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Synthesis of 3*H*-Quinazolin-4-ones and 4*H*-3,1-Benzoxazin-4-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation using Potassium Iodide-*tert*-Butyl Hydroperoxide

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Abstract: A simple and elegant method for benzylic activation was demonstrated employing the potassium iodide/*tert*-butyl hydrogen peroxide catalytic system. This methodology was further extended for the synthesis of biologically important heterocycles namely, 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones including mecloqualone and etaqualone which are important quinazolinone-based drugs used for the treatment of insomnia in good yields.

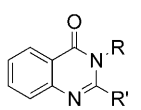
Keywords: 4*H*-3,1-benzoxazin-4-ones; oxidation; peroxides; potassium iodide; 3*H*-quinazolin-4-ones

Introduction

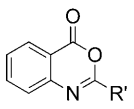
3*H*-Quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones (Figure 1) are core structural subunits that exist in a number of bioactive natural products.[1] 3*H*-Quinazolin-4-ones exhibit a broad spectrum of biological and pharmaceutical activities including antihypertensive,[2] antidiabetic,[3] anti-inflammatory,[4] antibacterial,[5] anticonvulsant,[6] antitumor,[7] central nervous system (CNS) depressant[8] and diuretic[9] activities. Along similar lines, 2-substituted-4*H*-3,1-benzoxazin-4-ones compounds act as chymotrypsin inactivators,[10a] inhibitors of human leukocyte elastase[10b,c] and serine protease.[10d]

Conventional methods for the preparation of 3*H*-quinazolin-4-ones employ the coupling of 2-aminobenzoic acid or its derivatives with acyl chloride or carboxylic acid anhydride to give benzoxazinone which on subsequent addition to an amine yields the desired product.[11] Other synthetic routes include the microwave-assisted three-component methodology from anthranilic acids,[12] solvent-free synthesis from isatoic anhydride and orthoester with primary amine employing silica-sulphuric acid (SSA)[13a] and a solid-phase traceless synthesis.[13b] Recently, Alper and co-worker reported the synthesis of quinazolin-4-(*3H*)-ones through palladium (Pd)-catalyzed cyclocarbonylation of *o*-iodoanilines with imidoyl chlorides and carbon monoxide.[14] Similarly, several methods have been reported for the synthesis of 2-substituted-4*H*-3,1-benzoxazin-4-ones, primarily from anthralinic acid or its derivatives. Other notable methods include oxidation of 2-substituted indoles and 2-phenylindolenin-3-one, electrochemical cyclization of *o*-trichloroacetylanilides, rearrangement of 2-phenylisatogen, etc.[15] Another strategy was through the Pd-catalyzed carbonylation of *o*-iodoanilines with unsaturated halides,[16a] triflates,[16b] or acid chlorides[16c] in the presence of CO. However, in terms of substrate scope, yields and the reaction conditions, these methods suffer from one or more drawbacks.

For the last few years we have been focussing on catalytic oxidative organic transformations using non-transition metals, particularly with halogens and their derivatives. In this regard, we have reported previous-



3*H*-quinazolin-4-one



4*H*-3,1-benzoxazin-4-one

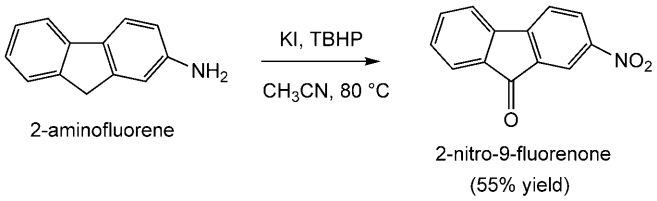
Figure 1. Basic structures of 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones.

ly that the combination of a catalytic amount of potassium iodide (KI) in the presence of 70% *tert*-butyl hydroperoxide in water (TBHP) as the external oxidant is effective for various oxidative transformations.[17] Recently, we have also demonstrated the construction of heterocycles like 2-quinazolines and 4*H*-benzo[*d*][1,3]oxazines *via* cross-dehydrogenative coupling using commercially available NaOCl.[18] Herein, we wish to report a new strategy for the synthesis of 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones *via* benzylic oxidation using potassium iodide/*tert*-butyl hydrogen peroxide (KI-TBHP).

Results and Discussion

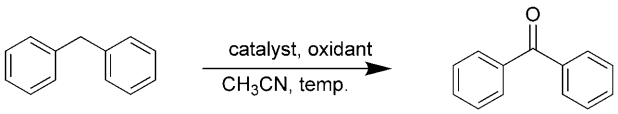
Benzylic Oxidation using KI/TBHP

During our earlier investigation on the selective oxidation of aromatic amines to nitro compounds with



Scheme 1. Oxidation of 2-aminofluorene to 2-nitro-9-fluorenone using KI-TBHP.

Table 1. Optimization studies for benzylic oxidation.[a]



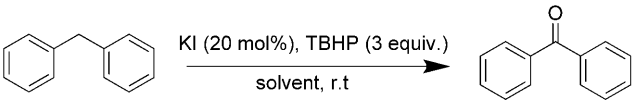
Entry	Catalyst [mmol]	Oxidant [mmol]	Temp. [°C]	Conversion [%][b]
1	KI (0.2)	-	r.t.	-
2	-	TBHP [3.0]	r.t.	08
3	KI (0.2)	TBHP [3.0]	r.t.	78
4	KI (0.2)	H_2O_2 [3.0]	r.t.	08
5	KI (0.2)	NaOCl [3.0]	r.t.	06
6	KI (0.2)	UHP [3.0]	r.t.	02
7	KI (0.2)	mCPBA [3.0]	r.t.	02
8	KI (0.1)	TBHP [3.0]	r.t.	64
9	KI (0.2)	TBHP [3.8]	r.t.	78
10	-	I_2 [3.0]	r.t.	-
11	KI (0.2)	TBHP [3.0]	80	43

[a] *Reaction conditions:* diphenylmethane (1 mmol), catalyst, oxidant, CH_3CN (3 mL), 21 h.
[b] Conversions based on GC with respect to diphenylmethane.

the KI-TBHP system,[17b] the reaction with 2-aminofluorene resulted in the formation of 2-nitro-9-fluorenone, which provided us the initial clue for benzylic oxidation with our catalytic system (Scheme 1).

Initially, we focused our attention on the benzylic oxidation of alkylarenes to yield their corresponding carbonyl compounds. Diphenylmethane was chosen as the model substrate for optimization studies. First, the role of the catalyst was ascertained by doing background experiments. No product was observed with 20 mol% of KI. A very low product conversion was observed with 70% aqueous TBHP at room temperature and CH_3CN as solvent (Table 1, entries 1 and 2). Under similar reaction conditions, use of 20 mol% of KI and 3.0 equivalents of oxidant afforded 78% of oxidized product (Table 1, entry 3), which clearly established the role of the catalyst for the benzylic oxidation. Furthermore, screening of various oxidants, such as hydrogen peroxide (30% v/v solution of H_2O_2), NaOCl (approx 4% w/v of available chlorine), urea hydrogen peroxide (UHP) and *m*-chloroperbenzoic acid (*m*CPBA) (3 equivalents of oxidants are taken in all these cases) could not improve the product conversion. The reaction did not proceed, when it was performed only with molecular iodine (I_2) (Table 1, entry 10). Similarly, no improvement was observed on variation of the catalyst and oxidant ratio (KI:TBHP varied from 0.1:2.0, 0.2:3.0 and 0.2:3.8). Hence, further solvent variations were carried out at room temperature (Table 2). The yields were low with CH_2Cl_2, THF, EtOAc, toluene, MeOH. Moderate to good conversions are observed with *t*-BuOH, aqueous

Table 2. Screening of solvents for benzylic oxidation.[a]

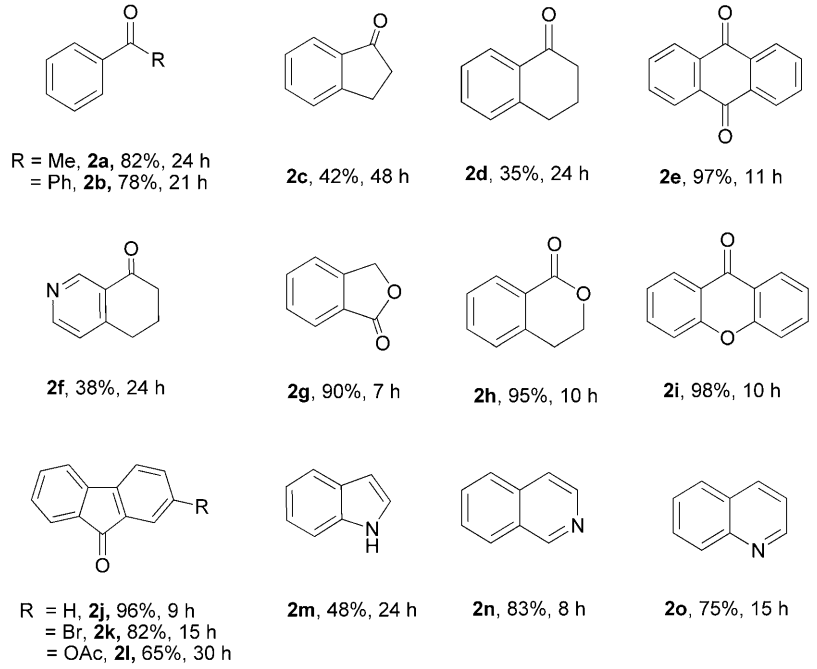


Solvent	Conversion [%][b]	Solvent	Conversion [%][b]
CH_3CN	78	CH_3OH	28
t-BuOH	70	Toluene	24
H_2O	83	EtOAc	41
aq. NH_3	69	CH_2Cl_2	40
DMSO	37	THF	06

[a] *Reaction conditions:* diphenylmethane (1 mmol), solvent (3 mL), 21 h.
[b] Conversions based on GC with respect to diphenylmethane.

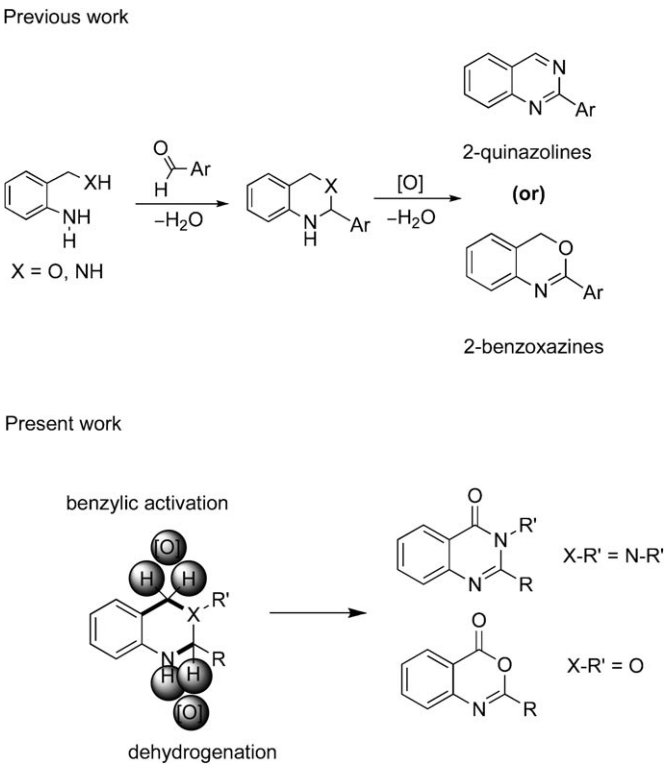
NH_3, CH_3CN and water. Although the maximum conversion was observed in water, owing to its limitation with respect to substrate solubility, CH_3CN was chosen as the solvent of choice for further studies. Thus, 20 mol% of KI in conjunction with 3 mmol of TBHP as oxidant in CH_3CN at room temperature proved to be the best reaction conditions (Table 1, entry 3).

The general applicability of this method was evaluated for structurally diverse alkylarenes (Scheme 2).



Scheme 2. Benzylic oxidation of alkylarenes catalyzed by KI-TBHP.

The reaction proceeds smoothly producing the required carbonyl compounds in moderate to excellent yields. In the case of indan, the reaction was slow and 42% of 1-indanone (Scheme 2, **2c**) was formed after 48 h. We have also observed the hydroxy derivative, i.e., 1-indanol as minor product, which was determined by GC and confirmed by GC-MS. In the case of 9,10-dihydroanthracene, the dicarbonyl product, 9,10-anthracenedione was formed with 6 equivalents of oxidant (Scheme 2, **2e**). When oxygen is present in the ring adjacent to the benzylic position, as in the case of 1,3-dihydroisobenzofuran and isochroman, the desired products were obtained in excellent yields after shorter reaction times (Scheme 2, **2g**, **2h**). For fluorene derivatives, the reactivity depends on the substituent present. Thus fluorene gave the required fluorenone almost quantitatively within 9 h (Scheme 2, **2j**), whereas when electron-withdrawing bromine or acetyl groups are present on the aromatic ring, the reaction was found to be slow (Scheme 2, **2k**, **2l**). In the case of N-heterocycles, instead of benzylic oxidation, the reaction proceeds to aromatization of the heterocyclic ring (Scheme 2, **2m–o)**.

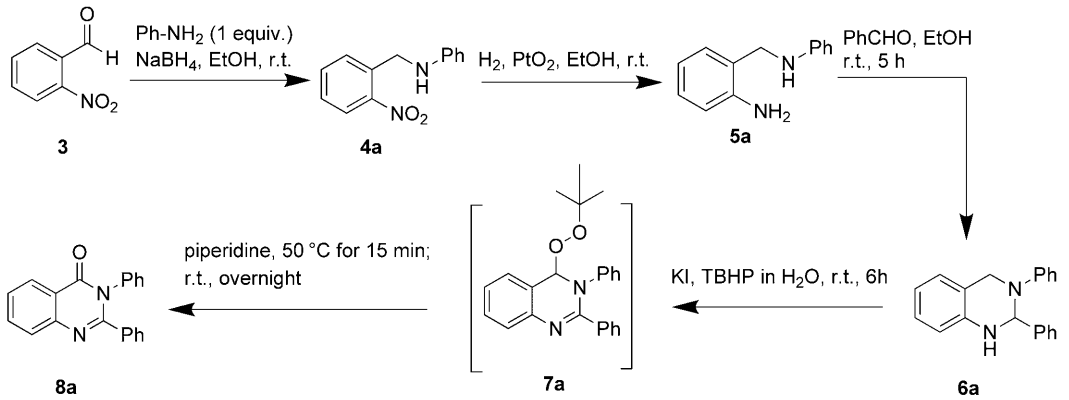


Scheme 3. Synthesis of 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones *via* benzylic oxidation.

One-Pot Synthesis of 3*H*-Quinazolin-4-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation

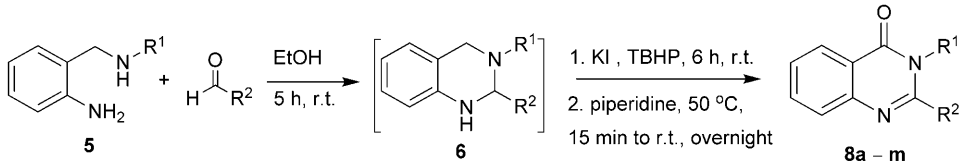
The higher activity of the benzylic C–H bond adjacent to a heteroatom like oxygen and nitrogen as well as our earlier work on the synthesis of 2-quinazolines and 4*H*-benzo[*d*][1,3]oxazines *via* cross-dehyderogenative coupling prompted us to explore the KI-TBHP system for the synthesis of 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones (Scheme 3). For this we have synthesized substituted *N*-(2-aminobenzyl)-amines as the starting material, presuming that benzylic oxidation will take over the aromatization of the condensed cyclic product.

A schematic representation for the synthesis of 3*H*-quinazolin-4-ones is given in Scheme 4. The initial coupling partner, i.e., *N*-(2-aminobenzyl)aniline (**5a**) was synthesized from 2-nitrobenzaldehyde (**3**) *via* reductive amination to yield **4a** followed by further reduction.[19] Initial studies were performed by treating **5a** with benzaldeyhde in ethanol to yield the cyclic product **6a** which, on further treatment with KI/TBHP, resulted in the desired product **8a** along with 4-*tert*-butylperoxy-2,3-diphenylquinazoline (**7a)** as the major product. The product **7a** was isolated and characterized by ^{1}H NMR. The formation of **7a** was rather obvious, considering the literature precedents for this intermediate in oxidative iminium ion formation from tertiary amine with TBHP as the oxidant.[20,21] How-

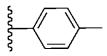
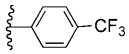
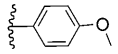
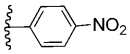
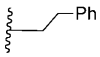
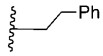


Scheme 4. Synthesis of 2,3-diphenyl-3*H*-quinazolin-4-one using the KI/TBHP catalytic system.

Table 3. Synthesis of 2,3-substituted-3*H*-quinazolin-4-ones using KI/TBHP.



5 **6** **8a – m**

Entry	R^1	R^2	Product	Yield [%][a]
1	Ph	Ph	**8a**	73
2	Ph		**8b**	84
3	Ph		**8c**	68
4	Ph	methyl	**8d**	68[b]
5	Ph	ethyl	**8e**	76
6		Ph	**8f**	57
7		methyl	**8g**	35[b]
8		methyl	**8h**	63[b]
9	butyl	Ph	**8i**	88
10	butyl		**8j**	60
11	butyl		**8k**	70
12			**8l**	61
13		Ph	**8m**	68

[a] Yields refer to the isolated yield of pure products.
[b] Acetaldehyde was dropped slowly into the solution of *N*-(2-aminobenzyl)substituted amines in ethanol at 0 °C.

ever, when **7a** was further treated with piperidine, the desired product **8a** was obtained in quantitative yield *via* Kornblum-type decomposition which was finally confirmed by ^{1}H NMR and ESI-MS.[22]

Further reactions were performed in one-pot without isolating the peroxy ether intermediates **7**. Various *N*-(2-aminobenzyl)-substituted amines were coupled with structurally diverse aromatic and aliphatic aldehydes to obtain 2,3-substituted 3*H*-quinazolin-4-ones (Table 3). When *N*-(2-aminobenzyl)aniline was taken as the amine variant along with various substituted benzaldehydes and aliphatic aldehydes, there was no appreciable change in terms of yields (Table 3, **8a–8e**). On the other hand, reactions with *o*-substituted *N*-(2-aminobenzyl)aniline resulted in lower yields, which may be due to the steric influence (Table 3, **8f**, **8g**). With aliphatic *N*-(2- aminobenzyl)amines, the yields were good irrespective of the aldehyde variant (Table 3, **8i** and **8j**). Some of these molecules possess biological importance and were used in quinazolinone-based drugs. For example, mecloqualone (**8g**) and etaqualone (**8h**) have sedative, hypnotic and anxiolytic properties, and are used for the treatment of insomnia. Similarly NPS 53574 (**8l**) is found to be potent calcium receptor antagonist.

Synthesis of Benzo[*d*][1,3]oxazin-4-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation

The above strategy was further applied for the synthesis of 2-phenylbenzo[*d*][1,3]oxazin-4-one using 2-aminobenzyl alcohol as the coupling partner. Under similar reaction conditions, treatment of 2-aminobenzyl alcohol with benzaldehyde yielded the cyclized product which, on further oxidation with KI/TBHP, resulted in 2-phenylbenzo[*d*][1,3]oxazin-4-one (**12a**) in a trace amount along with undesired products. So, instead of performing the reaction in one pot, we have synthesized 2-phenyl-4*H*-benzo[*d*][1,3]oxazine (**11a**) by our earlier reported method[18] which, on further treatment with KI/TBHP at room temperature, resulted in the desired product **12a** along with the cleaved product **13a** (Scheme 5).

Experiments for optimization of the conditions for the construction of 2-penylbenzo[*d*][1,3]oxazin-4-one (**12a**) from 2-phenyl-4*H*-benzo[*d*][1,3]oxazine (**11a**) with different solvents and oxidants are given in Table 4. Control runs showed that the catalyst was crucial for this oxidative transformation (Table 4, entries 1–3). Screening of various solvents, such as THF, 1,4-dioxane, DCM, DMSO and DMF did not improve the yield of the desired product (Table 4, entries 4–8). When the reaction was examined with different oxidants such as H_2O_2, urea hydrogen peroxide, *m*CPBA, TBHP in decane and NaOCl, the yields were negligible (Table 4, entries 9–13). There was no significant improvement in yield of the desired product when molecular iodine was used as the catalyst (Table 4, entry 15). When the reaction was carried out with iodine (I_2) as an oxidant, it did not proceed (Table 4, entry 16). There was a dramatic decrease in the yield when a lesser amount of oxidant was employed (Table 4, entry 17). From these optimization studies it is clear that 0.2 equivalents of KI as catalyst, 3.8 equivalents of TBHP as oxidant in 3 mL of CH_3CN under reflux conditions proved to be the best (Table 4, entry 14).

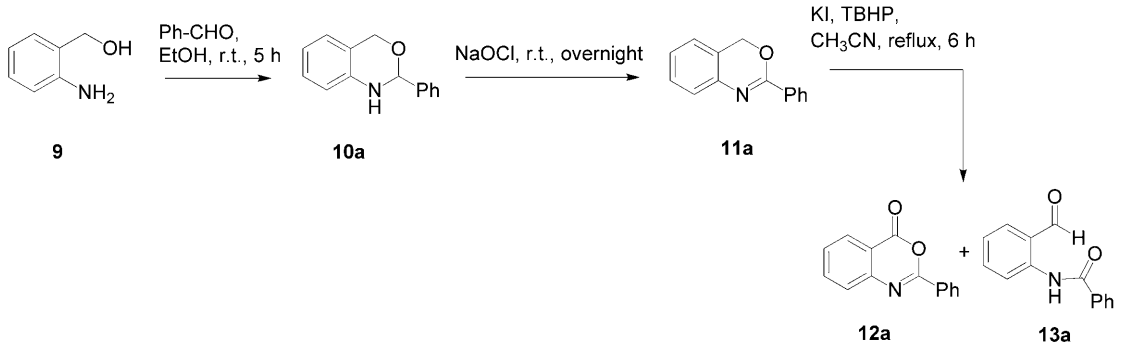
With the optimized reaction condition in hand, we have performed the reactions with pre-synthesized 2-substituted 4*H*-benzo[*d*][1,3]oxazines **11a–e** (Table 5). Irrespective of the electronic nature of the substrates, all the oxidized products **12a–e** were obtained in moderate to good yields.

Mechanistic Considerations

Although the exact mechansim is not clear right now, a possible pathway involving three key steps for the formation of 3*H*-quinazolin-4-ones is shown in Scheme 6. The first step involves the oxidation of KI with TBHP to molecular iodine and potassium hydroxide, which subsequently oxidizes the cyclic compound **6** to hypothetical intermediates $\mathbf{In_1}$ and $\mathbf{In_2}$ in the second step. Finally, the intermediates react with one equivalent of TBHP to form the product **7**, which was isolated and well characterized. The following experiments have been carried out to establish the above proposed mechanism.

To prove that TBHP oxidizes KI to iodine, a blank reaction with 0.2 mmol of KI in the presence of 3 equivalents of TBHP in water as well as CH_3CN was performed, where we could observe an immediate change in colour (dark brown solution). The liberation of iodine was further confirmed by addition of starch solution which instantaneously changed to bluish black. The liberation of iodine occurs very rapidly (within 1 min) which is much faster than the time scale of our reaction. Apart from the formation of I_2 and KOH in the first step, the involvement of other species such as *t*-BuOI cannot be ruled out. It has been reported that under alkaline conditions iodine participates in multiple equilibria, in which hypoiodous acid is one of the possible intermediates.[23] A similar intermediate was also proposed under acidic conditions with NaI and H_2O_2 in the α-iodination of ketones.[24]

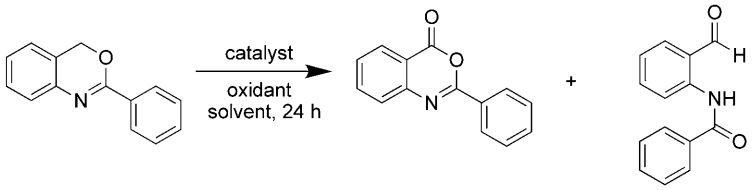
Regarding the second step, we have performed two experiments, one with cyclic product **6** in the presence



9 10a 11a 12a 13a

Scheme 5. Synthesis of 2-phenylbenzo[*d*][1,3]oxazin-4-ones using KI/TBHP.

Table 4. Optimization of the reaction conditions for construction of 2-subsitituted benzo[*d*][1,3]oxazin-4-ones.[a]

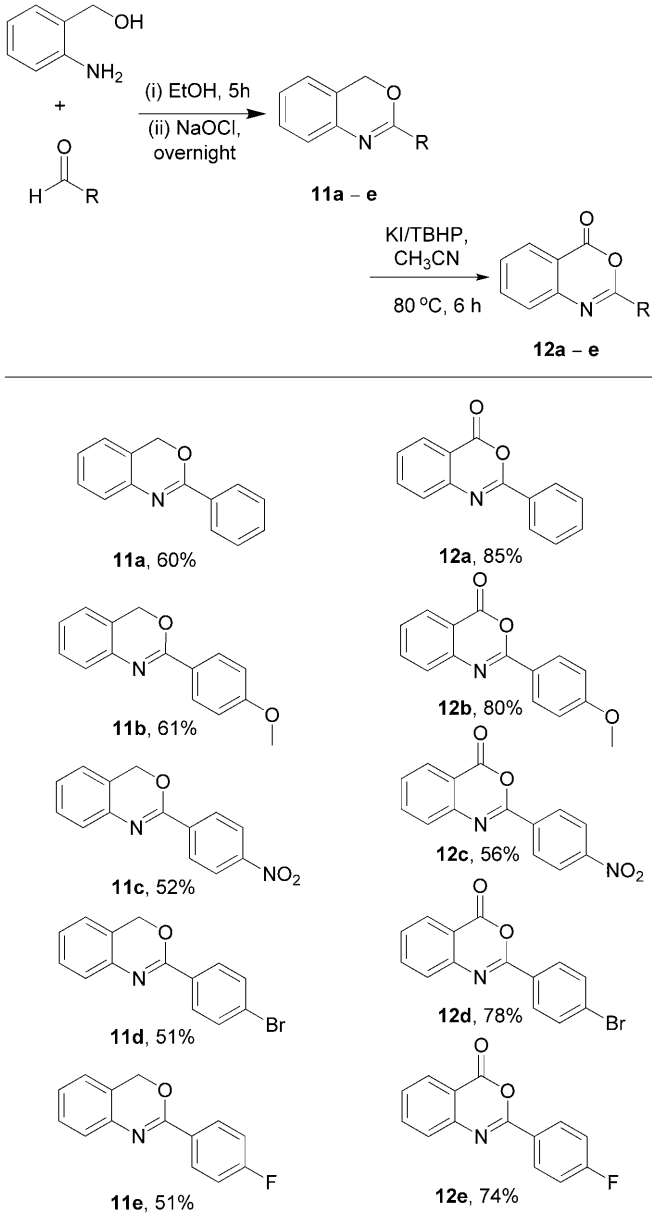


11a **12a** **13a**

Entry	Catalyst	Oxidant	Solvent	Conversion [%][b]	
				12a	**13a**
1	–	TBHP	CH_3CN	10	15
2	KI	–	CH_3CN	–	–
3	KI	TBHP	CH_3CN	30	70
4	KI	TBHP	THF	20	15
5	KI	TBHP	1,4-dioxane	15	15
6	KI	TBHP	DCM	10	13
7	KI	TBHP	DMSO	06	10
8	KI	TBHP	DMF	11	10
9	KI	H_2O_2	CH_3CN	–	05
10	KI	NaOCl	CH_3CN	–	–
11	KI	UHP	CH_3CN	–	10
12	KI	*m*CPBA	CH_3CN	–	–
13	KI	TBHP in decane	CH_3CN	10	05
14	KI	TBHP	CH_3CN[c]	90	10
15	I_2	TBHP	CH_3CN[c]	85	15
16	–	I_2	CH_3CN[c]	–	–
17	KI	TBHP	CH_3CN[c,d]	60	10

[a] *Reaction conditions:* **11a** (1 mmol), catalyst (0.2 equiv.), oxidant (3.8 equiv.), solvent (3 mL).
[b] Conversion based on GC with respect to **11a**.
[c] Reaction was carried out at 80 °C for 6 h.
[d] 3 equiv. of TBHP were used.

Table 5. Synthesis of 2-subsitituted benzo[*d*][1,3]oxazin-4-ones using KI/TBHP.[a]



[a] *Reaction conditions:* **11a–e** (1 mmol), KI (0.2 mmol), TBHP (3.8 equiv.), CH_3CN (3 mL), 80 °C, 6 h. Yields refer to the isolated yield of pure products.

of three equivalents of I_2 and KOH and the second one with I_2 and KOH with cyclic product **6** in the presence of TBHP. In the former case we could not observe any product, however, in the later case we have observed a small amount of **7** along with some undesired products. This clearly indicates the unstable nature of intermediates $\mathbf{In_1}$ and $\mathbf{In_2}$ which require the presence of TBHP for the formation of product **7**. Similar to iminium ion, $\mathbf{In_2}$ intermediates are known to occur through benzylic *tert*-amine oxidation in the presence of I_2 and base,[20] which upon nucleophilic capture yield **7**.[21] Treatment of **7** with piperidine yields the desired product **8** through a Kornblum-type decomposition.[22]

To investigate the possibility for the generation of any radical type of intermediates, the reaction was performed by adapting the earlier reported procedure.[25] To a solution of *N*-(2-aminobenzyl)aniline (**5a**) (3 mmol) in 12 mL of ethanol, benzaldehyde (3 mmol) was added and stirred at room temperature for 5 h. To the same solution KI (0.6 mmol) was added and the reaction vessel was sealed with a septum, allowing inclusion of air. An empty balloon was added to capture any oxygen generated during the course of the reaction. To the reaction mixture 70% TBHP in H_2O (2.1 mL, 5 equivalents) was added in one portion *via* syringe and stirred at room temperature for 6 h. There was no inflation of the balloon suggesting that there is no oxygen evolution, implying that there is no formation of radical intermediates, i.e., *tert*-butylperoxy radical, which is known to dimerize to di-*tert*-butyl tetraoxide which in turn releases oxygen.[25]

In similar lines, the conversion of **11** to **12** occurs *via* oxidation followed by ring cleavage to yield $\mathbf{In_3}$, which is equilibrium with $\mathbf{In_4}$. The intermediate $\mathbf{In_3}$ was isolated and characterized by ^{1}H NMR and ESI-mass spectral analysis.

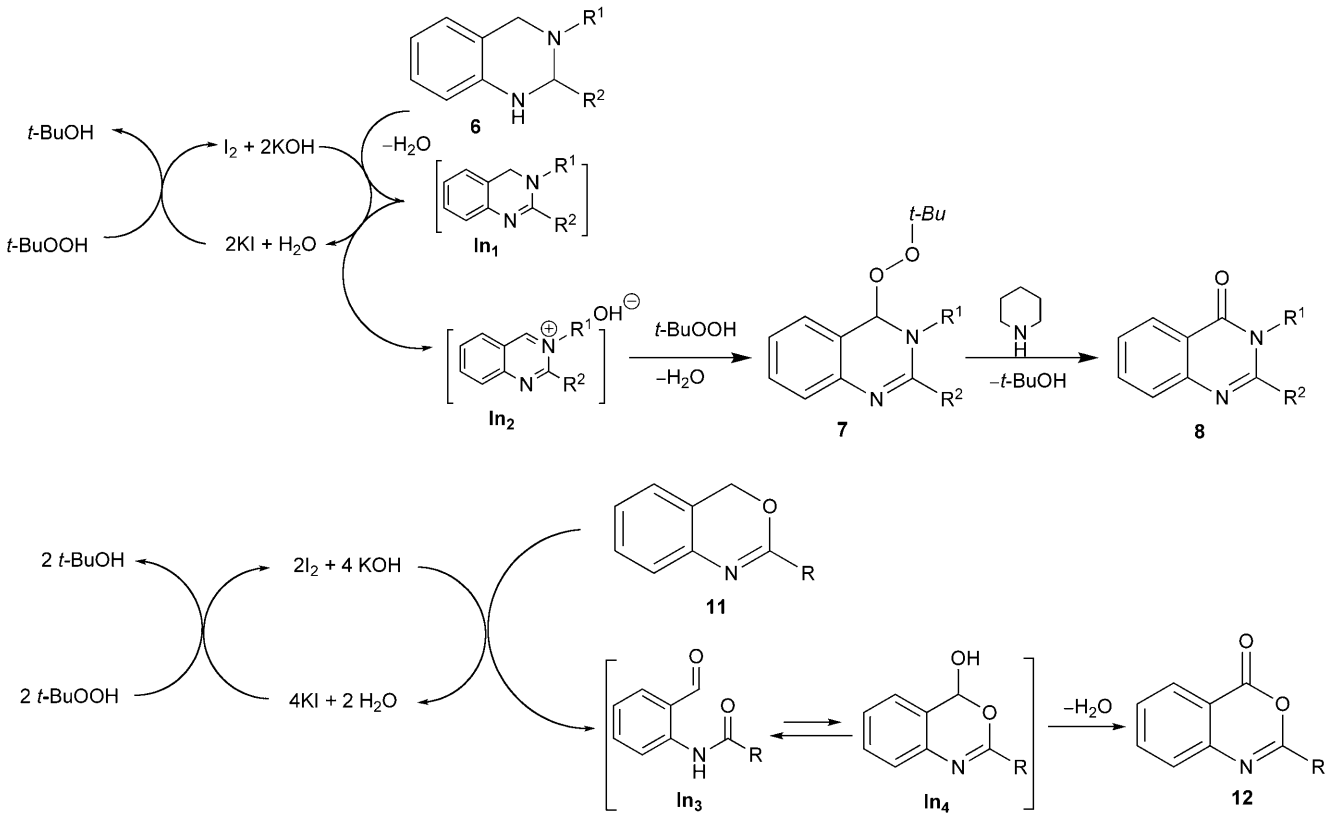
Conclusions

In summary, we have demonstrated an elegant and simple method for benzylic C–H oxidation using KI/TBHP as the catalytic system. By employing the same catalytic oxidation strategy, we have demonstrated the construction of biologically important heterocycles, namely, 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones, including mecloqualone and etaqualone which are important quinazolinone-based drugs used for the treatment of insomnia. Further research on the application of this methodology for the synthesis of biologically important molecules having 3*H*-quinazolin-4-ones and 4*H*-3,1-benzoxazin-4-ones as a core structure is ongoing in our laboratory.

Experimental Section

General Procedure for Benzylic Oxidation of Alkylarenes

To a solution of alkylarene (1.0 mmol), potassium iodide (0.20 mmol) in 3 mL of CH_3CN, was added a solution of 70% aqueous TBHP (3.0 mmol) dropwise over a period of 30 min and stirred at room temperature. Progress of the re-



Scheme 6. Plausible mechanism for the formation of 3*H*-quinazolin-4-ones and 2-subsitituted-benzo[*d*][1,3]oxazin-4-ones.

action was monitored by TLC and the reaction mixture was quenched after the stipulated time with saturated aqueous $Na_2S_2O_3$, washed with brine, extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate mixture and was analyzed by ^{1}H NMR, ^{13}C NMR, GC and GC-MS.

General Procedure for the One-Pot Synthesis of Substituted Quinazoline-4(3*H*)-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation using KI/TBHP

To a solution of *N*-(2-aminobenzyl)-substituted amines (1 mmol) in 4 mL of ethanol, aldehyde (1 mmol) was added and stirred at room temperature for 5 h. To the same solution, KI (0.2 mmol) and 0.66 mL of 70% TBHP in H_2O (5 equiv.) was added dropwise for 5 min and stirred at room temperature for 6 h. The solvent was removed under reduced pressure. The residue was treated with 0.5 mL of piperidine. The mixture was heated to 50 °C for 15 min, allowed to cool to room temperature and stirred overnight. The residue was mixed with water and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and solvent was removed by rotary evaporation. The product was isolated by column chromatography using hexane/ethyl acetate mixture as eluent and was analyzed by ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and ESI-HR-MS.

General Procedure for Synthesis of 2-Substituted Benzo[*d*][1,3]oxazin-4-ones *via* Benzylic Oxidation using KI/TBHP

To a solution of 2-substituted 4*H*-benzo[*d*][1,3]oxazine (1 mmol) in 3 mL of CH_3CN, KI (0.2 mmol) and 0.5 mL of 70% TBHP in H_2O (3.8 equivalents) were added dropwise for 5 min. Then the reaction mixture was refluxed for 6 h and allowed to cool to room temperature. The solvent was evaporated under reduced pressure. The residue was mixed with water and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and solvent was removed by rotary evaporation. The product was isolated by column chromatography using hexane/ethyl acetate mixture as eluent and was analyzed by ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and ESI-HR-MS.

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