalytic pathway.

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. Studies on evaluation of biological activity of synthesized compounds and further investigations to extend the strategy to various useful heterocycles are now underway.

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Notes and references

1 (*a*) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123; (*b*) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; (*c*) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed.*, 2009, **48**, 9052; (*d*) M. Kirihara, Y. Asai, S. Ogawa, T. Noguchi, A. Hatano and Y. Hirai, *Synthesis*, 2007, 3286.

2 (*a*) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376; (*b*) M. Uyanik, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed.*, 2010, **49**, 2175.

3 (*a*) M. Uyanik and K. Ishihara, *ChemCatChem*, 2012, **4**, 177; (*b*) P. Fenkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, 979.

4 For C–O bond formation: (*a*) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu and X. Wan, *Chem. – Eur. J.*, 2011, **17**, 4085; (*b*) W. Wei, C. Zhang, Y. Xu and X. Wan, *Chem. Commun.*, 2011, **47**, 10827; (*c*) Q. Xue, J. Xie, P. Xu, K. Hu, Y. Cheng and C. Zhu, *ACS Catal.*, 2013, **3**, 1365; (*d*) W. Wang, J. Xue, T. Tian, J. Zhang, L. Wei, J. Shao, Z. Xie and Y. Li, *Org. Lett.*, 2013, **15**, 2402; (*e*) C. Zhu and Y. Wei, *ChemSusChem*, 2011, **8**, 1082.

5 For C–N bond formation: (*a*) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett.*, 2011, **13**, 3754; (*b*) L. Ma, X. Wang, W. Yu and B. Han, *Chem. Commun.*, 2011, **47**, 11333; (*c*) Y. Lv, Y. Li, T. Xiong, Q. Liu and Q. Zhang, *Chem. Commun.*, 2014, **50**, 2367.

6 For C–C bond formation: (*a*) A. Rodrguez and W. J. Moran, *Org. Lett.*, 2011, **13**, 2220; (*b*) Y.-C. Wong, C.-T. Tseng, T.-T. Kao, Y.-C. Yeh and K.-S. Shia, *Org. Lett.*, 2012, **14**, 6024.

7 (*a*) S. M. Johnson, S. Connelly, I. A. Wilson and J. W. Kelly, *J. Med. Chem.*, 2008, **51**, 260; (*b*) A. D. Rodriguez, C. Ramirez, I. Rodriguez and E. Gonzalez, *Org. Lett.*, 1999, **1**, 527; (*c*) J. P. Davidson and E. J. Corey, *J. Am. Chem. Soc.*, 2003, **125**, 13486; (*d*) M. Ueki, K. Ueno, S. Miyadoh, K. Abe, K. Shibata, M. Taniguchi and S. Oi, *J. Antibiot.*, 1993, **46**, 1089; (*e*) S. Park, S. Kim, J. Seo and S. Y. Park, *Macromolecules*, 2005, **38**, 4557; (*f*) H. Razavi, S. K. Palaninathan, E. T. Powers, R. L. Wiseman, H. E. Purkey, N. N. Mohamedmohaideen, S. Deechongkit, K. P. Chiang, M. T. A. Dendle, J. C. Sacchettini and J. W. Kelly, *Angew. Chem., Int. Ed.*, 2003, **42**, 2758.

8 (*a*) D. L. Boger, H. Sato, A. E. Lerner, M. P. Hedrick, R. A. Fecik, H. Miyauchi, G. D. Wilkie, B. J. Austin, M. P. Patricelli and B. F. Cravatt, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 5044; (*b*) M. Seierstad and J. G. Breitenbucher, *J. Med. Chem.*, 2008, **51**, 7327; (*c*) M. E. Mcgrath, P. A. Sprengeler, C. M. Hill, V. Martichonok, H. Cheung, J. R. Somoza, J. T. Palmer and J. W. Janc, *Biochemistry*, 2003, **42**, 15018; (*d*) D. C. Tully, A. Vidal, A. K. Chatterjee, J. A. Williams, M. J. Roberts, H. M. Petrassi, G. Sparggon, B. Bursulaya, R. Pacoma, A. Shipway, A. M. Schumacher, H. Danahay and J. L. Harris, *Bioorg. Med. Chem. Lett.*, 2008, **51**, 23; (*e*) B. E. Maryanoff and M. J. Costanzo, *Bioorg. Med. Chem.*, 2008, **16**, 1562; (*f*) M. J. Myllymakiki, S. M. Saario, A. O. Kataja, J. A. Castillo-Melendez, T. Nevalainen, R. O. Juvonen, T. Jarvinen and A. M. P. Koskinen, *J. Med. Chem.*, 2007, **50**, 4236.

9 (*a*) N. K. Harn, C. J. Gramer and B. A. Anderson, *Tetrahedron Lett.*, 1995, **36**, 9453; (*b*) P. Lassalas, F. Marsais and C. Hoarau, *Synlett*, 2013, 2233; (*c*) Q. Y. Toh, A. McNally, S. Vera, N. Erdmann and M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 3772; (*d*) X.-F. Wu, P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 7316; (*e*) X. Fan, Y. He, X. Zhang, S. Guo and Y. Wang, *Tetrahedron*, 2011, **67**, 6369; (*f*) S. Sharma, I. A. Khan and A. K. Saxena, *Adv. Synth. Catal.*, 2013, **355**, 673.

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

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

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