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Quinazolin-4(3*H*)-ones: A Tangible Synthesis Protocol via an Oxidative Olefin Bond Cleavage Using Metal-Catalyst Free Conditions

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Abstract: An efficient and selective oxidative procedure for the synthesis of quinazolinones from readily available *o*-aminobenzamides and styrenes was developed. A number of potentially pharmacologically relevant quinazolinones were prepared using metal- and catalyst-free conditions. The synthesis procedure highlights the sustainable operation, low-priced, free from perilous materials, green solvent and environmental affability. The synthesized products were isolated in moderate to excellent yields.

Keywords: catalysis; metal-free; catalyst-free; quinazolinone; styrene; *o*-aminobenzamide; antioxidant; anticancer

1. Introduction

Oxidative cleavage of unsaturated hydrocarbons is one of the most significant and efficient approaches to produce carbonyl compounds in organic chemistry, petrochemical industry as well as the conversion of biomass [1–4]. Aldehydes and ketones are important precursors to acids and alcohols as well as widely used in pharmaceutical, agriculture and most importantly in the fine chemical industry. The direct oxidative cleavage of olefins is still a challenge and greatly dependent on the use of conventional methods, for instance using ozone [5–8], $KMnO_4$ [9,10], oxone [11,12], $NaIO_4$ [13], OsO_4 [14], high valance I_2 [15,16], *m*-chloroperbenzoic acid, etc. [17,18]. However, these methods suffer from the long reaction period, over oxidation, low selectivity, limited substrate scope, poor functional group tolerance and environment unfriendliness.

There is need for development of environment benign synthetic methodologies, procedures not requiring use of hazardous materials and expensive reagents. In order to match the request of green chemistry some methodologies were developed for the oxidation of alkenes using the palladium catalyst under high pressure of oxygen [19]. Our group has also developed several metal-free oxidative methodologies [20–22]. Although these methodologies show progress towards oxidative cleavage of unsaturated hydrocarbons, nevertheless, there is still much room for the development of synthetic methodologies that provide the generality of substrate scope for the synthesis of fine chemical building blocks.

Quinazolinone heterocycles are an important class of fundamental building blocks in modern organic synthesis with recognized importance in natural products, bioactive compounds and pharmaceutical industry. A broad range of medicinal properties are reported for quinazolinones, such as anticancer [23–27], antibacterial [28–30], antifungal [31–35], antimalarial [36], antiviral [37,38] as well as anti-microbial cholinesterase inhibitors [39,40], making quinazolinone a privileged class of *N*-containing heterocyclic scaffolds (Figure 1).

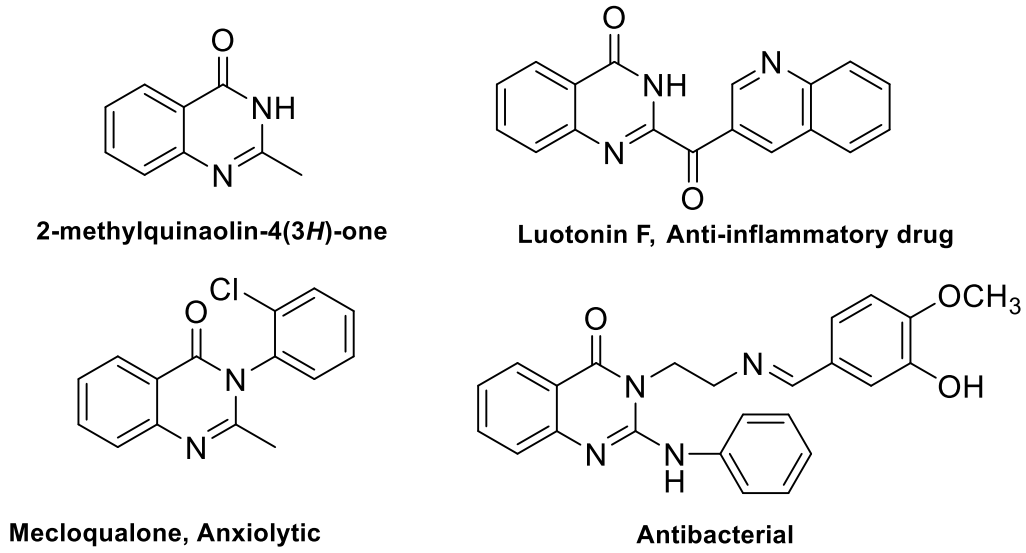


Figure 1. Selected examples of bio-active drugs with a quinazolinone skeleton.

Due to diverse biological applications in pharmaceutical industry numerous synthetic methodologies were developed for the synthesis of quinazolinones [41–58]. These methods furnish the quinazolinones through reactions of readily available anthranilamide (2-aminobenzamide) with aldehydes, alcohols, esters, carboxylic acids, methyl arenes and amines under harsh reaction conditions in the presence of transition metals, etc. [41–58]. Despite a high number of synthetic methodologies in literature, there is not much known for the synthesis of quinazolinones via oxidative reactions of 2-aminobenzamide with industrially important unsaturated hydrocarbons, i.e., olefins. Recent examples of oxidation-annulation reactions of 2-aminobenzamide and olefins were discovered by Liu et al. [59] and An et al [60] using transition metals Pd-ligand and Ru-cluster/ceria/CO respectively (Figure 2). More recently, Abdullaha et al. [61] has reported metal-free, iodine catalyzed reactions to synthesize quinazolinones from *o*-aminobenzamide and alkynes/alkenes (Figure 2). Furthermore, a very interesting discovery, metal and catalyst free electrochemical synthesis of quinazolinones from *o*-aminobenzamide and alkenes was reported by Teng et al. [62] (Figure 2).

Nevertheless, most of the reported work depend on expensive metals, ligands, higher temperature and special equipment, etc. which, as a result, limit the synthesis of biologically active compounds because of the presence of metal impurities in the products. Therefore, a significant need for improvement of environmentally benign methodologies for the preparation of quinazolinones under metal-based-catalyst free reaction conditions is still needed. Based on our continuing interest in the maturity of green, novel and sustainable synthetic methodologies for fine chemicals [63–65] as well as pharma related products where we have developed methodology for the synthesis of quinazolinones by reaction of 2-aminobenzamides and benzylic alcohols [66]. Thus, we report a metal-catalyst-free, synthesis of quinazolin-4(3*H*)-ones from *o*-aminobenzamide and direct oxidation-cyclization of in situ prepared aldehydes from styrenes. General preparation; characterization of the synthesized compounds and figures of the NMR spectra can be seen in supplementary material.

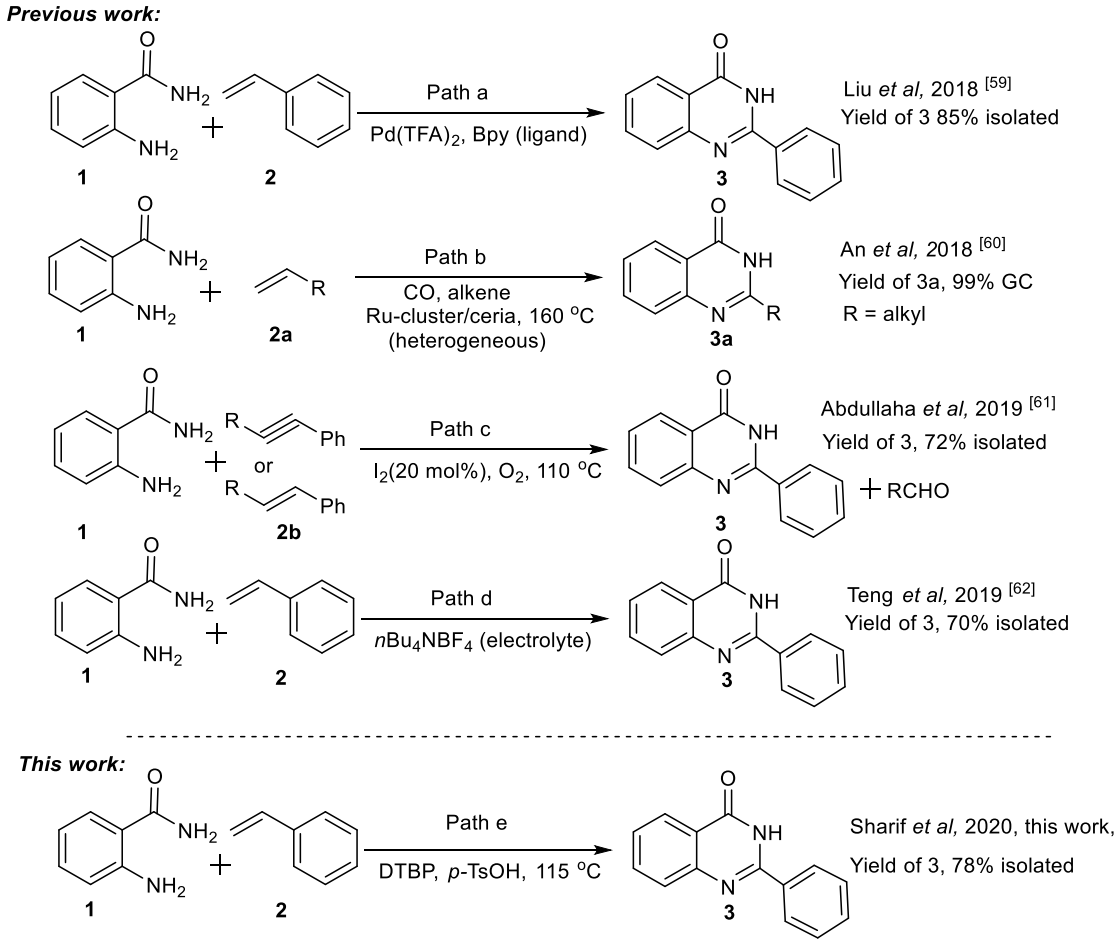


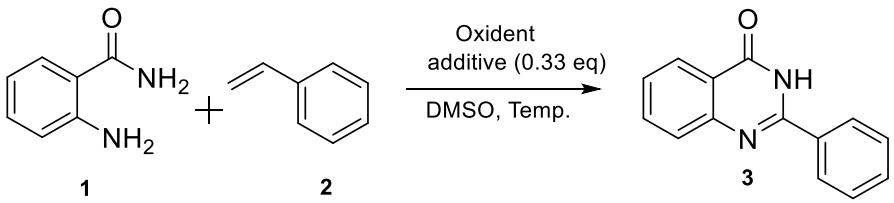
Figure 2. Different routes for the synthesis of Quinazolin-4(3*H*)-ones.

2. Results and Discussion

2.1. Model Reaction for Synthesis of Quinazolin-4(3H)-one

Initially, o-aminobenzamide 1 and styrene 2 in the presence of an oxidant TBHP (70% in H_2O, 5.8 eq., 1.5 mL w.r.t 2) were employed as a model reaction for screening the best reaction conditions. As shown in Table 1, different reaction parameters, oxidant, solvent, temperature, additive and time were screened. To our contentment, as expected, desired product 3, was obtained in 56% yield using a neat reaction, without solvent (Table 1, entry 1). The lower yields of the anticipated product 3 were observed with variations of solvents (H_2O, 2 mL), (DMSO, 2 mL), oxidant amount and temperature respectively (Table 1, entries 2–5). Then, further screening with another oxidant DTBP using only (0.54 eq) in the presence of DMSO as solvent 35% yield of 3 was found (Table 1, entry 6). Delightedly, the addition of p-TsOH showed the improvement in yield (Table 1, entry 7). Several screenings were performed by varying the amounts of the additives, temperatures and time and it was observed that DTBP (1.1 eq, TsOH 0.33 eq) furnished the improved yield (Table 1, entry 8). It was observed that DTBP was the more efficient oxidant as compared to TBHP (*tert*-butyl hydroperoxide) (Table 1, entries 7–13). At increased amount of additive TsOH, decrease in yield was observed (Table, entry 17). The controlled experiments implied the need of oxidant and TsOH by showing no and lower activity respectively (Table 1, entries 14 and15).

Table 1. Model reaction for synthesis of quinazolin-4(3H)-one [a].

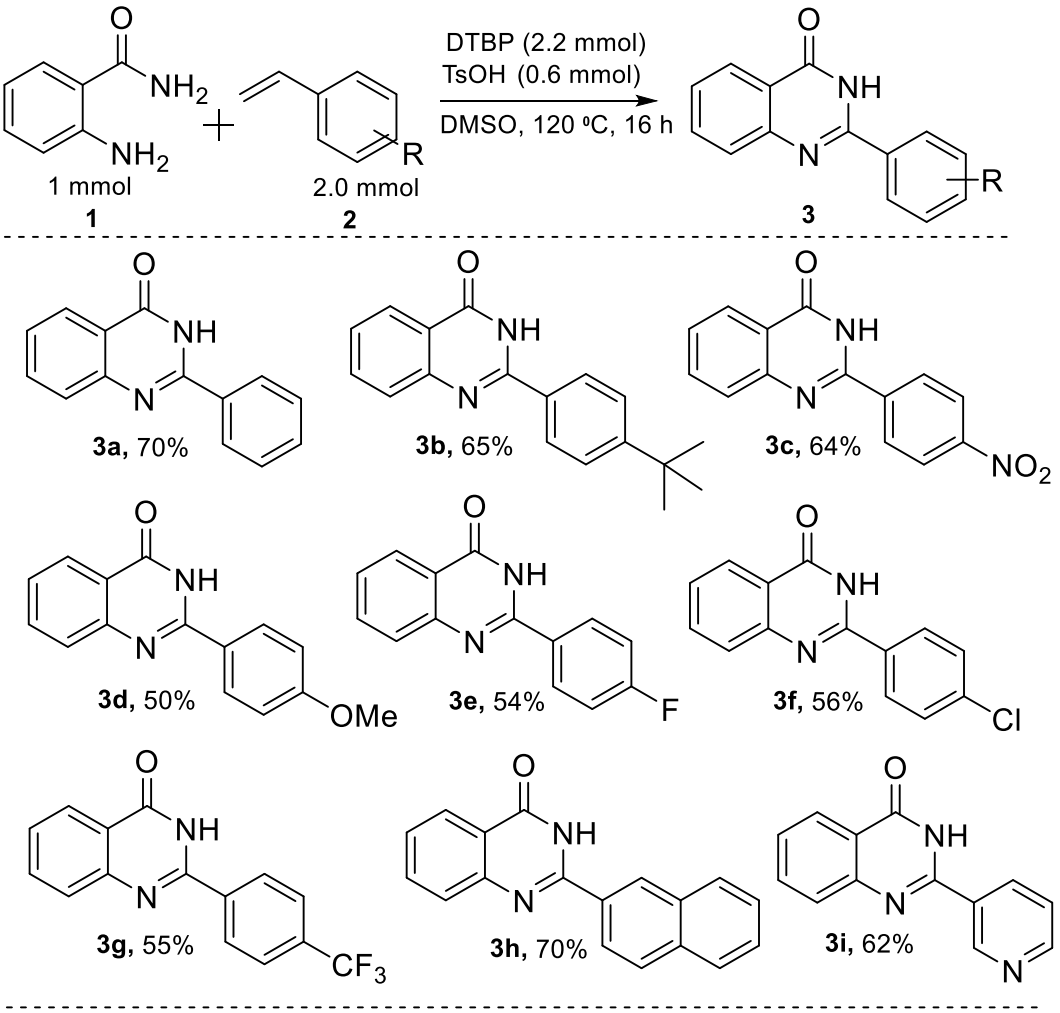


Entry	Oxidant (Equiv) [e]	Additive	Temp., Time	Solvent	Yield % [b]
1	TBHP (5.8)	-	105 °C	-	56
2	TBHP (5.8)	-	105 °C	H_2O	30
3	TBHP (5.8)	-	105 °C	DMSO	40
4	TBHP (1.5)	-	80 °C, 24 h	-	20
5	TBHP (1.5)	-	120 °C, 24 h	-	30
6	DTBP (0.54)	-	110 °C	DMSO	35
7	DTBP (0.54)	*p*-TsOH	110 °C	DMSO	58
8	DTBP (1.09)	*p*-TsOH	120 °C	DMSO	70
9	DTBP (0.8)	*p*-TsOH	105 °C	DMSO	45
10	DTBP (1.09)	*p*-TsOH	105 °C	DMSO	50
11	DTBP (1.4)	*p*-TsOH	105 °C	DMSO	14
12	DTBP (1.6)	*p*-TsOH	105 °C	DMSO	23
13	DTBP (2.1)	*p*-TsOH	105 °C	DMSO	65
14	-	-	120 °C	DMSO	0
15	-	*p*-TsOH	120 °C	DMSO	20
16 [c]	DTBP (1.4)	*p*-TsOH	120 °C	CH_3CN	60
17 [d]	DTBP (1.09)	*p*-TsOH	120 °C	DMSO	50

[a] *Reaction conditions*: **1** (1 mmol), **2** (2.0 mmol), additive (0.66 mmol), DMSO (2 mL), [b] Isolated yields, [c] **2** (3 mmol), [d] p-TsOH (1.2 eq), [e] equiv. with respect to **2**.

2.2. Synthesis of Quinazolin-4(3H)-one: Substrate Scope

The best optimized conditions obtained in entry 8 of Table 1, were employed to assess the substrate scope, generality and limitations of the present protocol. A reaction of *o*-aminobenzamide and wide range of substituted styrenes were studied under best conditions in hand. As presented in Figure 3, several substituted styrenes showed functional group tolerance under given condition and furnished the desired quinazolin-4(3*H*)-ones in good to high yields. Styrenes bearing common electron donating functional groups, *tert*-$(CH_3)_3$ (Figure 3, **3b**), -OCH_3 (Figure 3, **3d**), which are generally sensitive to strong oxidants exhibited very good tolerance under the optimized reaction conditions and were transformed to corresponding quinazolin-4(3*H*)-ones providing moderate yields 65%, 50% respectively (Figure 3). 54–56% yields were isolated in case of reaction of *o*-aminobenzamide **1**, with *para*-fluoro and *para*-chloro substituted styrenes (Figure 3, **3e, 3f**), whereas *para* substituted trifluoromethyl (CF_3) styrene was also tested which smoothly worked and afforded 55% yields on annulation with *o*-aminobenzamide **1** (Figure 3, **3g**). Furthermore, another interesting fused ring styrenes (2-vinylnaphtalene) also worked very well and afforded the anticipated product in 70% (Figure 3, **3h**). Interestingly, another *para*-substituted electron withdrawing group (*p*-NO_2) afforded corresponding quinazolinone in 64% yield (Figure 3, **3c**). In addition a heteroatom containing styrenes (2-vinylpyridine) was also efficiently annulated with *o*-aminobenzamide **1** giving the subsequent quinazolin-4(3*H*)-one (Figure 3, **3i**) in 62% yield.

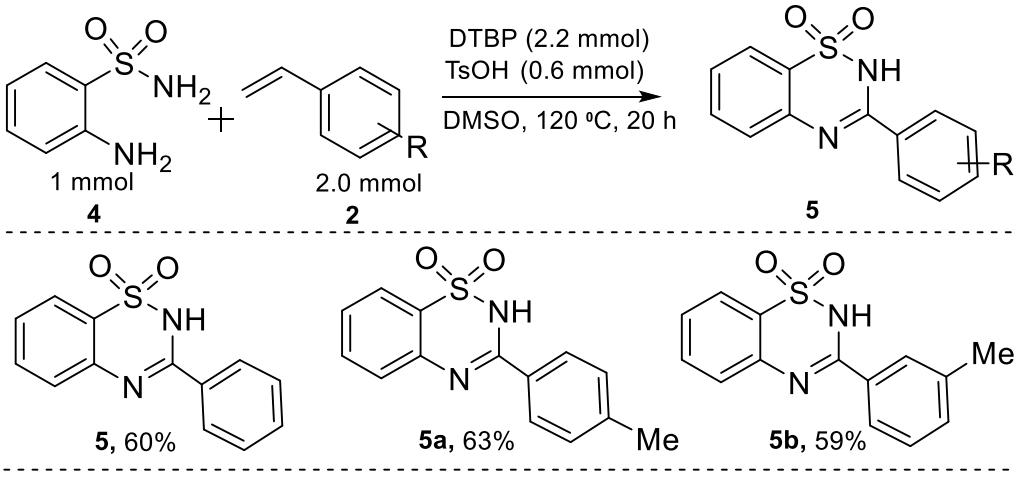


[a] ***Reaction conditions*****: 1** (1 mmol, 136 mg), **2** (2.0 mmol, 2.0 equiv.), *p*-TsOH (0.66 mmol, 114 mg), DTBP (2.2 mmol, 0.40 mL), DMSO (2 mL), 120 °C, 16h.

Figure 3. Synthesis of quinazolin-4(3*H*)-one: substrate scope [a].

2.3. Synthesis of Benzothiadiazine-1,1-dioxides: Substrate Scopes

In view of our previous knowledge in the advancement of synthetic methodologies [61,62] for quinazolinones synthesis [63,64] and the promising results are shown in the Figure 3, the methodology was further extended to benzothiadiazine-1,1-dioxides synthesis [67] from o-aminobenzenesulfonamide and styrenes (Figure 4, **5a–b**). Surprisingly, when *o*-aminobenzenesulfonamide 4 and different functional group bearing styrenes were subjected to the identical condition as Table 1, the expected product **5** was observed in 60% yield (Figure 4). Subsequently, meta- and para-methyl substituted styrenes gave **5a** and **5b** in 63% and 59% respectively (Figure 4). This is the novel oxidative method for benzothiadiazine-1,1-dioxides synthesis from o-aminobenzenesulfonamide and styrenes (Figure 4).



[a] ***Reaction conditions*: 1** (1 mmol, 172 mg), **2** (2.0 mmol, 2.0 equiv.), *p*-TsOH (0.66 mmol, 114 mg), DTBP (2.2 mmol, 0.40 mL), DMSO (2 mL), 120 °C, 20 h.

Figure 4. Synthesis of benzothiadiazine-1,1-dioxides: substrate scope [a].

2.4. Understanding of the Reaction Mechanism

To have better understanding of the reaction pathway, several control experiments were performed. Initially, the reaction of styrene was performed without using oxidant and *o*-aminobenzamide, no oxidation product was detected in GC showing the starting material only. Whereas, an oxidation reaction of styrene under optimized reaction conditions (without *o*-aminobenzamide) afforded the expected benzaldehyde in 78% GC yield (Figure 5). Based on the above experiments a plausible reaction mechanism for the synthesis of quinazolinones from styrene and *o*-aminobenzamide is proposed (Figure 5). It is established that benzaldehyde is an oxidation product of styrene which on condensation with *o*-aminobenzamide afforded imine intermediate that eventually, through cyclization-oxidation afforded the quinazolinone.

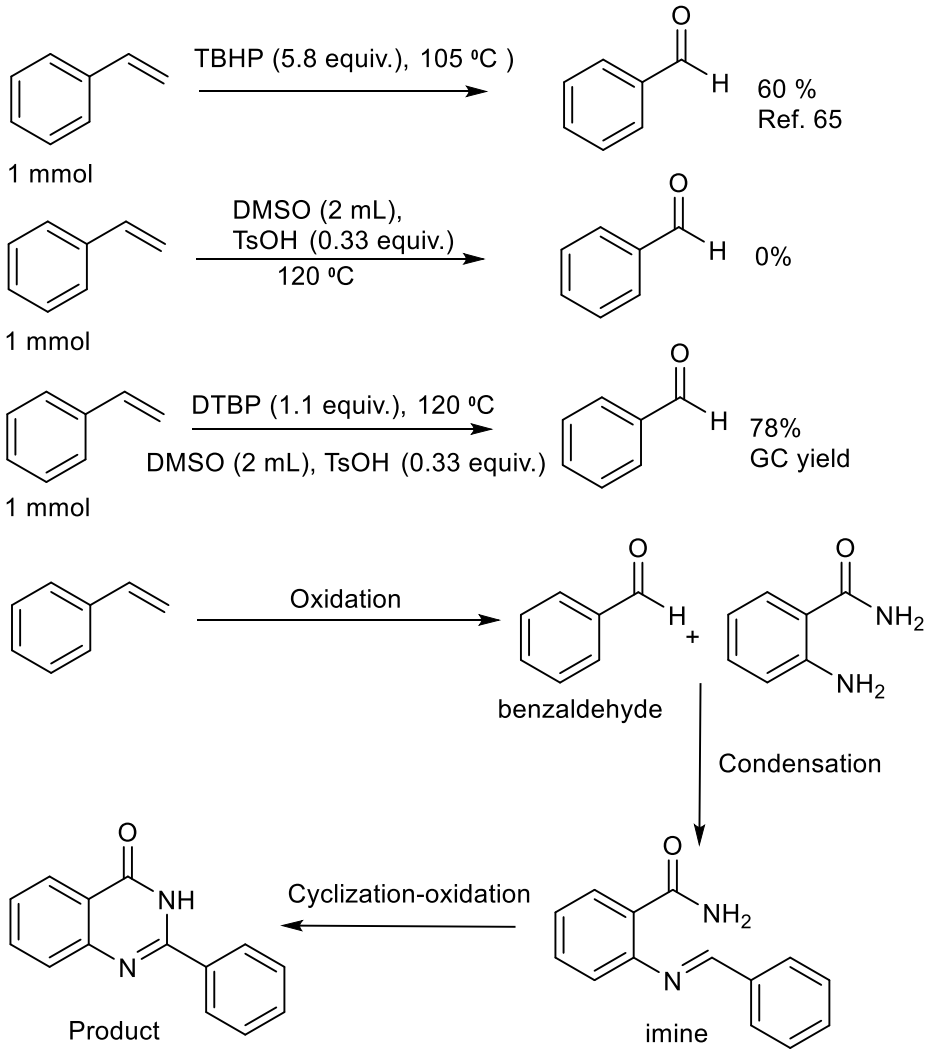


Figure 5. Control experiment and proposed mechanism.

3. Materials and Methods

3.1. Typical Experimental Procedure for Synthesis of Quinazolin-4(3H)-ones

2-aminobenzamides (1.00 mmol, 136 mg), styrenes (2.0 mmol, 2.0 eq) were placed in an ace-pressure tube that was equipped with a stirring bar. DMSO (2 mL) and *p*-TsOH (0.66 mmol, 114 mg) were then added into the mixture. In the end, DTBP (2.2 mmol, 0.4 mL) added to the mixture by the syringe and ace-pressure tube sealed with Teflon cap. The final reaction mixture in the pressure tube was placed in an aluminum heating block and stirred at a temperature of 120 °C for 16 h. The reaction mixture was cooled to room temperature and worked up by diluting with ethyl acetate and washed with water. The compound was extracted with 45 mL ethyl acetate. After the solvent was evaporated in vacuum, products were purified using column chromatography on silica gel with hexane and ethyl acetate (2:1) (Figure 3, 3–3i).

2-phenylquinazolin-4(3H)-one (3)

Yield: (156 mg, 70%); ^{1}HNMR (300 MHz, DMSO-d_6): δ = 7.53–7.60 (m, 4H), 7.77–7.80 (m, 1H), 7.84–7.88 (m, 1H), 8.18–8.25 (m, 3H), 12.6 (s, 1H, NH); ^{13}CNMR (DMSO-d_6): δ = 122.8 (C), 126.7 (CH), 127.4 (CH), 128.3 (C), 128.6 (2CH), 129.4 (2CH), 132.2 (CH), 133.6 (C), 135.4 (CH), 149.6 (C), 153.2 (C),

163.5 (CO); GCMS (EI, 70 eV): m/z (%) [M^+] 222 (83), 119 (99), 104 (12), 92 (15), 90 (11), 77 (21); HRMS (ESI): Calc. for $C_{14}H_{10}N_2O$: 222.07876; found: 222.07887 [66].

3.2. Typical Procedure for Synthesis of Benzothiadiazine-1,1-dioxides

2-aminobenzenesulfonamide (1.00 mmol, 172 mg), styrenes (2.0 mmol, 2.0 eq) were placed in an ace-pressure tube that was equipped with stirring bar. DMSO (2 mL) and *p*-TsOH (0.66 mmol, 114 mg) were then added into the mixture. At the end, DTBP (2.2 mmol, 0.4 mL) added to the mixture by the syringe and ace-pressure tube sealed with Teflon cap. The final reaction mixture in pressure tube was placed aluminum heating block and stirred at temperature of 120 °C for 20 h. The reaction mixture was cooled to room temperature and worked up by diluting with ethyl acetate and washed with water. The compound was extracted with 45 mL ethyl acetate. After the solvent was evaporated in vacuum, products were purified using column chromatography on silica gel with hexane and ethyl acetate (2:1) (Figure 4, 5–5b).

3-phenyl-2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (5)

Yield: (155 mg, 60%); ^{1}HNMR (300 MHz, DMSO-d_6): δ = 7.51–7.814 (m, 6H), 7.92 (d, J = 7.70 Hz, 1H), 8.11 (d, J = 7.70 Hz, 2H), 12.2 (s, 1H, NH); ^{13}CNMR (DMSO-d_6): δ = 119.3 (CH), 122.3 (C), 124.2 (CH), 127.6 (CH), 129.1 (2CH), 129.8 (2CH), 132.7 (C), 133.7 (CH), 134.0 (C), 136.3 (C), 155.7 (C); GCMS (EI, 70 eV): m/z (%) [M^+] 258 (55), 194 (11), 155 (100), 91 (65), 64 (19); HRMS (ESI): Calc. for $C_{13}H_{10}N_2O_2S_1$: 258.04575; found: 258.04581 [66].

4. Conclusions

In conclusion, we have established an efficient, novel metal-and catalyst-free protocol for the synthesis of pharmaceutically important, potential bio-active quinazolin-4(3*H*)-ones and benzothiadiazine-1,1-dioxides in modest to fairly good yields. Readily accessible starting materials were applied as substrate in presence of DTBP as an oxidant and *p*-TsOH as an additive. Remarkable, no transition metal catalyst was used for this effective transformation.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3417/10/8/2815/s1, General information, data for compounds, **3a–3i** and, **5a–b**, Figures S1–S23: NMR spectra for compounds **3**, **3a–3i** and **5**, **5a–b**.

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Conflicts of Interest: The author declares no conflict of interest.

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