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Molecular iodine mediated synthesis of polysubstituted oxazoles by oxidative domino cyclization in water

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A simple and efficient iodine-mediated domino protocol has been developed to construct poly substituted oxazoles through the C-hetero atom bond formation in water from readily available β-ketoesters and primary amines in high yields. The reaction proceeds smoothly under metal and peroxide-free conditions.

The principles of green chemistry demands for the development of new chemical reactivities and reaction conditions that can substantially improve chemical synthesis in terms of atom economy, and energy efficiency, product selectivity, operational simplicity and environmental safety.[1] As a result recently the demand for greener methods, such as organocatalysis, multi component reactions, metal-free C-heteroatom bond formation reactions due to their atom economy. Recent time's extensive research has been carried out for construction of biologically significant heterocycles through the direct C-N and C-O bond formation.[2] In this context transition metal catalyzed transformations have been achieved excellent results.[3] On the other hand, metal-free approaches also gained considerable attention in recent years for the development of eco-friendly methods.

In this context iodine catalyzed C–H bond functionalization has been extensively explored. Especially using iodine in combination with peroxides, *viz*. quaternary ammonium iodide and TBHP catalyzed C–H functionalization to construct various heterocycles through C–O, C–N bonds were well demonstrated by Ishihara,[4] Nachtsheim,[5] Yu and Han,[6] Wan,[7] and Zhu.[8] Molecular iodine and TBHP promoted functionalization of a C–H bond was explored by Wang,[9] Jiang,[10] Prabhu,[11] and Wang.[12] In all these approaches combination of iodine and peroxides is essential for C-H activation and oxidative cyclization.

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Avoiding toxic metals, peroxides and organic solvents is necessary towards the development of new synthetic methodologies to address the environmental problems. To the best of our knowledge there is no literature report on peroxide free oxidative cyclization in water for the synthesis of oxazoles. We desired to utilize the iodine promoted C-H functionalization for accessing poly substituted oxazoles under metal and peroxide free conditions.

The oxazole moieties are significant structures found in many natural products and pharmaceuticals (Figure 1).[13] Many compounds containing an oxazole motif exhibit potent biological activities.[14]

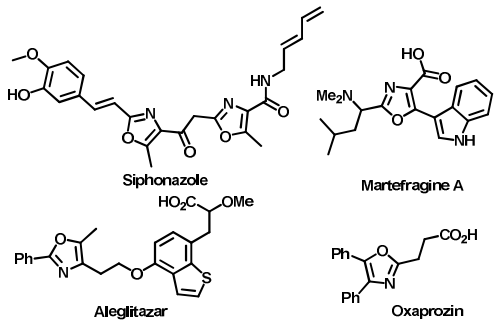


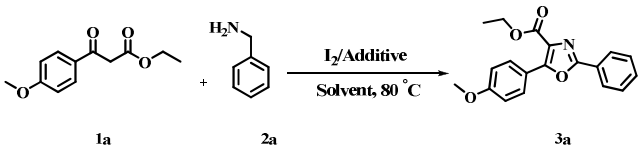
Figure 1: Representative examples of oxazoles in pharmaceuticals and other biologically active compounds.

Moreover, they are also versatile synthetic building blocks in organic synthesis.[15] Plethora of methods for construction of oxazoles has been developed over the years including cyclisation of acyclic precursors,[16] oxidation of oxazolines,[17] and the coupling of the prefunctionalized oxazoles with other organometallic reagents.[18] Cyclization of acyclic precursors to access prefunctionalized oxazoles from readily available materials has attracted intensive attention.[19] However there are some limitations associated with them, such as harsh reaction conditions as well as the use of toxic

transition metals and peroxides. In this study we have explored a efficient route to produce poly substituted oxazoles from simple and readily available β-ketoesters and benzylamines using molecular iodine as a promoter and oxidizing agent.

We began our investigation with β-keto ester **1a** (ethyl 3-(4-methoxyphenyl)-3-oxopropanoate) and benzylamine (**2a**) as model substrates. When the initial experiment was carried out in water as solvent in the presence of iodine (3 equiv.) at 80 °C, we were pleased to observe the desired oxazole **3a**, however the yield was relatively low, and the starting material **1a** was recovered. In order to increase the yield we conducted the reactions at elevated temperatures (100-120 °C) then we observed the total consumption of starting materials, however there was no improvement in the yield, presumably due to the decomposition of **1a.** Thus we turned our attention towards the introduction of oxidizing agent to increase the yield of desired poly-substituted oxazoles. Most of such cases peroxides play a prominent role in the oxidation process. But we aspired to avoid toxic oxidizing agents and develop peroxide-free method therefore; we focused our attention to investigate whether an internal oxidizing agent in a reaction system could be generated. It is known that iodine in alkaline media is converted to hypoiodous acid (HIO). The resultant conjugate base of HIO disproportionate to $2I^-$ and O_2, which can enhance the oxidizing process in presence of air.[20] We therefore screened I_2 as internal oxidizing agent with various bases (Table 1) and found $NaHCO_3$ (2.5 equiv.) to be the best choice for our reaction in terms of yield. We also replaced the iodine with a different catalyst, like N-bromo, N-chloro and N-iodosuccinamides, but the desired product (oxazole) was not obtained. This suggests that only iodine is the most efficient for oxazole formation in presence of base ($NaHCO_3$). Various solvents were investigated (Table 1, Entry 13-15), and H_2O was found to be the most efficient solvent for the transformation. Subsequently temperature effect on the reaction was also screened. When the temperature was increased, we observed slightly decreased yields and finally 80 °C was established to be the suitable temperature. After several experimental studies, we identified 1.0 equiv. of β-keto esters, 2.5 equiv. of benzylamine, 2. 5 equiv. of iodine and $NaHCO_3$ and 80 °C temperatures (Table 1, Entry 10) are optimized reaction conditions.

Table 1 Optimization of the reaction conditions[a]



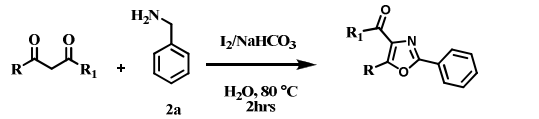
1a **2a** **3a**

Entry	Oxidant (equiv.)	Additive (equiv.)	Solvent	T °C	Time (h)	Yield[b] %
1	I_2 (3.0)	-	H_2O	80	2	30
2	I_2 (5.0)	-	H_2O	80	2	35
3	I_2 (3.0)	-	H_2O	100	2	36
4	I_2 (3.0)	$NaHCO_3$(1.5)	H_2O	100	2	62
5	I_2 (3.0)	$NaHCO_3$ (1.5)	H_2O	100	4	60
6	I_2 (3.0)	$NaHCO_3$ (1.5)	H_2O	80	4	65
7	I_2 (3.0)	$NaHCO_3$ (1.5)	H_2O	80	6	65
8	I_2 (3.0)	$NaHCO_3$ (2.0)	H_2O	80	4	70
9	I_2 (3.0)	$NaHCO_3$ (2.5)	H_2O	80	2	78
10	**I_2 (2.5)**	**$NaHCO_3$(2.5)**	**H_2O**	**80**	**2**	**78**
11	I_2 (2.5)	$NaHCO_3$ (2.5)	H_2O	80	4	73
12	I_2 (1.5)	$NaHCO_3$ (2.5)	H_2O	80	2	58
13	I_2 (2.5)	$NaHCO_3$ (2.5)	DMSO	80	2	52
14	I_2 (2.5)	$NaHCO_3$ (2.5)	DMF	80	2	<20
15	I_2 (2.5)	$NaHCO_3$ (2.5)	EtOH	80	2	32
16	I_2 (2.5)	K_2CO_3 (2.5)	H_2O	80	2	60
17	I_2 (2.5)	Cs_2CO_3 (2.5)	H_2O	80	2	63
18	NBS (2.5)	$NaHCO_3$ (2.5)	H_2O	80	2	0
19	NCS (2.5)	$NaHCO_3$ (2.5)	H_2O	80	2	0
20	NIS (2.5)	$NaHCO_3$ (2.5)	H_2O	80	2	0

[a] Conditions: **1a** (1.0 equiv.), **2a** (2.5 equiv.), I_2 (2.5 equiv.), $NaHCO_3$ (2.5 equiv.), solvent (5 mL). [b] ^{1}H NMR yield based on **1a**

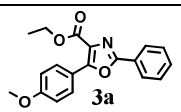
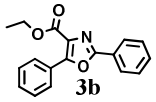
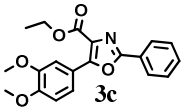
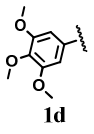
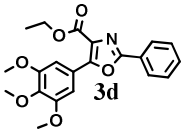
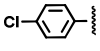
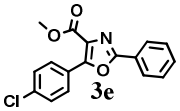
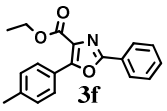
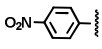
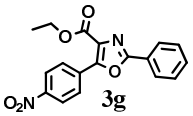
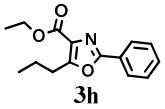
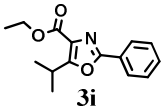
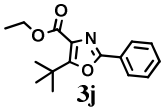
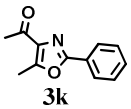
With the optimized conditions in our hand, we explored the scope of this protocol on a series of β-keto esters (**1a**-**1g**) with benzylamine (**2a**). Both the electron directing and withdrawing groups on the aromatic ring of β-keto esters are well tolerated and smoothly afforded the desired oxazoles (**3a**-**3g**) in good yields. Aliphatic β-keto esters gave better yields profile than the aromatic β-keto esters (Table 2, Entry 9-11). It is noteworthy to mention here that when we used 1, 3-diketone i.e. acetyl acetone (**1k**) instead of β-keto ester, we observed the formation of **3k** in very low yield.

Table 2 Synthesis of 2, 4, 5-trisubstituted oxazoles (**3a-3k**) with different β-ketoesters (**1a-1j**) and 1, 3-diketone (**1k**)[a]



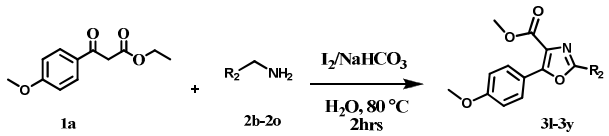
1a-1d and **1f-1j**: $R_1 = OC_2H_5$
1e: $R_1 = OCH_3$
1k: $R_1 = CH_3$

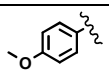
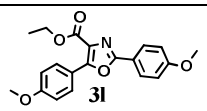
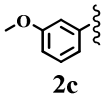
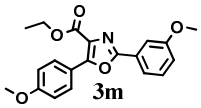
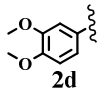
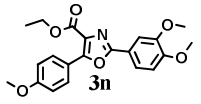
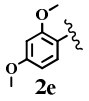
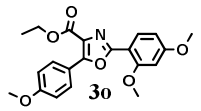
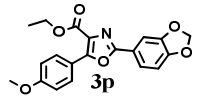
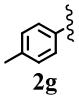
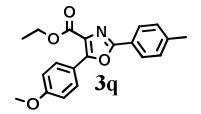
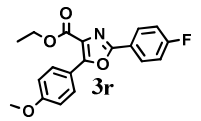
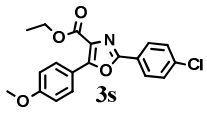
3a-3d and **3f-3j**: $R_1 = OC_2H_5$
3e: $R_1 = OCH_3$
3k: $R_1 = CH_3$

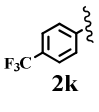
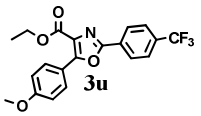
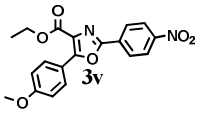
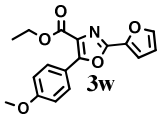
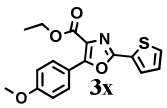
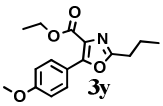
Entry	R	Product	Yield [b] %
1	 **1a**	 **3a**	78
2	 **1b**	 **3b**	75
3	 **1c**	 **3c**	80
4	 **1d**	 **3d**	81
5	 **1e**	 **3e**	75
6	 **1f**	 **3f**	78
7	 **1g**	 **3g**	83
8	 **1h**	 **3h**	80
9	 **1i**	 **3i**	85
10	 **1j**	 **3j**	85
11	CH_3 **1k**	 **3k**	<10

Then we proceeded to study the scope of different amines (**2b-2o**) with β-keto ester (**1a**) under optimized conditions. It was found that electron-rich and electron deficient substituents on benzylamines were well tolerated. Heterocyclic amines such as **2m** and **2n** also gave good yields (Table 3, Entry 12 and 13). However with aliphatic amine (**2o**) as substrate, the desired oxazole product (**3y**) was not observed (Table 3, Entry 14).

Table 3 Synthesis of 2, 4, 5-trisubstituted oxazoles (**3l-3y**) with different primary amines (**2b-2o**)[a]

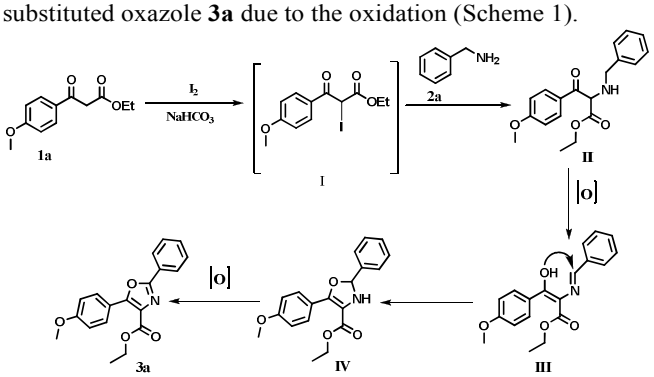


Entry	R_2	Product	Yield [b] %
1	 **2b**	 **3l**	85
2	 **2c**	 **3m**	85
3	 **2d**	 **3n**	82
4	 **2e**	 **3o**	81
5	 **2f**	 **3p**	85
6	 **2g**	 **3q**	79
7	 **2h**	 **3r**	80
8	 **2i**	 **3s**	88
9	 **2j**	**3t**	91

10	 2k	 3u	75
11	 2l	 3v	79
12	 2m	 3w	64
13	 2n	 3x	74
14	 2o	 3y	0

Conditions [a]: **1a** (1.0 equiv.), **2a** (2.5 equiv.), I_2 (2.5 equiv.), $NaHCO_3$ (2.5 equiv.), water (5mL). [b] isolated yields

The possible reaction mechanism for the formation of poly-substituted oxazoles appears to be β-keto ester **1a** reacts with benzylamine in the presence of iodine and $NaHCO_3$ to furnish intermediate **II**,[21] *via* the α-iodo-β-keto ester derivative **I**. Cyclization followed by oxidation of intermediate **II** provides the ethyl 2,3-dihydrooxazole derivative **IV** and the resultant intermediate **IV** might have aromatized to give stable poly-substituted oxazole **3a** due to the oxidation (Scheme 1).



Scheme 1: Proposed mechanism for the synthesis of poly substituted oxazoles

In summary we have developed the metal and peroxide-free route to furnish the polysubstituted oxazole derivatives by the oxidative domino cyclization in presence of molecular iodine and $NaHCO_3$ in water for the first time. This method constitutes metal free and peroxide free, easy to handling, avoided toxic by-products of metals and solvents for reaction medium and purification.

Experimental section

^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 200FT, Bruker Robotics, Bruker DRX 300 and 400 Spectrometers at 200, 300, 400 MHz (1H) and 50, 75, 100 MHz (^{13}C). Experiments were recorded in $CDCl_3$ and DMSO-d_6 at 25°C. The data are accounted as follows: Chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations' for multiplicity are as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. Purification of reaction mixtures were performed with Methanol for recrystallization methods. Reagents and solvents were commercial grade and were used as supplied without further purification, unless otherwise stated

General procedure for the synthesis of 2, 4, 5,-Trisubstituted oxazoles:

Iodine (2.5 equiv) and H_2O (5mL) were added to β- keto ester (1.0 equiv.), benzyl amine (2.5 equiv. added in two portions) and $NaHCO_3$ (2.5 equiv.) in 50mL round bottom flask. The resulting solution was stirred at 80°C and the reaction monitored by TLC. Upon reaction completion, the reaction was allowed to cool to room temperature before the addition of a 15mL ethyl acetate and saturated solution of $Na_2S_2O_3$ (10mL). The mixture was then separated. The organic phase was dried with Na_2SO_4 and solvent was evaporated under vacuum. The impurities were removed by rinsing the crude material with methanol (3X5ml) to get the pure oxazole derivatives.

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Notes and references

†Electronic Supplementary Information (ESI) available: All the spectral data of the compounds and experimental procedures associated with this article is available online at. See DOI: 10.1039/b000000x/

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