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Citric Acid-Catalyzed Three-Component Synthesis of (*E*)-3-Aryl-2-styryl-2,3-dihydroquinazoline-4(1*H*)-ones and Their Mild Oxidation with I_2/DMSO System into (*E*)-3-Aryl-2-styrylquinazolin-4(3*H*)-ones

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Abstract: We hereby report a simple and efficient method for the preparation of (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4-(1*H*)-ones, from isatoic anhydride, anilines, and cinnamaldehydes in the presence of 20 mol% citric acid in methanol at 60 °C for 2 h. The styryl-dihydroquinazolin-4-(1*H*)-one products were obtained in moderate and good yields (30–80%) through the three-component condensation reaction, under an environment-friendly protocol. The latter were easily transformed into styrylquinazolin-4-(3*H*)-one derivatives with 57–91% yields using a mild oxidation with an I_2/DMSO system for less than 60 min.

Keywords: three-component condensation reaction; 2,3-dihydroquinazolin-4-(1*H*)-ones; quinazolin-4-(3*H*)-ones; styryl derivatives; organocatalysis; citric acid; catalytic iodine/DMSO system

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Academic Editor: Bartolo Gabriele

Received: 5 February 2025
Revised: 3 March 2025
Accepted: 14 March 2025
Published: 16 March 2025

Citation: Kouznetsov, V.V.; Peñaranda Gómez, A.; Puerto Galvis, C.E. Citric Acid-Catalyzed Three-Component Synthesis of (*E*)-3-Aryl-2-styryl-2,3-dihydroquinazoline-4(1*H*)-ones and Their Mild Oxidation with I_2/DMSO System into (*E*)-3-Aryl-2-styrylquinazolin-4(3*H*)-ones. *Chemistry* **2025**, *7*, 42. https://doi.org/10.3390/chemistry7020042

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1. Introduction

The quinazolinone skeletons (dihydroquinazolin-4-(1*H*)-ones and quinazolin-4-(3*H*)-ones) are the main structural parts for numerous secondary metabolites and privileged scaffolds in medicinal chemistry [1–5], especially in cancer drug research [6,7] and epilepsy treatment [8]. The chemical characteristics of the quinazolinone core (aromatic ring, two not equivalent nitrogen atoms in the pyrimidine ring, group C=O, π-conjugated lactam-aryl motif, and polarized endocyclic imine C=N function) make simple functionalized quinazolinones attractive, proper, and versatile models or/and precursors for use in agrochemical and luminescent settings [9–12].

Particularly, Quinethazone and Fenquizone are diuretics employed to treat hypertension [13], while Methaqualone ("Quaaludes") is a sedative–hypnotic medication with effects similar to barbiturates. Currently, it has no accepted medical use due to its addictive nature [14] (Figure 1). The alkaloid Penipanoid C displayed high cytotoxic activity [15]. Fluorophore ELFTM 97 is insoluble in aqueous media but exhibits strong fluorescence in the solid state [16]. The 4-oxo-3-dihydroquinazolin-2-yl derivative AQTA exhibited superior sub-micromolar antiproliferative activity against the NSC lung cancer cell line NCI-H460, functioning as a potent EGFR inhibitor [17]. Piriqualone serves as an anticonvulsant agent for treating neurodegenerative and CNS-trauma-related conditions [18]. The compound 6-MeO-SQ inhibited tubulin polymerization and the growth of murine leukemia cells L12102 [19], while the fluorinated 2-styryl quinazolinone DKD-NIPERA derivative shows

promise for oral cancer, demonstrating cytotoxicity in CAL-27 cancer cells (squamous cell carcinoma tumor) [20]. The alkaloid Z-Bogorin displayed good antifungal activity and moderate cytotoxic activity against *Artemia salina* [21].

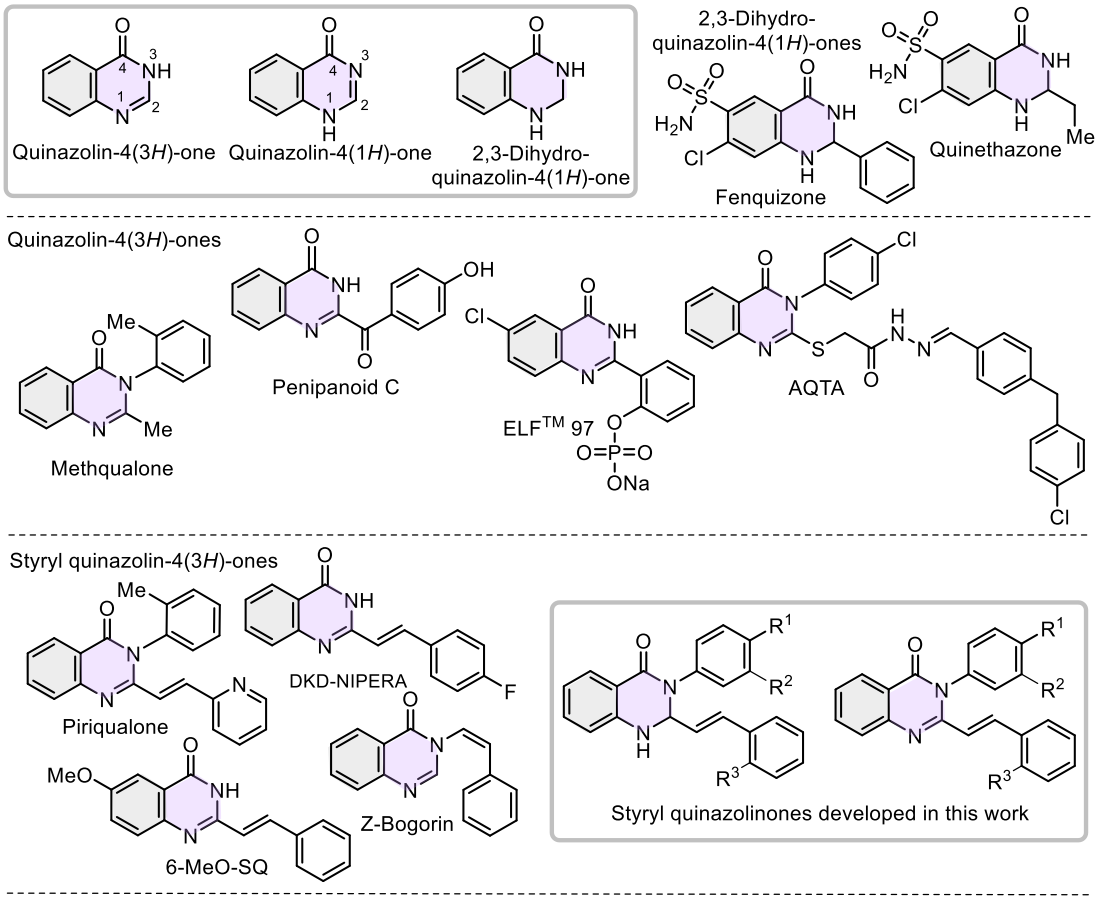


Figure 1. Selected quinazolinone skeletons as pharmaceuticals and fluorophores according to structural classification, and styryl quinazolinones developed in this work.

Subsequently, there is a considerable review of the literature on their synthesis [22–29]. Among the synthesis methods, environmentally benign approaches, i.e., solid acid-catalyzed, nanocatalyzed, or organocatalyzed syntheses, stand out as promising green alternative methods for constructing quinazolinone skeletons [27–29].

Generally, the substituted 2,3-dihydroquinazolin-4(1*H*)-ones and quinazoline-4(3*H*)-ones are easily prepared using different principal starting materials, including 2-substituted aryl amines, such as anthranilic acid (2-aminobenzoic acid), its close derivatives, or 2-aminobenzaldehydes and 2-aminoaryl ketones. Direct synthesis of quinazolinone derivatives through cyclocondensation of 2-aminobenzamide derivatives and aldehydes in the presence of various metal catalysts remains the most popular method [25], although several new techniques have been developed for the synthesis of the substituted quinazolinone derivatives [30–33]. Another equally popular starting material in synthesizing 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones, which are valuable intermediates in organic synthesis, are isatoic anhydrides. Several methods for the synthesis of 2-aryl(alkyl)- or 2,3-diaryl-(2,3-dihydro)-quinazolinones have been reported, which are usually based on the condensation of isatoic anhydride, aldehydes, and ammonium salts or primary amines in the presence of numerous different catalysts [34], including organocatalysts such as *p*-TsOH [35], ethylene diamine diacetate [36], dodecylbenzenesulfonic acid [37], L-proline [38], β-cyclodextrin [39], room-temperature ionic liquids [40],

acetic [41], glutamic [42] or citric [43] acids, etc. The latter is the organocatalyst of choice in the present work. Notably, none of the organocatalysts mentioned above were used in the title compounds.

Although 2-styryl-dihydroquinazolin-4(1*H*)-ones and 2-styrylquinazolin-4(3*H*)-ones, compounds that merge the medicinally significant stilbene and quinazolinone frameworks, are of considerable interest to synthetic and medicinal chemists, their synthetic methodologies are less developed than those for 2-aryl- or 2,3-diaryl-quinazolinones and exhibit notable limitations. These methods utilizing starting materials such as 2-aminobenzamide, 2-methyl-3,1-benzoxazin-4-one, or 2-methylquinazolin-4(3*H*)-one derivatives typically require multi-step reactions, harsh conditions, prolonged reaction times, and the use of toxic or costly catalysts [44–49]. Notably, even the few reports describing one-pot procedures for synthesizing 2-styryl-2,3-dihydroquinazolin-4(1*H*)-ones and 2-styrylquinazolin-4(3*H*)-ones from readily available isatoic anhydride suffer similar drawbacks [50–52]. Specifically, Zhang and co-workers reported just two examples of synthesizing 3-phenyl (or 2-methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-ones in the presence of a CuO-nanocatalyst in aqueous ethanol using an ultrasound irradiation technique [52]. Although the yields of these styryl derivatives are excellent (84–85%), copper oxide nanoparticles (CuO NPs) have limitations, including toxicity, high production costs, and the use of hazardous materials [53,54]. In contrast, citric acid is a compound naturally found in citrus and many other foods. It is generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA) [55].

In light of the aforementioned facts and our ongoing commitment to exploring the synthesis of novel bioactive small heterocyclic molecules under environmentally friendly reaction conditions [56–58], we established a simple green procedure for the synthesis of (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4-(1*H*)-ones and corresponding quinazolin-4(3*H*)-one derivatives. Therefore, this study presents new practical and direct syntheses of potentially pharmacologically active styryl-quinazolinone derivatives through a three-component condensation reaction involving isatoic anhydride, anilines, and cinnamaldehydes. The reaction, conducted in methanol with 20 mol% citric acid, yields (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-ones. Notably, three-component reactions are excellent for multiple bond-forming events between several substrates. They are highly efficient one-pot processes in which three reactants combine to form target molecules, effectively incorporating most starting materials. These reactions occur in a single step and show excellent atom economy, reducing the number of synthetic operations [59,60].

The obtained dihydroquinazolinone intermediates are subsequently oxidized using an environmentally friendly iodine/DMSO catalytic system to produce smoothly the corresponding 3-aryl-2-styryl-quinazolin-4(3*H*)-ones. A key highlight of our research is the development of two simple, cost-effective procedures under sustainable reaction conditions, enabling the preparation of a diverse series of styryl-quinazolinones. These compounds represent privileged scaffolds and valuable medicinal chemistry and organic synthesis building blocks.

2. Materials and Methods

2.1. Materials and Instruments

The solvents and reagents used for synthesizing the intermediate and final compounds were of synthesis-grade purity. All chemicals were sourced from Merck and Aldrich Chemical Co (Sigma-Aldrich and Merck, St. Louis, MO, USA) and were utilized without additional purification. Reaction progress and product purity were monitored using thin-layer chromatography (TLC) on Silufol UV254 plates (0.25 mm thickness). Visualization was performed under UV light at 254 nm or using an ethanolic solution of phosphomolybdic–

sulfuric acids. Melting points were determined with Fisher-Johns apparatus and are reported as uncorrected values.

Nuclear magnetic resonance (NMR) spectra for ^{1}H and ^{13}C were acquired using a Bruker Avance–400 spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C). Chemical shifts (δ) are reported in parts per million (ppm), referenced to solvent signals: DMSO-d_6: δ 2.50 ppm (comp. **4a**, **4c**–**4e**) or $CDCl_3$: δ 7.28 ppm (comp. **4b**, **5a**–**5d**). Coupling constants (*J*) are provided in Hz, and signal multiplicity is denoted as follows: (s) singlet, (d) doublet, (dd) doublet of doublets, (ddd) doublet of doublet of doublets, and (m) multiplet. The coupling constants *J* are expressed in Hz. The aromatic protons of the N3-aryl fragment are designated as H_{Ph}, and those of 2-styryl moiety are shown as H_{Ar}.

Infrared spectra were recorded using a Bruker Tensor 27 FTIR spectrophotometer (Bruker Corporation, Billerica, MA, USA) equipped with a platinum ATR cell, operating at 31 scans with a resolution of 2 cm^{-1}. Elemental analyses were performed on a Thermo Scientific CHNS-O analyzer (model: Flash 2000) (Thermo Fisher Scientific, Waltham, MA, USA) with results within ±0.4 of theoretical values.

2.2. General Procedure for the Synthesis of (E)-3-Aryl-2-styryl-2,3-dihydroquinazolin-4(1H)-one derivatives **4a**–**e**

To a solution of isatoic anhydride **1** (1.4 mmol) in 1 mL of methanol, 20 mol% of citric acid monohydrate (CAM) was added, and the mixture was stirred for 20 min. Subsequently, the respective aniline derivatives **2a**–**e** (1.6 mmol) and cinnamaldehydes **3a**–**b** (1.3 mmol) were added sequentially. The resulting mixture was heated at 60 °C for 2 h, with progress monitored by TLC. After the reaction was complete, the mixture was cooled to room temperature. Methanol was distilled off, and the crude solids were washed with a cold solution of 85% ethanol and filtered to yield products **4a**–**e**, which were purified by column chromatography, using alumina as the stationary phase and a petroleum ether/ethyl acetate (1:2) mixture as the eluent. Characterization data for the styryl-dihydroquinazolinone compounds **4a**–**e** are provided below.

2.2.1. 3-(4-Methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one (**4a**)

3-(4-Methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (**4a**) was synthesized following the general procedure using isatoic anhydride **1** (0.23 g, 1.32 mmol), 4-methoxyaniline **2a** (0.20 g, 1.62 mmol), cinnamaldehyde **3a** (0.17 mL, 1.27 mmol), and 20 mol% CAM (65 mg, 0.31 mmol). After reaction, isolation, and recrystallization, a white solid (0.40 g, 1.12 mmol, 80%) was obtained. Rf = 0.27 (1:2, petroleum ether/ethyl acetate); Mp = 234–236 °C (ethanol). IR (ATR, νmax): 3311 (N–H), 2810 (OCH_3), 1630 (C=O), 1507 (ArC=C), 1389 and 1239 (C–N), 762 and 535 (ArC–H) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.72 (1H, d, *J* = 7.7 Hz, 5-H), 7.37–7.34 (2H, m, H_{Ar}), 7.34–7.31 (1H, m, 7-H), 7.27 (5H, m, H_{Ph} and H_{Ar}), 7.23 (1H, m, 6-H), 6.98–6.91 (2H, m, H_{Ph}), 6.82 (1H, d, *J* = 15.1 Hz, $=H_{\alpha}C_{Ar}$), 6.75 (1H, m, *J* = 15.0 Hz, $=H_{\beta}C_{Quin}$), 6.47 (2H, d, *J* = 3.1 Hz, 8-H and N–H), 5.61–5.57 (1H, m, 2-H), 3.74 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.8, 157.6, 146.8, 135.4, 133.5, 133.3, 131.9, 128.7 (2), 128.6 (2), 128.1, 127.9, 126.7, 126.6 (2), 117.4, 115.0, 114.7, 113.9 (2), 73.0, 55.2. Anal. calcd. for $C_{23}H_{20}N_2O_2$ (356.43): C, 77.51; H, 5.66; N, 7.86%. Found: C, 77.76; H, 5.53; N, 7.61%.

2.2.2. 3-Phenyl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one (**4b**)

3-Phenyl-2-styryl-2,3-dihydroquinazolin-4(1H)-one (**4b**) was synthesized following the general procedure using isatoic anhydride **1** (0.25 g, 1.53 mmol), aniline **2b** (0.14 mL, 1.52 mmol), cinnamaldehyde **3a** (0.19 mL, 1.52 mmol), and 20 mol% CAM (69 mg, 0.33 mmol). After reaction, isolation, and recrystallization, a pale yellow solid (0.27 g, 0.83 mmol, 54% yield) was obtained. Rf = 0.23 (1:2, petroleum ether/ethyl acetate);

Mp = 192–194 °C (ethanol) (lit. 198–200 °C [52]). IR (ATR, νmax): 3310 (N–H), 3058 (ArC–H), 1631 (C=O), 1488 (ArC=C), 1395 (C-N), 748 and 629 (ArC–H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (1H, dd, *J* = 7.8, 1.6 Hz, 5-H), 7.43–7.38 (4H, m, H_{Ph}), 7.36–7.32 (5H, m, H_{Ar}), 7.28–7.21 (3H, m, 6-H, 7-H, and H_{Ph}), 6.85 (1H, d, *J* = 15.0 Hz, $=H_{\alpha}C_{Ar}$), 6.76 (1H, m, *J* = 15.0 Hz, $=H_{\beta}C_{Quin}$), 6.49 (2H, d, *J* = 4.7 Hz, 8-H and N-H), 5.69 (1H, m, 2-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 161.7, 146.7, 140.6, 135.4, 133.6, 131.9, 128.7 (2), 128.6 (2), 128.1, 128.0, 127.0 (2), 126.7, 126.6 (2), 126.4, 117.5, 115.1, 114.8, 72.5. Anal. calcd. for $C_{22}H_{18}N_2O$ (326.40): C, 80.96; H, 5.56; N, 8.58%. Found: C, 80.84; H, 5.71; N, 8.40%.

2.2.3. 3-(3,4-Dimethoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one (**4c**)

3-(3,4-Dimethoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (**4c**) was synthesized following the general procedure using isatoic anhydride **1** (0.21 g, 1.30 mmol), 3,4-dimethoxyaniline **2c** (0.22 g, 1.44 mmol), cinnamaldehyde **3a** (0.16 mL, 1.30 mmol), and 20 mol% CAM (58 mg, 0.28 mmol). After reaction, isolation, and recrystallization, a white solid (0.35 g, 0.90 mmol, 70 %) was obtained. Rf = 0.10 (1:2, petroleum ether/ethyl acetate); Mp = 227–228 °C (ethanol). IR (ATR, νmax): 3306 (N–H), 2919 (OCH_3), 1630 (C=O), 1507 (ArC=C), 1389 and 1230 (C–N), 752 (ArC–H) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.73 (1H, d, *J* = 7.8 Hz, 5-H), 7.39–7.35 (2H, m, H_{Ar}), 7.34–7.31 (1H, m, 7-H), 7.29 (3H, d, *J* = 3.7 Hz, H_{Ar}), 7.27–7.22 (1H, m, H_{Ph}), 6.98–6.95 (1H, m, 6-H), 6.94 (1H, s, H_{Ph}), 6.87 (1H, dd, *J* = 8.5, 2.3 Hz, H_{Ph}), 6.83 (1H, d, *J* = 15.0 Hz, $=H_{\alpha}C_{Ar}$), 6.75 (1H, m, *J* = 15.0 Hz, $=H_{\beta}C_{Quin}$), 6.50 (2H, d, *J* = 3.2 Hz, 8-H and N–H), 5.64–5.57 (1H, m, 2-H), 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.8, 148.5, 147.4, 146.8, 135.5, 133.5 (2), 132.0, 128.6 (2), 128.1, 128.0, 126.8, 126.6 (2), 119.6, 117.4, 115.0, 114.7, 111.8, 111.4, 73.0, 55.5 (2). Anal. calcd. for $C_{24}H_{22}N_2O_3$ (386.45): C, 74.59; H, 5.74; N, 7.25 %. Found: C, 74.40; H, 5.89; N, 7.13 %.

2.2.4. 3-(4-Methoxyphenyl)-2-(2-methoxystyryl)-2,3-dihydroquinazolin-4(1*H*)-one (**4d**)

3-(4-Methoxyphenyl)-2-(2-methoxystyryl)-2,3-dihydroquinazolin-4(1H)-one (**4d**) was synthesized following the general procedure using isatoic anhydride **1** (0.21g, 1.30 mmol), 4-methoxyaniline **2a** (0.17 g, 1.43 mmol), 3-(2-methoxyphenyl)acrylaldehyde **3b** (0.21 g, 1.29 mmol), and 20 mol% CAM (59 mg, 0.28 mmol). After reaction, isolation, and recrystallization, a brown solid (0.31 g, 0.80 mmol, 61%) was obtained. Rf = 0.16 (1:2, petroleum ether/ethyl acetate); Mp = 162–164 °C (ethanol). IR (ATR, νmax): 3306 (N–H), 2832 (OCH_3), 1628 (C=O), 1604 and 1508 (ArC=C), 1391 and 1242 (C–N), 751 (ArC–H) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.72 (1H, dd, *J* = 7.8, 1.4 Hz, 5-H), 7.37 (1H, dd, *J* = 7.7, 1.6 Hz, H_{Ar}), 7.33–7.30 (1H, m, 7-H), 7.29–7.26 (3H, m, H_{Ar}), 7.25–7.20 (1H, m, 6-H), 6.97–6.92 (3H, m, 8-H and H_{Ph}), 6.88–6.80 (3H, m, H_{Ph} and N–H), 6.76–6.69 (1H, m, *J* = 15.0, $=H_{\alpha}C_{Ar}$), 6.43 (1H, m, *J* = 15.9, $=H_{\beta}C_{Quin}$), 5.60 (1H, m, 2-H), 3.74 (3H, s, OCH_3), 3.72 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.9, 157.5, 156.4, 146.9, 133.4, 133.3, 129.4, 128.7 (2), 127.9, 127.0, 126.7, 126.5, 123.9, 120.5, 117.3, 115.0, 114.7, 113.9 (2), 111.4, 73.3, 55.4, 55. Anal. calcd. for $C_{24}H_{22}N_2O$ (386.45): C, 74.59; H, 5.74; N, 7.25%. Found: C, 74.68; H, 5.61; N, 7.33%.

2.2.5. 3-(4-Bromophenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one (**4e**)

3-(4-Bromophenyl)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (**4e**) was synthesized following the general procedure using isatoic anhydride **1** (0.20 g, 1.30 mmol), 4-bromoaniline **2d** (0.23 g, 1.35 mmol), cinnamaldehyde **3a** (0.15 mL, 1.23 mmol), and 20 mol% CAM (63 mg, 0.30 mmol). After reaction, isolation, and recrystallization, a white solid (0.14 g, 1.12 mmol, 30%) was obtained. Rf = 0.46 (1:2, petroleum ether/ethyl acetate); Mp = 183–185 °C (ethanol). IR (ATR, νmax): 3306 (N–H), 3067 (ArC–H), 1726 (C=O), 1613 and 1485 (ArC=C),

1391 (C–N), 1010 (C–Br), 751 (ArC–H) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.92 (1H, dd, *J* = 7.9, 1.1 Hz, 5-H), 7.60–7.57 (2H, m, H_{Ph}), 7.38–7.34 (5H, m, H_{Ar}), 7.27–7.24 (2H, m, H_{Ph}), 7.16 (2H, d, *J* = 8.2 Hz, 6-H and 7-H), 6.84 (1H, d, *J* = 15.2 Hz, $=H_\alpha C_{Ar}$), 6.74–6.69 (1H, m, *J* = 15.0 Hz, $=H_\beta C_{Quin}$), 6.51–6.46 (2H, m, 8-H and N–H), 5.71 (1H, m, 2-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.8, 159.8, 147.0, 146.8, 141.3, 132.5, 132.1, 131.6 (2), 128.6 (2), 128.4, 128.2, 126.6 (2), 126.5, 123.4, 117.5, 115.32 (2), 114.9, 72.3. Anal. calcd. for $C_{22}H_{17}BrN_2O$ (405.30): C, 65.20; H, 4.23; N, 6.91%. Found: C, 65.37; H, 4.11; N, 6.82%.

2.3. General Procedure for the Synthesis of (E)-3-Aryl-2-styrylquinazolin-4(3H)-one derivatives **5a–d**

The oxidation of 2,3-dihydroquinazolin-4(3*H*)-ones (**4a–d**) was conducted as follows: A total of 0.20 g (0.56 mmol) of the corresponding substrate, dissolved in 2 mL of DMSO was introduced into a vial under constant stirring. Subsequently, 20 mol% of I_2 was added, and the reaction was maintained at 100 °C, with progress monitored via TLC for 1 h. The reaction mixture was then extracted with ethyl acetate and washed with brine (3 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Final purification was achieved through column chromatography (silica gel) using petroleum ether/ethyl acetate mixtures (10:1). Characterization data for the synthesized compounds **5a–d** are provided below.

2.3.1. 3-(4-Methoxyphenyl)-2-styrylquinazolin-4(3*H*)-one (**5a**)

3-(4-Methoxyphenyl)-2-styrylquinazolin-4(3H)-one (**5a**) was synthesized following the general procedure using 2,3-dihydroquinazolinone **4a** (0.20 g, 56 mmol) and 20 mol% of I_2 (28 mg, 0.11 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.18 g, 0.52 mmol, 91%) was obtained. Rf = 0.53 (1:2, petroleum ether/ethyl acetate); Mp = 166–168 °C (ethanol). IR (ATR, νmax): 2922 (ArC–H), 2838 (OCH_3), 1671 (C=O), 1548 (ArC=C, ArC=N), 1245 (C–N), 689 (ArC–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (1H, d, *J* = 7.9 Hz, 5-H), 7.97 (1H, d, *J* = 15.5 Hz, $=H_\alpha C_{Ar}$), 7.80–7.76 (2H, m, 6-H and 7-H), 7.46 (1H, d, *J* = 8.2 8-H), 7.38–7.29 (5H, m, H_{Ar}), 7.25–7.19 (2H, m, H_{Ph}), 7.11–7.05 (2H, m, H_{Ph}), 6.47 (1H, d, *J* = 15.5 Hz, $=H_\beta C_{Quin}$), 3.91 (3H, s, 4′-OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 162.7, 160.0, 152.2, 147.9, 139.9, 135.4, 134.6, 129.8 (2), 129.7, 129.5, 128.9 (2), 127.9 (2), 127.4, 127.3, 126.6, 121.0, 120.1, 115.2 (2), 55.7. Anal. calcd. for $C_{23}H_{18}N_2O_2$ (354.41): C, 77.95; H, 5.12; N, 7.90%. Found: C, 77.82; H, 5.37; N, 7.76%.

2.3.2. 3-Phenyl-2-styrylquinazolin-4(3*H*)-one (**5b**)

3-Phenyl-2-styrylquinazolin-4(3H)-one (**5b**) was synthesized following the general procedure using 2,3-dihydroquinazolinone **4b** (0.20 g, 0.61 mmol) and 20 mol% of I_2 (31 mg, 0.12 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.11 g, 0.35 mmol, 57%) was obtained. Rf = 0.50 (1:2, petroleum ether/ethyl acetate); Mp = 195–197 °C (ethanol). (lit. 150–152 °C [49], 196–197 °C [50]). IR (ATR, νmax): 3055 (ArC–H), 1665 (C=O), 1550 (ArC=N), 1467 (ArC=C), 1352 (C–N), 689 (ArC–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.31 (1H, d, *J* = 7.7 Hz, 5-H), 7.98 (1H, d, *J* = 15.5 Hz, $=H_\alpha C_{Ar}$), 7.81–7.78 (2H, m, 6-H and 7-H), 7.63–7.55 (3H, m, H_{Ph}), 7.47 (1H, d, *J* = 8.2 Hz, 8-H), 7.35–7.32 (2H, m, H_{Ph}), 7.32–7.29 (5H, m, H_{Ar}), 6.40 (1H, d, *J* = 15.5 Hz, $=H_\beta C_{Quin}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 162.4, 151.8, 147.9, 140.0, 137.1, 135.4, 134.7, 130.0 (2), 129.7, 129.4, 128.9 (2), 128.8 (2), 127.8 (2), 127.4, 127.2, 126.7, 121.0, 120.0. Anal. calcd. for $C_{22}H_{16}N_2O$ (324.38): C, 81.46; H, 4.97; N, 8.64%. Found: C, 81.21; H, 4.82; N, 8.53%.

2.3.3. 3-(3,4-Dimethoxyphenyl)-2-styrylquinazolin-4(3*H*)-one (**5c**)

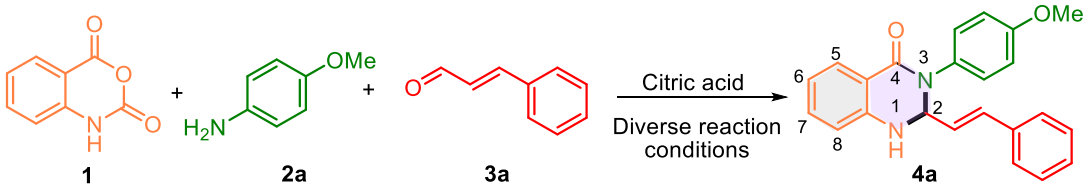
3-(3,4-Dimethoxyphenyl)-2-styrylquinazolin-4(3H)-one (**5c**) was synthesized following the general procedure using 2,3-dihydroquinazolinone **4c** (0.20 g, 52 mmol) and 20 mol% of I_2 (26 mg, 0.10 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.17 g, 0.47 mmol, 87 %) was obtained. Rf = 0.30 (1:2, petroleum ether/ethyl acetate); Mp = 232–233 °C (ethanol). IR (ATR, νmax): 3005 (ArC–H), 2915 (OCH_3), 1673 (C=O), 1551 (ArC=C, ArC=N), 1228 (C–N), 697 (ArC–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (1H, d, *J* = 7.9 Hz, 5-H), 7.98 (1H, d, *J* = 15.5 Hz, $=H_\alpha C_{Ar}$), 7.82–7.75 (2H, m, 6-H and 7-H), 7.50–7.43 (1H, m, 8-H), 7.37–7.30 (5H, m, H_{Ar}), 7.03 (1H, d, *J* = 8.4 Hz, H_{Ph}), 6.87 (1H, dd, *J* = 8.4, 2.3 Hz, H_{Ph}), 6.82 (1H, d, *J* = 2.4 Hz, H_{Ph}), 6.48 (1H, d, *J* = 15.5 Hz, $=H_\beta C_{Quin}$), 3.98 (3H, s, OCH_3), 3.88 (3H, s, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 162.7, 152.1, 150.0, 149.6, 147.9, 140.0, 135.4, 134.7, 129.8, 129.7, 128.9 (2), 127.9 (2), 127.4, 127.2, 126.7, 121.0 (2), 120.0, 111.7, 111.6, 56.2 (2). Anal. calcd. for $C_{24}H_{20}N_2O_3$ (384.44): C, 74.98; H, 5.24; N, 7.29%. Found: C, 74.71; H, 5.37; N, 7.40%.

2.3.4. 3-(4-Methoxyphenyl)-2-(2-methoxystyryl)-quinazolin-4(3*H*)-one (**5d**)

3-(4-Methoxyphenyl)-2-(2-methoxystyryl)-quinazolin-4(3H)-one (**5d**) was synthesized following the general procedure using 2,3-dihydroquinazolinone **4d** (0.20 g, 52 mmol) and 20 mol% of I_2 (26 mg, 0.10 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.17 g, 0.45 mmol, 86%) was obtained. Rf = 0.43 (1:2, petroleum ether/ethyl acetate); Mp = 189–190 °C (ethanol). IR (ATR, νmax): 3057 (ArC–H), 2935 (OCH_3), 1671 (C=O), 1550 (ArC=C, ArC=N), 1245 (C–N), 772 (ArC–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.29 (1H, ddd, *J* = 8.0, 1.4, 0.6 Hz, 5-H), 8.19 (1H, d, *J* = 15.6 Hz, $=H_\alpha C_{Ar}$), 7.82–7.74 (2H, m, 6-H and 7-H), 7.44 (1H, d, *J* = 8.2, 6.6, 1.7 Hz, 8-H), 7.29–7.25 (2H, m, H_{Ar}), 7.23 (2H, d, *J* = 9.0 Hz, H_{Ph}), 7.08 (2H, d, *J* = 9.0 Hz, H_{Ph}), 6.92–6.84 (2H, m, H_{Ar}), 6.67 (1H, d, *J* = 15.6 Hz, $=H_\beta C_{Quin}$), 3.90 (3H, s, OCH_3), 3.76 (3H, s, $4OCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 162.8, 159.9, 158.3, 152.9, 148.0, 135.6, 134.5, 130.8, 129.9, 129.8 (2), 129.5, 127.5, 127.2, 126.4, 124.5, 121.3, 120.9, 120.7, 115.1 (2), 111.1, 55.7, 55.3. Anal. calcd. for $C_{24}H_{20}N_2O_3$ (384.44): C, 74.98; H, 5.24; N, 7.29%. Found: C, 74.83; H, 5.41; N, 7.11%.

3. Results and Discussion

Drawing on previous reports of 3-aryl-2,3-dihydroquinazolione synthesis catalyzed by organocatalysts [34–43], we selected citric acid as the catalyst. This naturally occurring Brønsted acid is inexpensive, readily available, and has performed well in preparing such heterocycles [43]. To explore its efficacy, we investigated the reaction of isatoic anhydride **1**, 4-methoxyaniline **2a**, and *trans*-cinnamaldehyde **3a** to synthesize 3-(4-methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **4a** using citric acid under varying reaction conditions (Scheme 1, Table 1).



Scheme 1. The model reaction of isatoic anhydride **1**, 4-methoxyaniline **2a**, and *trans*-cinnamaldehyde **3a** to afford 3-(4-methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **4a** evaluating reaction parameters.

Table 1. Study of the optimal reaction conditions for the preparation of 3-(4-methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one (**4a**) [a].

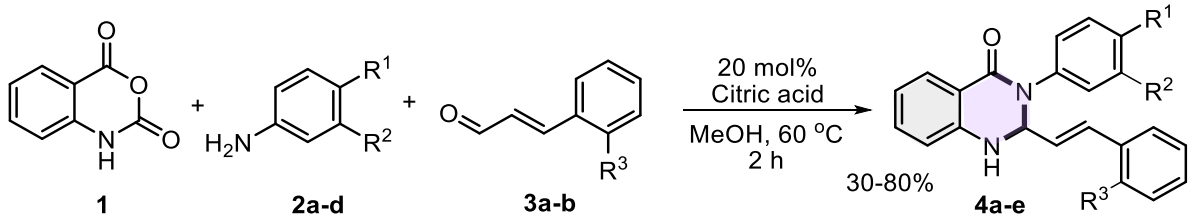
Entry	Citric Acid (mol%)	Dissolvent	t, °C	T (h)	Yield, %
1	40	Methanol	60	2	76
2	40	Methanol	100 [b]	10 min	40
3	40	Methanol	160 [b]	15 min	20
4	20	Methanol	60	2	80
5	--	Urea/$ZnCl_2$	110	1	20 [c]

[a] Reaction conditions: 4-methoxyaniline **2a** (1.62 mmol, 1.1 equiv), isatoic anhydride **1** (1.39 mmol, 1 equiv), *trans*-cinnamaldehyde **3a** (1.27 mmol, 1 equiv), mol % of citric acid monohydrate, 1 mL of methanol (MeOH), time and temperature. [b] Microwave heating (min). [c] Catalytic system with eutectic solvent urea/$ZnCl_2$ (3.5:1).

Based on the prior literature on the construction of similar systems, the formation of the target compound **4a** was initially investigated using 40 mol% citric acid as a catalyst, yielding 76% (Entry 1, Table 1). Despite this promising result, our goal was to develop a more user-friendly and efficient protocol to accelerate the reaction rate and improve the selective synthesis of dihydroquinazolinones. To this end, microwave radiation (MW) was employed as a heating source under various time and temperature conditions. While MW-assisted synthesis of similar 2,3-dihydroquinazolinones has been documented [61–63], no reports exist for synthesizing 2-styryl derivatives. Experiments using MW revealed a significant decrease in yield (40% and 20%, respectively) as the temperature and reaction time increased (Entries 2–3, Table 1), indicating that these conditions adversely affected the reaction's progress toward the desired 2-styryl-2,3-dihydroquinazoline systems.

Subsequently, citric acid catalyst loading was reduced to 20 mol% under conventional heating. The reaction, monitored via TLC and completed in two hours, successfully yielded **4a** with an improved 80% yield (Entry 4, Table 1). Finally, a urea/zinc chloride eutectic solvent system (3.5:1 molar ratio) was tested, inspired by recent reports on synthesizing 2,3-diaryl-dihydroquinazolinones in deep eutectic solvents [64]. However, under these conditions, the efficient formation of **4a** could not be achieved (Entry 5, Table 1).

Following the optimization of reaction conditions, a small series of 2-styryl-dihydroquinazolinones **4a–e** was successfully synthesized (Scheme 2). The reaction employed isatoic anhydride **1**, selected anilines **2a–d**, and cinnamaldehydes **3a–b** in the presence of 20 mol% citric acid as a catalyst using methanol as the solvent at 60 °C for 2 h. The resulting 2,3-dihydroquinazolin-4(1*H*)-ones **4a–e** were obtained in yields ranging from 30% to 80%.



Scheme 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **4a–e** using citric acid as catalyst.

The lowest yield (30%) was observed for molecule **4e**, likely due to the diminished nucleophilicity of 4-bromoaniline **2d**, which impeded its interaction with isatoic anhydride during the initial condensation step. Moreover, no product was formed with 4-nitroaniline (not shown in the scheme), underscoring the essential role of aniline nucleophilicity in successfully creating the target compounds. In contrast, 2,3-dihydroquinazolin-4(1*H*)-one **4a** and those bearing electron-donating substituents **4b–c** were obtained in moderate to

excellent yields. Purified through column chromatography (alumina) using petroleum ether/ethyl acetate mixtures (1:2), dihydroquinazolinones resulted in stable powders of different colors (from white to pale yellow and brown) with well-defined melting points (Table 2), allowing for determination of their characterization by spectroscopic techniques to elucidate the structure of these heterocyclic systems.

Table 2. 2-Styryl-dihydroquinazolinone derivatives **4** obtained through a citric acid-catalyzed three-component condensation reaction.

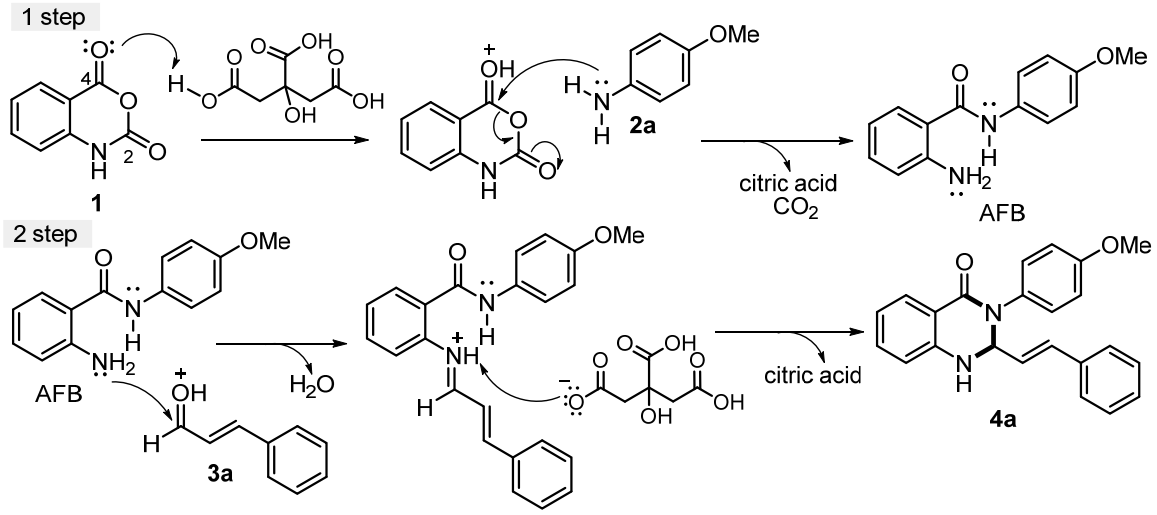
Comp.	R^1	R^2	R^3	Mp., °C	Yield, %
4a	OMe	H	H	234–236	80
4b	H	H	H	192–194	54
4c	OMe	OMe	H	227–228	70
4d	OMe	H	OMe	162–164	61
4e	Br	H	H	183–185	30

Their structures were elucidated using spectroscopic and analytical techniques, including IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. The ^{1}H NMR spectra provided clear evidence for the molecular structure, with all proton signals and their couplings consistent with the spatial arrangement of the molecule. Key features confirming the skeleton construction included the C-2 proton and the olefinic protons of the styryl fragment, $=H_\alpha C_{Ar}$ and $=H_\beta C_{Quin}$, which were observed in the regions of 5.57–5.73 ppm, 6.67–6.85 ppm, and 6.43–6.76 ppm, respectively. The olefinic protons were confirmed to have a *trans*-configuration, as indicated by the H_α signals appearing as doublets with coupling constants J = 15.0–15.9 Hz. Meanwhile, the H_β protons were deshielded and appeared as multiplets due to interactions with the two quinazolinone nitrogen atoms and the adjacent C-2 proton (see Figure S17 for example).

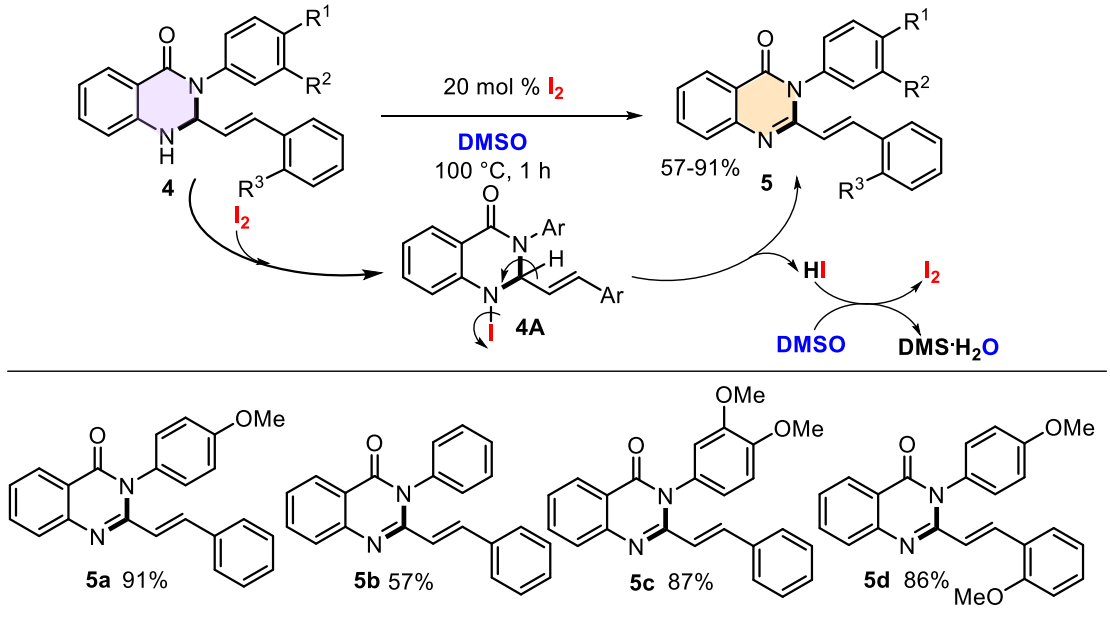
As noted in previous studies [34,62,65], the synthesis of the 2,3-dihydroquinazolin-4(1*H*)-one series depends mainly on the balance between the acidity of the reaction medium and the nucleophilicity of the starting anilines. In the initial step, the carbonyl group at the C-4 position of isatoic anhydride **1** undergoes protonation by citric acid, which enhances its electrophilicity and promotes a nucleophilic attack by the amino group of 4-methoxyaniline **2a**. This reaction produces the intermediate 2-amino-N-phenylbenzamide (AFB), which then forms the desired product. Under the same conditions, the second step proceeds as the carbonyl group of cinnamaldehyde **3a**, activated by citric acid, reacts with the amino group at the C-2 position of the intermediate AFB. This nucleophilic attack is followed by dehydration and subsequent protonation facilitated by citric acid in the reaction medium. These steps culminate in cyclization, yielding 2,3-dihydroquinazolin-4(1*H*)-one **4a** as an example (Scheme 3).

The products obtained hold significant value not only for medicinal applications but also for their synthetic potential. Typically, 2,3-diaryl-dihydroquinazolinones can be converted into their corresponding quinazolin-4(3*H*)-one derivatives through oxidation. Established methods include potassium *tert*-butoxide and tetrabutylammonium bromide in dry THF [66] for 4–6 h or 5% $KMnO_4$ in acetone for 8 h [38]. Additionally, a catalyzed cyclization–oxidation coupling of isatoic anhydride with benzaldehydes and amines in the presence of iodine (1 equiv.) and acetic acid (10 mol%) in a MeCN-H_2O mixture was reported in 2010, yielding 2,3-diarylquinazolin-4(3*H*)-ones [67]. Seeking an efficient method for the oxidation of 3-aryl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-ones **4** to their respective 2-styrylquinazolinones **5**, we explored the I_2/DMSO catalytic system. This system has gained considerable attention due to its green chemistry attributes, high efficiency, atom

economy, low cost, and mild reaction conditions [68–70]. Drawing on these advantages and our prior experience with the system [71], we subjected compounds **4** to oxidation using 20 mol% iodine in DMSO at 100 °C for 1 h. This approach successfully produced the corresponding quinazolin-4(3*H*)-one derivatives **5** in good to excellent yields, demonstrating that this oxidative catalytic system is also reproducible for this type of quinazoline system (Scheme 4).



Scheme 3. Proposed mechanism of 2,3-dihydroquinazolin-4(1*H*)-ones via multicomponent reaction.



Scheme 4. Synthesis of 3-aryl-2-styrylquinazolin-4(3*H*)-ones **5** promoted by the environmentally friendly iodine/DMSO catalytic system and its mechanistic insights.

Under the used reaction conditions, iodine acts as a mild Lewis acid catalyst, and DMSO acts as an oxidant, solvent, and oxygen source, as a general law [68,72]. Thus, the nitrogen (N1) lone pair of dihydroquinazolinones **4** first reacts with molecular iodine (I_2) (i.e., N-iodination reaction) to form iodine intermediate **4A**. The dehydroiodination process (intramolecular HI elimination) can expand the π-conjugation system to form cyclic imine bonds, producing the desired quinazolin-4(3*H*)-ones **5**. The oxidation of I_2 in the presence of DMSO produces $(CH_3)_2S$ (DMS), water, and iodine, which can act as a catalyst that may

be regenerated in the subsequent catalytic cycle [68] (Scheme 4). The reaction system's remarkable characteristics are that it is metal-free, peroxide-free, and acid–base-free.

The obtained quinazolin-4(3*H*)-ones **5a–d** were isolated as stable, pale yellow solids, facilitating the determination of their physical properties and characterization through infrared spectroscopy and nuclear magnetic resonance analysis. A clear comparison of the IR spectra of the dehydro-product **4d** and its oxidized counterpart **5d** reveals the absence of the characteristic peak at 3306 cm^{-1}, corresponding to the NH group. This confirms the successful and complete oxidation of dihydroquinazolinone **4d** (Figure S10). Additionally, the NMR spectra of the oxidized products display well-defined signals for the olefinic protons. The olefinic H_β protons (=$H_\beta C_{Quin}$) appear as doublets at 6.40–6.67 ppm (J = 15.5–15.6 Hz), while the H_α protons (=$H_\alpha C_{Ar}$) are observed as doublets at 7.97–8.19 ppm, exhibiting identical coupling constants (see Figure S27 as an example).

4. Conclusions

In summary, we have developed an organocatalytic approach for synthesizing 3-aryl-quinazolinones incorporating a *trans*-stilbene unit. This synthetic method, executed in a straightforward and eco-friendly one-pot process, is particularly interesting in heterocyclic chemistry. Citric acid, the organocatalyst, exhibited remarkable efficiency in facilitating these dehydro-products. These intermediates were then efficiently transformed into 2-styryl-quinazolinones through a metal-free catalytic system using iodine/DMSO under mild oxidative conditions.

The synthetic strategies introduced here enable the construction of two diverse series of saturated and aromatic 3-aryl-2-styryl-quinazolinone frameworks. The workup procedures are also simple, cost-effective, and use readily available commercial reagents. Both structural series could have significant potential in medicinal chemistry, such as cancer drug discovery. This study presents an accessible and practical method for creating novel libraries of styryl-quinazolinones from various amines and cinnamaldehydes.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/chemistry7020042/s1, synthetic procedures, FT-IR and NMR spectra of the obtained compounds.

Author Contributions: Conceptualization, V.V.K.; methodology, A.P.G.; formal analysis, A.P.G., C.E.P.G. and V.V.K.; writing—original draft preparation, V.V.K.; writing—review and editing, C.E.P.G. and V.V.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Synthetic procedures and FT-IR and NMR are reported in Supplementary Materials.

Acknowledgments: We thank Escuela de Química of the Universidad Industrial de Santander for financial support.

Conflicts of Interest: The authors declare no conflicts of interest.

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