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One-pot protocol for the synthesis of quinoxalines from styrenes, o-phenylenediamine and benzo[c][1,2,5]thiadiazole-4,5-diamine using triiodoisocyanuric acid

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Abstract: Triiodoisocyanuric acid (TICA) controlled one-pot and easy-operational protocol has been developed for the synthesis of substituted phenylquinoxalines (**3a-3i**) and phenyl-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5a-5f**) from styrenes with o-phenylenediamine and benzo[c][1,2,5]thiadiazole-4,5-diamine respectively. The reaction involves co-bromination and oxidation for the formation of an a-bromo ketone as an intermediate in the presence of triiodoisocyanuric acid, followed by condensation with the o-phenylenediamine and benzo[c][1,2,5]thiadiazole-4,5-diamine for the formation of phenylquinoxalines (**3a-3i**) and phenyl-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5a-5f**) in 55-79% yield. This protocol environmentally benign and economically viable. Substituted quinoxalines were obtained in good to excellent yields with wide substrate scope and functional-group tolerance.

Keywords: Quinoxalines; one-pot protocol; triiodoisocyanuric acid; styrenes.

1. Introduction

Quinoxalines are ubiquitous motifs, which have found in a variety of natural products and synthetic pharmaceuticals, many of which exhibit favorable biological activities (Figure1) and has always been an attractive heterocycle to biochemists because of its valuable contribution in biological sciences[1]. In particular, many of these quinoxaline derivatives have exhibit wide range of biological activities, such as antimalarial[2] antitumour[3], anticancer[4], antiproliferative[5] and antileishmanial[6]. Quinoxaline derivatives play an important role in amyloid fibril detection owing to their outstanding fluorescence properties[7]. As of now, several methods have been proposed as a common method to afford simple and substituted quinoxalines by oxidative coupling[8], MnO_2 [9], $POCl_3$ [10], ceric ammonium nitrate [11], iodine[12], montmorillonite K-10[13], $Ga(OTf)_3$ [14], silica gel[15], citric acid[16], Oxalic acid/EtOH[17], sulfated TiO_2 [18], sulfated TiO_2-P25 [19], acetic acid/copper catalyzed oxidative cyclization of a-hydroxy ketones with 1,2-diamines[20] and cellulose sulfuric acid [21]. Nevertheless, most of the existing methodologies suffer from one or more disadvantages in the process of synthesis which are

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unsatisfactory yields, longer reaction time, difficulties procedure to this scaffold is still valuable synthesis of quinoxaline.

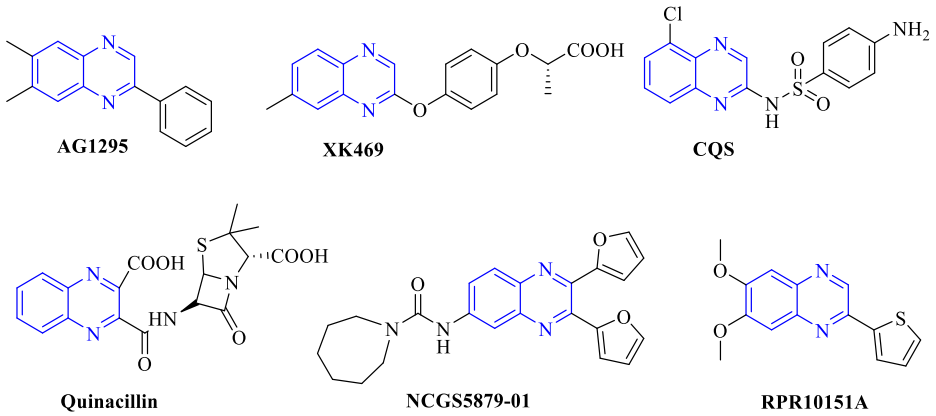


Figure 1. Quinoxaline cored natural and bioactive compounds.

In the product isolation process, moreover the use of highly expensive and detrimental metal precursors, drastic reaction conditions were observed and also no agreement with the green chemistry protocols, which limit their use. Hence it is highly essential to develop a convenient, economical and environmentally benign synthesis this context, one pot tactics are widespread in the literature for the synthesis of heterocycles using N-halo reagents[22-23]. Among the N-halo reagents, especially trihaloisocyanuric acids are commercially available or easily prepared from available chemicals. This trihaloisocyanuric acids are most effective and stable electrophilic halogenating reagents[24-25] and are able to transfer up to three halogen atoms to a substrate[26] . In addition, by-products formed from the reaction using trihaloisocyanuric acids can be reusable to produce further trihaloisocyanuric acid [27]. In continuation our interest on methodologies[28-48], we report herein the synthesis of quinoxalines using TICA[49] as a catalyst promoted conversion of styrenes into quinoxalines through a one-pot approach of three consecutive reactions.

2. Experimental

2.1. General

Melting points are uncorrected and were determined in open capillaries. The reactions were monitored by thin layer chromatography (TLC) and visualized with UV light. NMR spectra on Agilent 400 MHz spectrometer using TMS as an internal standard. Spectral analyses were carried out in $CDCl_3$ or DMSO-d_6 for both ^1H and ^{13}C spectra. Chemical shifts were measured in δ parts per million (*ppm*) and coupling constants (*J*) were measured in hertz (Hz). All solvents and reagents were purchased from Aldrich.

2.2. General Procedure for the Synthesis of Quinoxalines

A round-bottom flask equipped with a magnetic stirring bar was charged with styrene (1) (1.0 mmol), TICA (3.0 mmol) and water (2.0 mL) at room temperature. The resulting mixture was heated to 80 ^OC for 1 h. Then, acetone was added and the reaction media was filtered, to this filtrate o-phenylenediamine (1 mmol) or benzo[c][1,2,5]thiadiazole-4,5-diamine (1 mmol) was added and stirred at room temperature for 30min. After completion of the reaction (monitored by TLC), the reaction mixture was poured over ice water, neutralized with NH_4OH and the precipitated solid was filtered off and recrystallized from EtOH to afford the corresponding pure products.

*2-phenylquinoxaline (**3a**)*[50] **:** Solid; 71 % Yield; m. 76-79 ℃. (Lit. m. 75-78 ℃); ^{1}H NMR (400 MHz, $CDCl_3$): 9.28 (s, 1H), 7.74-8.16 (m, 4H), 7.73-7.66 (m, 2H), 7.47-7.54 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ151.75, 143.3, 142.26, 141.56, 136.73, 130.21, 130.14, 129.6, 129.47, 129.1, 127.51 ppm. EIMS, 70 ev, *m/z*: 207.3 $(M+H)^+$.

*6-fluoro-2-phenylquinoxaline (**3b**)*[50] **:** Solid; 76 % Yield; m. 118-120 ℃. (Lit. m. 120-122 ℃) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47(s, 1H), 9.01(s, 1H), 8.54 (d, *J*=6.0 Hz, 1H), 8.28 (s, 1H), 8.23-8.27 (m, 2H), 7.57-7.59 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.46. 131.37, 131.51, 129.39, 1273.91, 125.64, 123.75 ppm. EIMS, 70 ev, *m/z:* 242.3 $(M+H)^+$.

*6-chloro-2-phenylquinoxaline (**3c**)*[50] : Solid; 74 % Yield; m. 142-143 ℃. (Lit. m. 142-144 ℃) ;^{1}H NMR (400 MHz, $CDCl_3$): 9.24 (s, 1H), 8.14 (d, *J*=8.0 Hz, 2H), 8.08 (s, 1H), 7.99 (d, *J*=8.8 Hz, 1H), 7.63 (d, *J*=8.8 Hz, 1H), 7.47-7.54 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 143.32, 142.55, 140.02, 136.22, 136.01, 130.5, 130.41, 130.29, 129.15, 128.44, 127.58 ppm. EIMS, 70 ev, *m/z*: 225.3 $(M+H)^+$.

*2-(2-fluorophenyl)quinoxaline (**3d**)*[51] **:**Solid; 72 % Yield; m. 60-62 ℃. (Lit. m. 60-61 ℃) ;^{1}H NMR (400 MHz, $CDCl_3$): 9.22 (s, 1H), 8.14 (t, *J*=9.2 Hz, 2H), 8.03 (d, *J*=8.8 Hz, 1H), 7.69 (d, *J*=8.8 Hz, 1H), 7.43-7.53 (m, 4H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.73, 152.36, 143.18, 138.74, 136.31, 131.17, 131.07, 130.43, 129.13, 127.55, 119.89, 113.1 ppm. EIMS, 70 ev, *m/z*: 226.2 $(M+H)^+$.

*2-(3-(trifluoromethyl)phenyl)quinoxaline (**3e**)*[52] : Solid; 70 % Yield; m. 118-120 ℃. (Lit. m. 119-121 ℃) 119-121 ;^{1}H NMR (400 MHz, $CDCl_3$): 9.39 (s, 1H), 8.40 (s, 1H), 8.19-8.25 (m, 3H), 7.59 (d, *J*=8.8 Hz, 1H), 7.54-7.59 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 144.61, 140.53, 136.02, 130.85, 130.8, 129.26, 127.72, 127.19,. 127.15, 125.94, 125.91 ppm. EIMS, 70 ev, *m/z*: 275.3 $(M+H)^+$.

*6-bromo-5-fluoro-2-phenylquinoxaline (**3f**):* Solid; 74 % Yield; m. 130-132 ℃;^{1}H NMR (400 MHz, $CDCl_3$): 9.35 (s, 1H), 8.17-8.19 (m, 2H), 7.87 (d, *J*=8.0 Hz, 1H), 7.73 (d, *J*=8.4 Hz, 1H), 7.53-7.58 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.07, 143.06, 143.03, 135.67, 130.91, 129.29, 127.73, 123.61, 123.32, 113.19, 112.98 ppm. EIMS, 70 ev, *m/z*: 303.2 $(M+H)^+$.

*2-(3-bromo-5-(trifluoromethyl)phenyl)quinoxaline (**3g**):*Solid; 79 % Yield; m. 102-104 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): 9.43 (s, 1H), 8.37 (s, 1H), 8.33 (d, *J*=8.0 Hz, 2H), 8.24 (s, 1H), 7.57-7.59 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.72, 144.82, 141.23, 135.43, 131.35, 129.43, 129.4, 129.36, 127.96, 126.82, 126.78, 125.96 ppm. EIMS, 70 ev, *m/z*: 352.9 $(M+H)^+$.

*6-bromo-2-phenylquinoxaline (**3h**)*[51] : Solid; 66 % Yield; m. 128-130 ℃. (Lit. m. 132-134 ℃) ; ^{1}H NMR (400 MHz, $CDCl_3$): 9.27 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J*=6.0 Hz, 2H), 7.93 (d, *J*=8.8 Hz, 1H), 7.77 (d, *J*=8.8 Hz, 1H), 7.47-7.54 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ152.36, 143.47, 142.84, 140.27, 136.21, 132.98, 131.84, 130.52, 129.17, 127.56, 124.24 ppm. EIMS, 70 ev, *m/z*: 285.1$(M+H)^+$.

*2-(3-chlorophenyl)quinoxaline (**3i**)*[53] : Solid; 76 % Yield; m. 130-132 ℃. (Lit. m. 132-134 ℃) ; ^{1}H NMR (400 MHz, $CDCl_3$): 9.53 (s, 1H), 8.59 (s, 1H), 8.30-8.32 (m, 2H), 8.27 (s, 1H), 7.57-7.59 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.34, 144.94, 140.7, 135.2, 131.59, 131.35, 131.3, 131.26, 129.44, 129.39, 128.0, 127.73, 124.5 ppm. EIMS, 70 ev, *m/z*: 242.3 $(M+H)^+$.

*7-phenyl-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5a**)*: Solid; 68 % Yield; m. 140-142 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): 9.37 (s, 1H), 8.21-8.18 (m, 2H), 7.88 (d, *J*=8.0 Hz, 1H), 7.79 (d, *J*=8.4 Hz, 1H),7.26-7.60 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.31, 145.30,145.27, 137.91, 133.15, 131.53, 129.97, 125.85, 125.56 115.43, 115.22 ppm. EIMS, 70 ev, *m/z*: 265.3 $(M+H)^+$. Chemical Formula: $C_{14}H_8N_4S$ Elemental Analysis: C, 63.62; H, 3.05; N, 21.20; S, 12.13.

*7-(2-chlorophenyl)-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5b**)*: Solid; 70 % Yield; m. 116-118 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): 9.48 (s, 1H), 8.09 (d, *J*=8.8 Hz, 1H), 7.78 (d, *J*=8.8 Hz, 1H), 7.69-7.71

(m, 1H) 7.53-7.55 (m, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.07, 161.59, 152.07, 143.59, 143.56, 142.74, 142.6, 138.83, 136.09, 131.83, 131.73, 131.09, 129.52, 127.98, 120.46, 120.2, 113.1, 112.89 ppm. EIMS, 70 ev, m/z: 299.4 $(M+H)^+$. Chemical Formula: $C_{14}H_7ClN_4S$ Elemental Analysis: , 56.28; H, 2.36; Cl, 11.87; N, 18.75; S, 10.73.

*7-(3-trifluoromethyl)-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5c**)*: Solid; 75 % Yield; m. 168-170 ℃ ; ^{1}H NMR (400 MHz, DMSO-d_6): 9.53 (s, 1H), 8.12 (s, 1H), 8.05 (d, *J*=8.8 Hz, 1H), 7.8 (d, *J*=8.8 Hz, 1H), 7.54-7.57 (m, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.24, 144.57, 142.23, 140.12, 136.01, 135.33, 131.18, 131.1, 130.81, 129.56, 128.26, 128.04 ppm. EIMS, 70 ev, *m/z*: 333.2 $(M+H)^+$. Chemical Formula: $C_{15}H_7F_3N_4S$ Elemental Analysis: C, 54.22; H, 2.12; F, 17.15; N, 16.86; S, 9.65.

*7-(3-bromo-2-fluorophenyl)-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5d**)*: Solid; 62 % Yield; m. 80-82 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): 9.32 (s, 1H), 7.90 (d, *J*=8.0 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 1H),7.53-7.58 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.31, 130.69, 129.24, 127.56, 124.39, 124.1, 112.78, 112.57 ppm. EIMS, 70 ev, *m/z*: 361.4 $(M+H)^+$. Chemical Formula: $C_{14}H_6BrFN_4S$ Elemental Analysis: C, 46.55; H, 1.67; Br, 22.12; F, 5.26; N, 15.51; S, 8.88.

*7-(2,3-dichlorophenyl)-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5e**)*: Solid; 65 % Yield; m. 150-152 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): 9.56 (s, 1H), 8.02 (d, *J*=8.8 Hz, 1H), 7.73 (d, *J*=8.8 Hz, 1H), 7.55-7.58 (m, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.21, 144.72, 142.55, 140.34, 136.03, 133.4, 131.56, 131.21, 131.18, 129.59, 128.06, 124.02 ppm. EIMS, 70 ev, *m/z*: 332.9 $(M+H)^+$. Chemical Formula: $C_{14}H_6Cl_2N_4S$ Elemental Analysis: C, 50.47; H, 1.82; Cl, 21.28; N, 16.82; S, 9.62.

*7-(2,3-difluorophenyl)-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5f**)*: Solid; 67 % Yield; m. 156-160 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): 9.48 (s, 1H), 8.59 (d, *J*=8.8 Hz, 1H), 7.92 (d, *J*=8.8 Hz, 1H), 7.59-7.61 (m, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.21, 144.72, 142.55, 140.34, 136.03, 133.4, 131.56, 131.21, 131.18, 129.59, 128.06, 124.02 ppm. EIMS, 70 ev, *m/z*: 301.1 $(M+H)^+$. Chemical Formula: $C_{14}H_6F_2N_4S$ Elemental Analysis: C, 56.00; H, 2.01; F, 12.65; N, 18.66; S, 10.68.

3. Results and Discussion

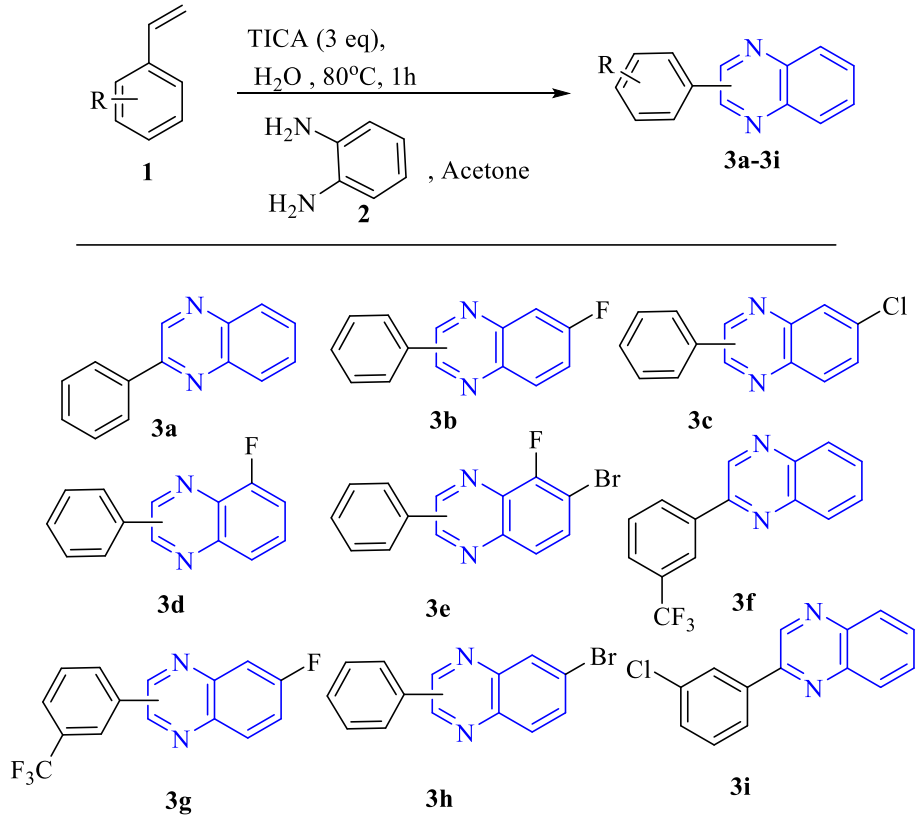
We started the initial study of the one-pot tandem reaction, the direct conversion of styrene into phenacyl iodide through with excess TICA having a double action, i.e. as an electrophilic halogen source to form the bromohydrin and an oxidant to convert it into the haloketone[54]. As shown Table 1, the reaction with styrene and TICA afforded the desired phenacyl iodide in 25 % yield when it was conducted in acetone: H_2O (1:1) at rt for 1h (Entry 1). To increase the yield of the product, several conditions were tested. The reactions in different solvents at different temperatures by increasing or decreasing time. Finally, when the reaction was carried out in acetone, H_2O (2:1) at rt for 15h, the desired product was formed in 100% yield (Entry 3) and when the reaction was carried out H_2O alone at 80 ^{O}C for 1h, the desired product was formed in 100% yield (Entry 7).

Table 1. Optimizations of reaction conditions

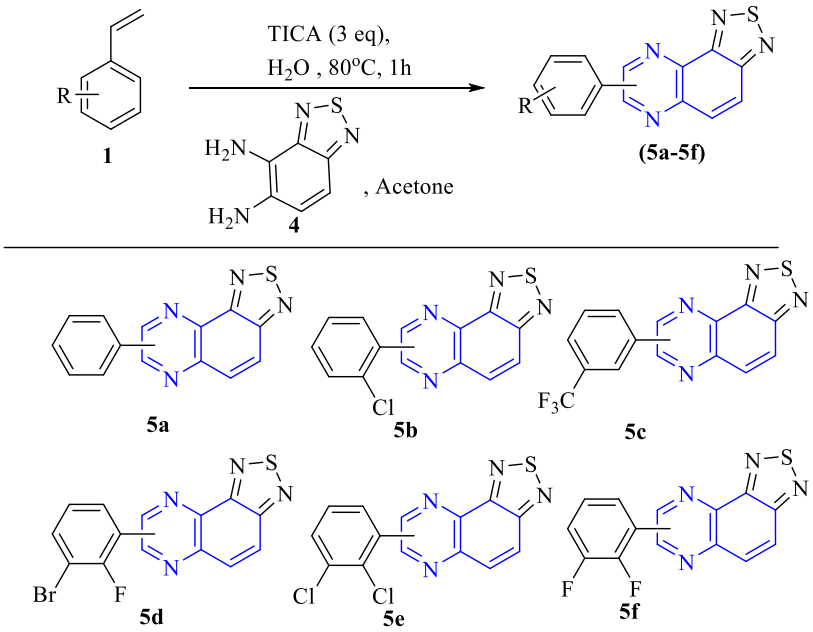
Solvent	Equiv.	Time	Temp.	Yield
Me_2CO: H_2O (1:1)	3.0	1h	r.t	25
Me_2CO: H_2O (2:1)	3.0	10h	r.t	80
Me_2CO: H_2O (2:1)	3.0	15h	r.t	100
1,4dioxane: H_2O (2:1)	3.0	20h	r.t	70
Acetonitrile: H_2O (2:1)	3.0	20h	r.t	80
H_2O	3.0	1h	rt	35
H_2O	3.0	1h	80 ^{o}C	100

With the optimal reaction conditions in hand, different substituted of styrenes were then reacted with TICA in water, followed by *o*-phenylene diamines (**2**) in acetone (Scheme 1) or benzo[c][1,2,5]thiadiazole-4,5-diamine (**3**) in acetone (Scheme-2) afforded substituted regioisomers

of phenylquinoxalines (**3a-3i**) and phenyl-[1,2,5]thiadiazolo[3,4-f]quinoxalines (**5a-5f**) with a combined yields. Formation of regioisomers depends on substituted *o*-phenylenediamines.



Scheme 1. Synthesis of substituted derivatives (**3a-3i**)



Scheme 2. Synthesis of substituted derivatives (**5a-5f**)

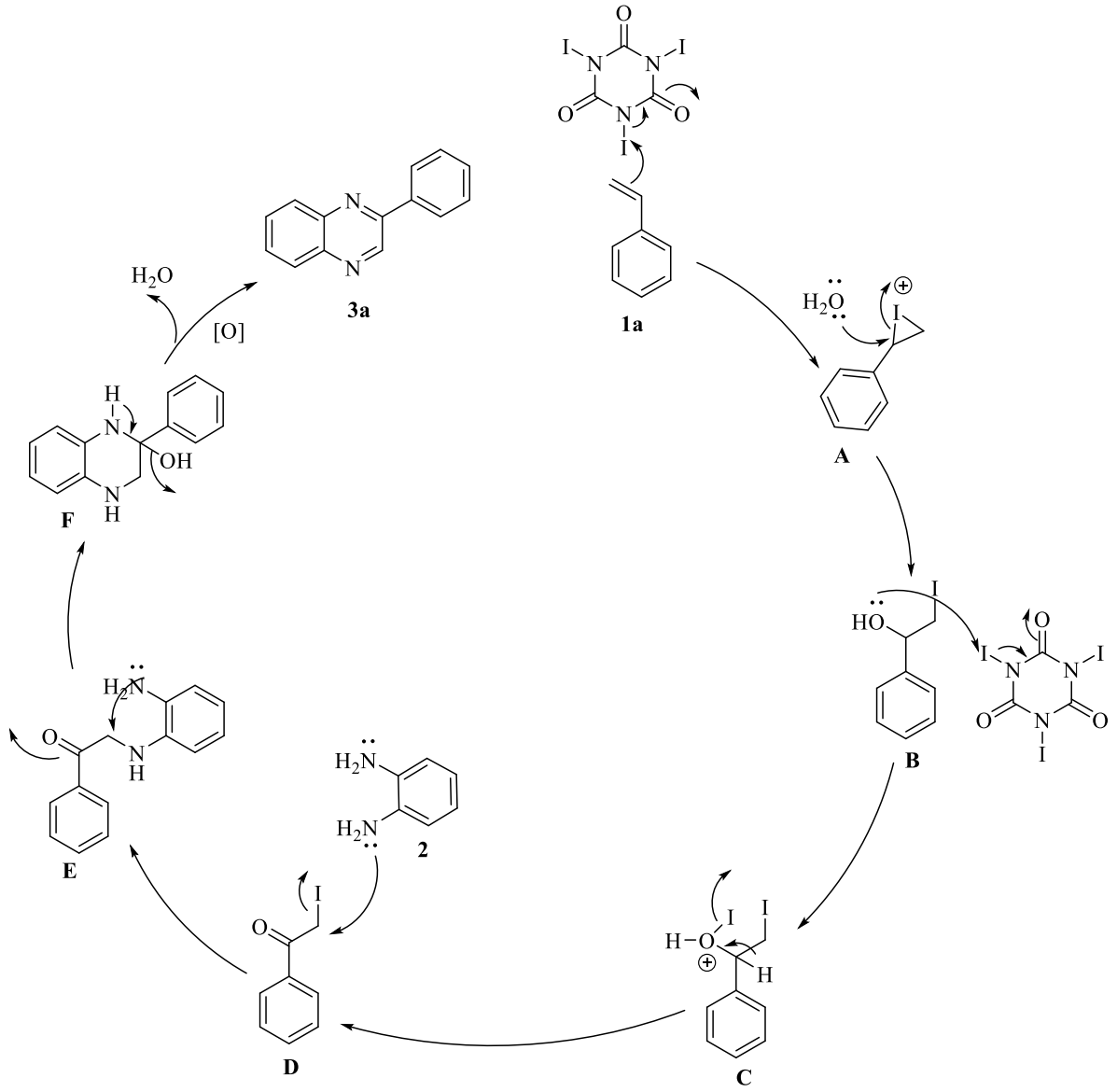


Figure 2. Proposed mechanism

Under the optimized reaction conditions, the substrate scope and versatility of the reaction was subsequently explored, and the results are summarized in Scheme-1 and Scheme 2. To our delight, the protocol was companionable with *o*-phenylenediame and styrenes containing a range of functional groups, little influence of electronic properties was observed on their reactivity. For example, *o*-phenylenediamine with electron-withdrawing group, such as F and styrene with electron-withdrawing group, such as CF_3, yielded the corresponding product in 79% (Scheme 1, compound **3g**). On the other hand, o-phenylenediamne bearing electron-withdrawing groups such as F, Cl also gave the desired product with a yields 76% to 74% respectively (Scheme-1, entries **3b** and **3c**). Results from scheme-2, styrene with electron-withdrawing group, such as CF_3, yielded the corresponding product in 75% (Scheme-2, compound **5c**). Based on the literature and our previous work, we have proposed a plausible mechanism depicted in Figure 2. Based on the literature[24], we have proposed a plausible mechanism depicted in Figure 2. In presence of TICA, styrene (**1a**) forms cyclic iodonium ion (**A**) which undergoes a ring opening through nucleophilic attack of H_2O to give bromohydrin (B) as an intermediate. Bromohydrin (**B**) in the presence of TICA undergoes oxidation via (**C**) to form α-iodoacetophenone (**D**). *o*-phenylenediamine was reacted with intermediate (**D)** via (**E** and **F**) forms quinoxaline (**3a**).

4.Conclusions

In summary, we have reported a triiodoisocyanuric acid promoted method for synthesis of key intermediate α-bromo ketone via co-bromination and oxidation for the formation of an intermediate in the presence of triiodoisocyanuric acid, followed by condensation with the o-phenylenediamine (**2**) and benzo[c][1,2,5]thiadiazole-4,5-diamine (**4**) for the synthesis of phenylquinoxalines (**3a-3i**) and phenyl-[1,2,5]thiadiazolo[3,4-f]quinoxaline (**5a-5f**) in 55-79% yield. This protocol is simple, broad substrate scope, good to excellent yields. We strongly believe that this protocol will serve as an encroachment to the existing methods and will be widely adopted for the synthesis of biologically important quinoxalines.

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Conflict of Interest

The authors declare that they have no conflict of interest

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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