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Ohmic Heating

Synthesis of (*E*)-3-Styrylquinolin-4(1*H*)-ones in Water by Ohmic Heating: a Comparison with Other Methodologies

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Abstract: Ohmic heating offers a very efficient way to perform organic reactions in aqueous media. Potentially bioactive (*E*)-3-styrylquinolin-4(1*H*)-ones were synthesized by the Heck reaction of 3-iodo-1-methylquinolin-4(1*H*)-one with styrenes in water and with ohmic heating. $Pd(OAc)_2$ was used as catalyst, and tetrabutylammonium bromide was used as phase-transfer catalyst in the presence of an inorganic base. Comparison with other established procedures highlight the benefits of this new methodology.

Introduction

One of the current priorities in organic chemistry is the development of efficient synthetic routes and heating processes that lead to target compounds and at the same time reduce or eliminate the use of toxic organic solvents in these synthetic procedures.

Ohmic heating (ΩH) is a highly energy-efficient heating process in which heat is generated directly within the reaction medium itself (which behaves as an electrical ohmic heater). An AC electrical current of tunable high frequency passes through a conductive reaction medium so that heat is generated in situ, which removes the heat-transfer step from the surroundings to the reaction medium by means of temperature gradients or hot surfaces.[1,2] Thus, heating is less dependent on the heat transfer to the medium, which results in a fast rate of heating that allows fast, volumetric and uniform heating (temperature homogeneity), and increased the dynamics of charged species in solution, which leads to shorter reaction times and increased yields.[2–5] In some cases better reaction selectivities were observed.[3] ΩH differs from other heating techniques by the presence of electrodes in contact with the reaction mixture that allow the use of a variable frequency and waveform; in general a sinusoidal waveform is selected.[2]

A combination of ΩH and water as solvent provides great opportunities for sustainable chemistry. Water is non-toxic, non-flammable, has a large heat capacity, is easily available at low cost,[6] and it is also known to enhance the rates and to affect the selectivity of a wide variety of organic reactions.[7]

We have demonstrated that ΩH can be used to heat reaction mixtures and that it is a competitive alternative to classical heating (CH) and to microwave (MW) irradiation methods.[2–5] To date, several different types of organic reactions have been performed by using ΩH, which include nucleophilic substitution reactions, *N*-alkylation of amines, Diels–Alder reactions, sequential Knoevenagel and hetero-Diels–Alder reactions, indium-promoted dehalogenations, and reductive elimination reactions.[2,3,5] Recently, we reported an efficient protocol for the synthesis of 3-arylquinolin-4(1*H*)-ones by using ΩH that involves the Suzuki–Miyaura cross-coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with several arylboronic acids in water under phase-transfer catalysis (PTC) conditions.[4] Now we aim to study the Heck reaction of the same scaffold **1** with several substituted styrenes **2a**–**2j** with ΩH to prepare a library of complex (*E*)-1-methyl-3-styrylquinolin-4(1*H*)-ones (**3a**–**3j**).

Quinolin-4(1*H*)-one is a common scaffold found in natural products and is considered as a privileged structure, especially for anti-infective medicines.[8] However, when conveniently functionalized these compounds have potential use as antitumor[9] and antiviral[9d] agents, and as CB_2 receptor agonists.[10] In particular, (*E*)-3-styrylquinolin-4(1*H*)-ones **3**, which are analogous to 3-arylquinolin-4(1*H*)-ones and aza analogues of (*E*)-3-styryl-4*H*-chromen-4-ones, are important compounds the biological potential of which remains unexplored (Figure 1). The structural similarity of (*E*)-3-styrylquinolin-4(1*H*)-ones with (*E*)-3-styryl-4*H*-chromen-4-ones (Figure 1), which show antifungal and antibacterial activity,[11] highlights the biological potential of these quinolone derivatives.

To date, only two methods for the synthesis of (*E*)-3-styrylquinolin-4(1*H*)-ones have been reported in the literature. One method is the Wittig reaction of 4-chloroquinoline and 1-substituted 4-quinolone-3-carbaldehydes with benzylic ylides.[12] (*Z*)-1-Methyl- and (*Z*)-1-tosyl-3-styrylquinolin-4(1*H*)-ones were obtained with high diastereoselectivity (38–72 %), relative to the isomeric (*E*)-1-methyl- and (*E*)-1-tosyl-3-styrylquinolin-4(1*H*)-

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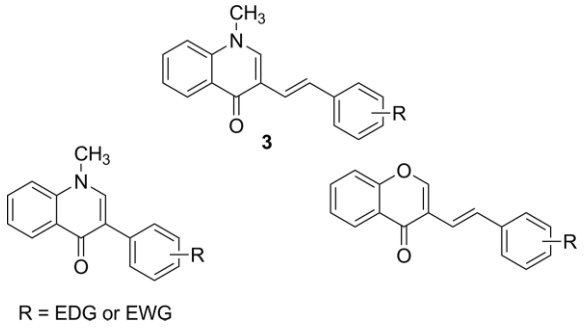

Figure 1. Structures of (*E*)-3-styrylquinolin-4(1*H*)-ones, 3-arylquinolin-4(1*H*)-ones, and (*E*)-3-styryl-4*H*-chromen-4-ones.

ones (4–24 %), from the reaction of 1-methyl- and 1-tosylquinolin-4(1*H*)-one-3-carbaldehyde with benzylic ylides, whereas (*E*)-3-styrylquinolin-4(1*H*)-ones were obtained in very good yield (85–99 %) as the sole product from the Wittig reaction of 4-chloroquinoline-3-carbaldehyde with benzylic ylides followed by acid hydrolysis.[12] The other method allows the synthesis of (*E*)-3-styrylquinolin-4(1*H*)-ones in a direct way, and involves the Mizoroki–Heck cross-coupling reaction of (*E*)-3-iodo-1-substituted quinolin-4(1*H*)-ones with styrenes to afford (*E*)-3-styrylquinolin-4(1*H*)-ones in moderate to good yields (55–65 %) after prolonged reaction times (5 h). In some cases, traces of branched regioisomer 1-methyl-3-(1-phenylethenyl)quinolin-4(1*H*)-ones were obtained as a by-product, which are a result of coupling at the α-position of the styrene moiety.[13] Silva and co-workers studied several reaction conditions[13] and the effect of MW heating for this reaction, which led to the shortening of the reaction time from 5 to 1.5 h, although the yields of the product were disappointingly low (30–48 %).[13]

The Mizoroki–Heck reaction is a highly versatile Pd^0-mediated carbon–carbon bond-forming reaction method used widely in the synthesis of natural products, fine chemicals, pharmaceuticals, polymers, and in materials science.[14] Due to its importance, it is highly desirable to develop milder and simpler procedures for this reaction. The pioneering work of Beletskaya and co-workers in 1989[15] showed that the Pd-catalyzed coupling reaction of aryl halides with acrylic acid and acrylonitrile in the presence of base ($NaHCO_3$ or K_2CO_3) in water at 80–100 °C provided an efficient method for the synthesis of substituted cinnamic acids and cinnamonitriles in high yields. Instead, the reactions could be carried out faster and at a lower temperature (50–60 °C) with KOAc as base.[15] Since then, the transition-metal-catalyzed Heck reaction in aqueous solvents has been developed by applying three major protocols: (a) without phosphane ligands by using transition-metal salts in water or aqueous organic solvents; (b) aqueous phosphane-assisted methods by using hydrophilic phosphane ligands in aqueous organic solvents; and (c) recyclable phase-separation methods by using heterogeneous systems in which the catalyst is within the aqueous phase, and the stock of substrates is within the hydrophobic organic phase that also receives the products of the reaction. Other protocols that involve the use of superheated or subcritical water have also been reported but, in general, show poor selectivity.[16,17]

One of the most attractive protocols developed for an aqueous Heck reaction uses water as solvent in the presence of a proper phase-transfer agent. This protocol was employed by Xia and co-workers that used polyethylene glycol (PEG; both as a polymeric support and PTC) in the coupling of PEG-supported 4-iodobenzoate with styrene and acrylic acid by using $Pd(OAc)_2$ (5 mol-%) and Na_2CO_3 in water at 60 °C for 1–4 h.[18] The expected products were obtained after resin cleavage in 94 and 76 % yield, respectively.

MW heating proved to be a very efficient way to couple a series of aryl iodides with styrene, methyl acrylate, and acrylic acid, in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol-%) as catalyst, together with tetrabutylammonium bromide (TBAB) and K_2CO_3 in water.[19] After 10 min of MW irradiation (at 375 W) under argon, the (*E*) diastereomers of the alkenes were exclusively obtained in high yields (86–93 %).

Cai and co-workers described the Heck arylation reaction of acrylonitrile with a variety of aryl iodides, which bore both electron-donating and electron-withdrawing substituents, in water, that led to corresponding (*E*)-cinnamonitriles in good yields.[20] Similarly, the Heck arylation of *n*-butyl acrylate and acrylamide with aryl iodides afforded (*E*)-cinnamates and (*E*)-cinnamamides in good yields.[21] By using Amberlite IRA-400 (basic) as base and PTC, good results were obtained in the stereoselective Heck reaction of bromobenzene, *p*-iodotoluene and *p*-iodoanisole with a variety of olefins.[22] Inspired by these findings we aim to develop a more efficient protocol for the ΩH-assisted Mizoroki–Heck reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with styrenes **2a**–**2j**.

Results and Discussion

Optimizing Conditions

The combination of water as solvent with ΩH has proved to be efficient for several types of reactions that include the Suzuki–Miyaura cross-coupling reaction.[2–4] By aiming to develop a more efficient protocol for the Mizoroki–Heck reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with styrenes **2a**–**2j**, to prepare potentially bioactive quinolin-4(1*H*)-ones, Silva and co-workers performed the reaction of quinolin-4(1*H*)-one **1** with styrene **2a** (the model reaction) in water in an ΩH reactor with 316 stainless steel based electrodes with $Pd(OAc)_2$ as catalyst, tetrabutylammonium bromide (TBAB) as PTC, and K_2CO_3 as base. 3-Iodo-1-methylquinolin-4(1*H*)-one (**1**) was synthesized by applying the methodology already published.[4] As reported, preparation of the analogous C-3-brominated derivative of **1** is more complicated, because the reaction is not regioselective and affords a complex mixture of products. It is also known that iodinated substrates are more reactive in Heck reactions than the corresponding brominated derivatives.

The use of ligand-free Pd catalysts in combination with tetraalkylammonium salts (Jeffery conditions) is of particular relevance to this work.[23] Under these reaction conditions, $Pd(OAc)_2$ is reduced in situ to Pd^0 (the alkene may act as the reducing agent), which initiates the catalytic cycle by oxidative addition to the aryl iodide.[23] The probable mechanism for the

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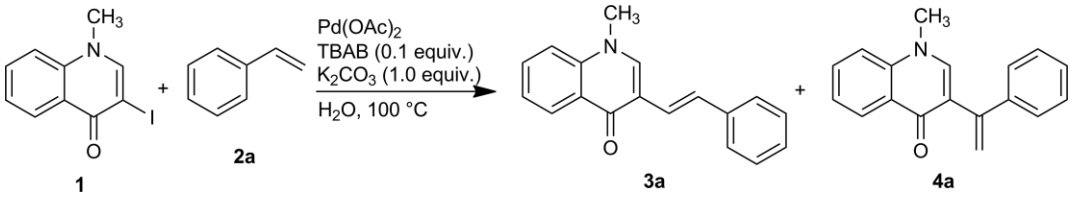
Table 1. Optimization of the Heck cross-coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with styrene **2a** and the effect of heating method on reaction yield.



Entry	Heating method	Styrene [mol-equiv.]	$Pd(OAc)_2$ [mol-equiv.]	Time [min]	Yield of **3a** [%][a]	Yield of **4a** [%]
1	ΩH	5	0.005	30	54	–
2	ΩH	5	0.05	30	68	10[b]
3	ΩH	3	0.05	45	37[c]	–
4	ΩH	5	0.05	15	53	–
5	ΩH	5	0.05	60[d]	80	–
6	MW	5	0.05	30	57[e]	traces
7	CH	5	0.05	240	16[f]	–

[a] Isolated yields. [b] Yield calculated by NMR spectroscopy. [c] Starting material **1** (33 %) was recovered. [d] Reaction time was 15 + 15 + 30 min. [e] Microwave-assisted reaction was carried out in a circular single-mode cavity instrument (300 W max. magnetron power output). Reaction was carried out in a closed vessel (10 mL) filled with the reaction mixture (4 mL) and closed with a cap. The temperature measurements were recorded by means of an infrared sensor, which monitors and controls the temperature conditions of the reaction vessel located in the instrument cavity. Medium stirring speed was used. [f] A round-bottom flask was immersed in an oil bath at 100 °C; starting material **1** (73 %) was recovered.

reduction of Pd^{II} to Pd^0 involves intramolecular nucleophilic attack of acetate onto the alkene (styrene or butyl acrylate) coordinated to Pd^{II}, followed by a β-hydride elimination to give HPdOAc and subsequent formation of Pd^0 in the presence of base (K_2CO_3).[24] In the presence of TBAB (or other $R_4N^+X^-$ salts) thermolytic decomposition of $Pd(OAc)_2$ occurs at 100–130 °C, and cleavage of the Pd–OAc bond generates $Bu_4N^+Br^-$-stabilized Pd^0 nanoparticles. One of the key advantages of these nanoparticles is that they are catalytically active in much lower amounts than molecular Pd catalysts, owing to the large surface area of the particles (ratio of atoms that remain at the surface). The homogeneous/heterogeneous character of the catalysis is still under debate, but probably it should be more closely related to heterogeneous catalysis.[23]

De Vries and Reetz have shown that the Heck reaction can be run with the addition of what they term "homeopathic" quantities of palladium catalysts (ideally, 0.01–0.1 mol-%), but at very low metal concentrations the rate of reaction is too slow to be practical.[25] Nevertheless, in a first attempt the reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with styrene **2a** was performed with a low amount of Pd catalyst (0.5 mol-%) and afforded expected (*E*)-3-styrylquinolin-4(1*H*)-one **3a** in 54 % yield after 30 min (Table 1, Entry 1). Based on our previous results in the study of the Suzuki–Miyaura reaction,[4] we performed the reaction of quinolin-4(1*H*)-one **1** with styrene **2a** with Pd catalyst (5 mol-%). After 30 min, product **3a** was obtained in 68 % yield, and another product, branched 1-methyl-3-(1-phenylethenyl)quinolin-4(1*H*)-one (**4a**), was obtained in 10 % yield (Table 1, Entry 2). Styrene polymerizes easily, so we decided to use 5 equiv. to ensure complete consumption of starting material **1**. This seems to be the ideal amount, because with 3 equiv. of styrene product **3a** was obtained in 37 % yield, and 33 % of starting material was recovered (Table 1, Entry 3). A shorter reaction time (15 min) led to a decrease in yield of **3a** to 53 % (Table 1, Entry 4). For prolonged reaction times (up to 1 h) product **3a** was obtained in 80 % yield (Table 1, Entry 5). With MW heating (*E*)-3-styrylquinolin-4(1*H*)-one **3a** was obtained in 57 % yield after 30 min. Thus, we can conclude that for the same reaction time (30 min) the reaction yield obtained by ΩH (68 %) was slightly better than that obtained under MW heating conditions (57 %; Table 1, Entries 2 and 6). For classical heating, a poor yield of **3a** (16 %) was obtained after 4 h, and 73 % of starting material **1** was recovered (Table 1, Entry 7). These results demonstrate that ΩH is the most efficient heating method for this reaction.

Scope and Limitations of Substrates

Having found the optimal reaction conditions, attention was turned to generalizing the process, and the substrate scope of the coupling reaction was studied in detail by varying the substituents in the styrene coupling partner. To highlight the usefulness and flexibility of this protocol, we employed styrenes that contained electron-withdrawing and electron-donating substituents as well as α-substituted styrenes. All reactions were performed in water (4 mL) with $Pd(OAc)_2$ (5 mol-%) as catalyst, and TBAB as PTC (0.1 equiv.) in the presence of K_2CO_3 (1.0 equiv.) as base, at 100 °C in ΩH. The results are summarized in Table 2 and Scheme 1. Reactions were monitored by TLC. The yields were moderate to good and, relative to conventional methodologies reported in the literature,[13] the reaction works efficiently without the use of a phosphane ligand, which is known to act as a reducing agent of Pd^{II} to give catalytically active Pd^0 species prior to the Heck catalytic cycle that often acts as a stabilizing ligand to prevent the formation of Pd black. As demonstrated in our previous work[4] and observed in this work, under ΩH the high heating rates at the beginning (see Supporting Information, Figure S48) may enhance the reduction of Pd^{II} to Pd^0, which is the species involved in the catalytic

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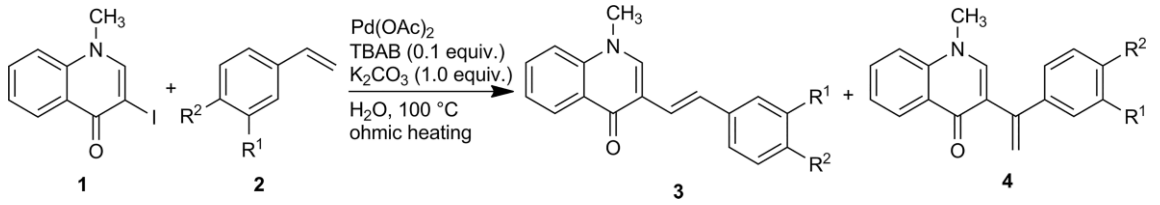
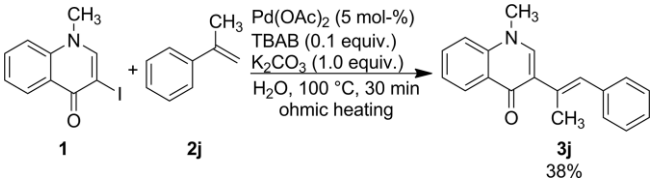
Table 2. Synthesis of (*E*)-3-styrylquinolin-4(1*H*)-ones **3a**–**3j** by a Heck cross-coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with styrenes **2a**–**2j** by ohmic heating. Reaction scope and yields.



Entry	Compound	R^1	R^2	Styrene [equiv.]	Reaction time [min]	Yield of **3** [%][a,b]	Yield of **4** [%][c]	Recovered **1** [%][a]
1[d]	**a**	H	H	5	30	68	10	–
2[d]	**a**	H	H	5	60	80	–	–
3	**b**	H	OCH_3	2.5	30	6	–	57
4	**b**	H	OCH_3	5	30	41	21	–
5	**c**	H	Cl	2.5	30	24	–	55
6	**c**	H	Cl	5	30	51	–	–
7	**d**	H	Br	5	30	63	–	33
8	**d**	H	Br	5	60	96	–	–
9	**e**	H	F	2.5	30	47	–	–
10	**e**	H	F	5	30	47	–	48
11	**f**	H	NO_2	5	30	78	–	22
12	**g**	H	CO_2CH_3	2.5	30	36	–	–
13	**g**	H	CO_2CH_3	5	30	19	12	48[c]
14	**h**	NO_2	H	5	30	96	–	–
15	**i**	OCH_3	OCH_3	5	60 (30 + 30)	38	20[a]	–

[a] Isolated yields. [b] Reaction conditions: 3-iodo-1-methylquinolin-4(1*H*)-one (**1**; 1.0 equiv.) was treated with appropriate styrene **2a**–**2j** (2.5 or 5.0 equiv.), $Pd(OAc)_2$ (0.05 equiv.), TBAB (0.1 equiv.), and K_2CO_3 (1.0 equiv.) in H_2O (4.0 mL) at 100 °C by ohmic heating. [c] Yields calculated by NMR spectroscopy. [d] Model reactions for analysis.

cycle of the Heck reaction. Moreover, the presence of TBAB, which is known to induce the formation and stabilization of Pd nanoparticles, will initially lead to the formation of Pd colloids, which are then deposited as thin films or Pd black on the electrodes.



Scheme 1. Heck reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with α-substituted styrene **2j**.

By analyzing the results presented in Table 2, we conclude that the reaction is sensitive to the electronic and steric effects of the styrene substituents. In general, the yield of the reaction is higher for styrenes that bear electron-withdrawing groups (EWG) and for neutral substituents (**3a**, R^2 = H, 68 and 80 %; **3c**, R^2 = Cl, 51 %; **3d**, R^2 = Br, 63 % and 96 %; **3e**, R^2 = F, 47 %; **3f**, R^4 = NO_2, 78 %; Table 2, Entries 1, 2 and 5–11) and lower for styrenes that have electron-donating groups (EDG; **3b**, R^2 = OCH_3, 41 %; Table 2, Entries 3 and 4) if substitution at the *para* position of the styrene moiety is considered. When 2.5 equiv. of styrene **2g** was used, 36 % of product **3g** was obtained (Table 2, Entry 12). In the presence of a higher excess of styrene **2g** (5 equiv.) the yield of **3g** decreased (19 %), and the formation of regioisomer **4g** (12 %) was observed (Table 2, Entry 13). Our results are in good agreement with the results reported in the literature.[26] It is known that EDGs considerably lower the reaction rate, so higher temperatures and longer reaction times are often required to achieve good yields of Heck product. Another important aspect is the influence of EDGs (**3b**, R^2 = OCH_3; **3i**, R^1 = R^2 = OCH_3; Table 2, Entries 4 and 15) and neutral substituents (**3a**, R^2 = H; Table 2, Entry 1), which favors formation of branched product **4**, which results from coupling at the α-position of the styrene. With regards to substitution at the *meta* position of the styrene, only compound **3h** is shown, which was obtained in very good yield (96 %; Table 2, Entry 14) as expected. Compound **3i**, which is a disubstituted compound, was obtained in low yield (38 %), and the branched regioisomer was formed in 20 % yield because of two EDGs at the *meta* and *para* positions (Table 2, Entry 15). The reaction with sterically more hindered styrene **2j** afforded product **3j** in 38 % yield (Scheme 1). Thus, the yield of the Heck reaction, under the experimental conditions adopted in this work, is clearly dependent on substituent electron-withdrawing strength and steric hindrance factors; however, these are not the only factors that affect the reaction outcome and selectivity. Competing coupling reactions at the α-position of the styrene moiety and isomerization of the (*E*) diastereomer to the (*Z*) diastereomer (which in some cases was extensive, such as for compound **3j**) make the purification processes and the isolation of the pure (*E*) diastereomer difficult. This photochemical (*E*) → (*Z*) isomerization was also observed for compound **3d** in solution. After 8 d in deuterated dimethyl sulfoxide (DMSO) at room temperature, 40 % of (*E*) diastereomer was converted into the (*Z*) diastereomer (see Supporting Information, Figures S39–S41 and S42–S47).

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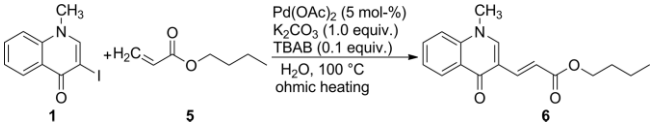
To broaden the scope of this new methodology we studied the coupling of (*E*)-3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with butyl acrylate (**5**). The reaction was performed in water (4 mL) with $Pd(OAc)_2$ (5 mol-%) as catalyst and TBAB as PTC (0.1 equiv.) in the presence of K_2CO_3 (1.0 equiv.) as base at 100 °C by ΩH (Scheme 2). In the first attempt, acrylate (2.0 equiv.) was added, and coupling product **6** was obtained in moderate isolated yield (52 %) after 45 min. Two other attempts were made to increase the reaction yield by prolonging the reaction time (60 min) and by increasing the amount of butyl acrylate (**5**; 4.0 equiv.), but in both cases the yields of **6** were lower than 52 %. For the first attempt the yield was 50 %, and for the second attempt 31 % of **6** and 41 % of starting material were recovered.



Scheme 2. Heck cross-coupling reaction of 3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with butyl acrylate (**5**).

Analysis with Conventional Methodologies

When analyzing the methodology developed here for the Heck reaction of (*E*)-3-iodo-1-methylquinolin-4(1*H*)-one (**1**) with styrenes **2a**–**2j** with other methodologies reported in the literature (Table 3), we found several advantages to our method, such as: (i) the use of water instead of toxic and more expensive organic solvents; (ii) the use of a low-cost and stable Pd catalysts with no need of additional ligands (some ligands are sensitive, toxic, expensive, and make purification procedures more complicated); and (iii) higher yields and shorter reaction times. Moreover, ΩH proved to give superior results relative to those obtained under MW irradiation with respect to reaction time and yield.

Table 3 presents the results obtained by using the new methodology developed and methodologies reported in the literature.[13] New (*E*)-3-styrylquinolin-4(1*H*)-one derivatives **3c**, **3d**, **3f**, **3g**, **3i**, and **3j** synthesized in this work were not included in Table 3. In general, the reactions performed in the ΩH reactor gave results similar to those obtained under classical heating conditions and with conventional methodology (Pd catalyst, phosphane ligand, organic solvent, and Et_3N as a base) in terms of global yield, but higher amounts of branched regioisomers were observed in the first case. In addition, significantly shorter reaction times were needed with ΩH. This methodology enables the preparation of (*E*)-3-styrylquinolin-4(1*H*)-ones in one step, which is more straightforward than the Wittig reaction of 1-substituted 4-quinolone-3-carbaldehydes or of the 4-chloroquinoline-3-carbaldehyde with benzylic ylides followed by acid hydrolysis.[12] Moreover the ΩH-assisted Heck reaction was performed in water, whereas dry organic solvents, anhydrous conditions (nitrogen or argon), and longer reaction times (1–3 h for ylide formation plus 0.75–21 h after addition of the carbonyl compound) are required for the Wittig reaction. The addition of the carbonyl compound in the Wittig reaction should be performed as soon as the ylide has been formed, otherwise the reaction may be ineffective. For the Wittig reaction with 4-chloroquinoline-3-carbaldehyde a further hydrolysis step (24 h) is required to convert the diastereomeric mixture of (*Z*)- and (*E*)-4-chloro-3-styrylquinoline derivatives into the corresponding unprotected (*E*)-3-styrylquinolin-4(1*H*)-ones.

Nuclear Magnetic Resonance

All the synthesized compounds were characterized by NMR spectroscopy. The main features in the ^1H NMR spectra that confirm the formation of expected (*E*)-3-styrylquinolin-4(1*H*)-ones **3a**–**3j** (Figure 2) are the signals that result from resonance of the vinylic protons, α-H and β-H, which appear as doublets at $\delta_{H\alpha}$ = 7.04–7.43 ppm and $\delta_{H\beta}$ = 7.64–7.94 ppm with large coupling constants ($J \approx 16.0$ Hz), which indicates (*E*) configuration. In the case of branched regioisomers **4a**, **4b**, **4g**, and **4i** (Figure 2) the signals of these protons also appear as doublets (δ_H = 5.28–5.60 ppm) but with small coupling constants (J = 1.7–1.8 Hz), which indicates geminal coupling. Typical signals for compounds **3a**–**3j** are: (i) the resonance of the 2-H proton, the signal of which appears as a singlet at high frequency values (δ_H = 8.18–8.52 ppm), that results from deshielding effects of the heterocyclic nitrogen atom (inductive effect) and of the carbonyl group (mesomeric effect); (ii) the resonance of the 5-H proton, which appears as a double doublet or as a doublet at high frequency values (δ_H = 8.23–8.32 ppm), that results from the mesomeric and anisotropic deshielding effects of the carbonyl group; and (iii) the singlet in the aliphatic region of the

Table 3. Analysis of the results obtained by using the new methodology developed with those already reported in the literature that use more conventional Heck cross-coupling reaction conditions.

Compound		Ohmic heating[a]		Classical heating[13][b]		Microwave heating[13][c]	
R^1	R^2	Reaction time [min]	Yield [%]	Reaction time [h]	Yield [%]	Reaction time [h]	Yield [%]
H	H	30	68 (**3a**); 10 (**4a**)	5	55 (**3a**); 14 (**4a**)[d]	1.5	40 (**3a**); – (**4a**)
H	H	60	80 (**3a**); – (**4a**)				
H	OCH_3	30	41 (**3b**); 21 (**4b**)	5	59 (**3b**); – (**4b**)[e]	1.5	36 (**3b**); traces (**4b**)
H	F	30	47 (**3e**); 21 (**4e**)	5	56 (**3e**); traces (**4e**)[e]	1.5	48 (**3e**); – (**4e**)
NO_2	H	30	96 (**3h**); – (**4h**)	5	65 (**3h**); – (**4h**)[d]	1.5	45 (**3h**); – (**4h**)

[a] Reaction conditions: 3-iodo-1-methylquinolin-4(1*H*)-one (**1**; 1.0 equiv.) was treated with appropriate styrene **2a**, **2b**, **2e**, or **2h** (5.0 equiv.), $Pd(OAc)_2$ (0.05 equiv.), TBAB (0.1 equiv.) and K_2CO_3 (1.0 equiv.) in H_2O (4.0 mL) at 100 °C for 30–60 min. [b] Reaction conditions: 3-iodo-1-methylquinolin-4(1*H*)-one (**1**; 1.0 equiv.) was treated with appropriate styrene **2a**, **2b**, **2e**, or **2h** (5.0 equiv.), appropriate Pd catalyst (0.05 equiv.), Ph_3P (0.1 equiv.), and Et_3N (1.0 equiv.) in *N*-methyl-2-pyrrolidone (3.0 mL) at 100 °C for 5 h. [c] Reaction conditions: the same conditions as in [b] but performed in a closed vessel under MW irradiation (2 min ramp to reach 100 °C and 1.5 h hold at 100 °C). [d] $Pd(PPh_3)_4$ as catalyst. [e] $PdCl_2$ as catalyst.

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spectra that results from resonance of the methyl group (δ_H = 3.91–3.94 ppm). Typical signals in the ^{13}C NMR spectra of **3a–3j** result from resonance of the *N*-methyl group (δ_C = 40.3–40.7 ppm) and of the carbonyl group (δ_C = 174.6–175.2 ppm). For compounds **3d** and **3j** the presence of the (*Z*) diastereomer was easily identified by the appearance of some signals in duplicate but at lower frequency values than those typical of the (*E*) diastereomer; namely the signals from resonances of the *N*-methyl group, 2-H, and 5-H. For compound **3d** it was also possible to observe the signals from resonance of α-H and β-H protons with a coupling constant of $^3J_{H\alpha,H\beta} \approx 12$ Hz, which is typical of (*Z*) configuration (see the Supporting Information for further details).

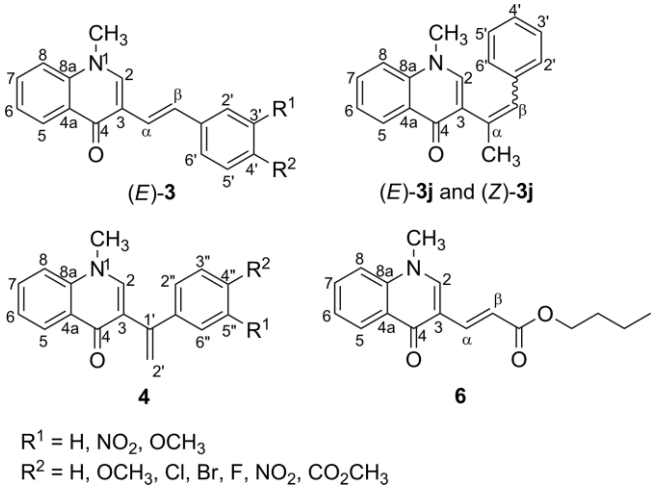

Figure 2. Structures and numbering systems of the compounds characterized by NMR spectroscopy.

The most typical signals in the ^1H and ^{13}C NMR spectra of acrylate **6**: (i) result from the resonance of protons and carbon atoms of the butyl group; and (ii) result from resonance of the *N*-methyl group (δ_H = 3.91 ppm and δ_C = 40.7 ppm) in the aliphatic region of the spectra. Typically, signals that arise from the resonance of the vinylic protons, which appear as doublets at $\delta_{H\alpha}$ = 7.57 ppm ($\delta_{C\alpha}$ = 140.0 ppm) and $\delta_{H\beta}$ = 7.16 ppm ($\delta_{C\beta}$ = 115.4 ppm) with large coupling constants (*J* = 15.8 Hz), indicate (*E*) configuration. α-H is more deshielded than β-H because of the mesomeric effect of the carbonyl group of the ester moiety; the resonance of the 2-H proton, which appears as a singlet at δ_H = 8.63 ppm (δ_C = 148.6 ppm), and the resonance of the 5-H proton, which appears as a double doublet at δ_H = 8.28 ppm (δ_C = 126.0 ppm), are also typical signals of compound **6**. Other characteristic signals in the ^{13}C NMR spectrum arise from the resonance of the carbonyl groups of the quinolone at δ_C = 174.9 ppm and of the ester group at δ_C = 167.5 ppm.

Conclusions

The Heck reaction provides a direct route to synthesize potentially bioactive 3-styrylquinolin-4(1*H*)-ones from appropriate styrenes and 3-iodo-1-methylquinolin-4(1*H*)-one as shown in this work. Acrylates can also be used as coupling partners to give different 3-substituted quinolin-4(1*H*)-ones. This methodology is of interest, because it is environmentally friendly, because of the use of water as a solvent, and there is no need for costly and toxic phosphine ligands. Yields, which were dependent on the styrene substitution pattern, were moderate to good and in most cases better than those obtained by conventional procedures that used organic solvents. Ohmic heating proved to be more efficient than conventional and microwave heating. Good substrate generality, ease of execution, short reaction time, and practicability make this method suitable for the generation of libraries of 3-styrylquinolin-4(1*H*)-ones.

Experimental Section

General: All reactions were carried out in air without any protection of inert gases. 3-Iodo-1-methylquinolin-4(1*H*)-one (**1**) was prepared according to a method reported in the literature by using methyl iodide and NaH in dry tetrahydrofuran (THF),[4] which required the use of a nitrogen as inert gas in this case. Styrenes, bases, and TBAB were purchased and used without further purification. Preparative thin-layer chromatography was carried out with silica gel (60 DGF_{254}) plates. Melting points were determined with a Büchi B-545 melting point apparatus. NMR spectra were recorded with 300 or 500 MHz [300.13 MHz (^1H), 75.47 MHz (^{13}C), or 500.13 MHz (^1H), 125.77 MHz (^{13}C)] NMR spectrometers with tetramethylsilane as the internal reference and with [D_6]DMSO as the solvent. Chemical shifts (δ) are quoted relative to TMS. Unequivocal ^{13}C assignments were made on the basis of 2D gHSQC ($^1H/^{13}C$) and gHMBC (delays for one-bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Positive-ion ESI mass spectra and high-resolution mass spectra were performed with an LTQ Orbitrap XL mass spectrometer (Thermo Fischer Scientific, Bremen, Germany) controlled by LTQ Tune Plus 2.5.5 and Xcalibur 2.1.0. The capillary voltage of the electrospray ionization (ESI) was set to 3100 V. The capillary temperature was 275 °C. The sheath gas flow rate (nitrogen) was set to 5 (arbitrary unit as provided by the software settings). The capillary voltage was 36 V and the tube lens voltage 110 V. For experiments carried out with ohmic heating, the 10 mL reactor was filled with the reaction mixture and closed, and the mixture was heated to reflux. For 4 mL of reaction mixture, the length of the electrodes immersed in the reaction medium was 9 mm, and the distance between the electrodes was 10 mm. Temperature measurements were performed with a type J glass-sheathed thermocouple located inside the reactor. Medium magnetic stirring speed (740 rpm) was used in all of the experiments carried out in the ohmic heating reactor. For the experiments carried out by using conventional heating (oil bath) under reflux conditions, a round-bottom flask filled with 4 mL of the reaction mixture was immersed in an oil bath at 100 °C. A medium magnetic stirring speed (740 rpm) was used. Microwave-assisted reactions were carried out in a CEM Discovery SP circular single-mode cavity instrument (300 W max. magnetron power output) from CEM Corporation. Reactions were performed at 100 °C with a closed 10 mL vessel filled with 4 mL of the reaction mixture and closed with a cap. Temperature measurements were recorded by using an infrared sensor, which monitors and controls the temperature conditions of the reaction vessel located in the instrument cavity. Medium stirring speed was used in the experiments performed.

General Procedure for the Heck Cross-Coupling Reaction of 3-Iodo-1-methylquinolin-4(1*H*)-one 1 with Styrenes 2a–2j: The ohmic heating reactor (10 mL) was charged with 3-iodo-1-methyl-

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quinolin-4(1*H*)-one (**1**; 80.0 mg, 0.28 mmol), appropriate styrene **2a**–**2j** (0.7 mmol or 1.4 mmol; see Table 2), K_2CO_3 (29.1 mg, 0.28 mmol), TBAB (9.02 mg, 0.028 mmol), $Pd(OAc)_2$ (3.15 mg, 0.014 mmol), and H_2O (4 mL). The reaction mixture was heated to reflux and stirred for the period described in Table 2. Then, the aqueous mixture was extracted with ethyl acetate (4 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. (*E*)-3-Styrylquinolin-4(1*H*)-ones **3a**–**3j** were isolated as the main products after TLC (ethyl acetate/hexane, 3:2).

(*E*)-1-Methyl-3-(2-phenylvinyl)quinolin-4(1*H*)-one (3a): Pale yellow solid (58.5 mg, 80 %). M.p. 117–118 °C. ^{1}H NMR (300.13 MHz, [D$_6$]DMSO): δ_H = 3.91 (s, 3 H, NC*H*$_3$), 7.18 (d, *J* = 16.3 Hz, 1 H, α-H), 7.20–7.29 (m, 1 H, 4′-H), 7.35 (d, *J* = 7.5 Hz, 2 H, 3′,5′-H), 7.44 (ddd, *J* = 8.1, 6.7, 1.4 Hz, 1 H, 6-H), 7.50 (d, *J* = 7.5 Hz, 2 H, 2′,6′-H), 7.69 (d, *J* = 8.6 Hz, 1 H, 8-H), 7.73 (d, *J* = 16.3 Hz, 1 H, β-H), 7.75 (ddd, *J* = 8.6, 6.7, 1.5 Hz, 1 H, 7-H), 8.30 (dd, *J* = 8.1, 1.5 Hz, 1 H, 5-H), 8.43 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ_C = 40.4 (N*C*H$_3$), 116.7 (C-3), 116.8 (C-8), 123.4 (C-α), 123.7 (C-6), 125.8 (C-2′,6′), 126.0 (C-5), 126.1 (C-4a), 126.6 (C-4′), 126.9 (C-β), 128.8 (C-3′,5′), 131.8 (C-7), 138.2 (C-1′), 139.2 (C-8a), 144.2 (C-2), 174.6 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 262 (100) [(M + H)$^+$]. HRMS (ESI$^+$): calcd. for $C_{18}H_{16}NO$ [M + H]$^+$ 262.1232; found 262.1224.

(*E*)-3-[2-(4-Methoxyphenyl)vinyl]-1-methylquinolin-4(1*H*)-one (3b): Pale yellow solid (33.4 mg, 41 %). M.p. 123–125 °C. ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ_H = 3.78 (s, 3 H, OC*H*$_3$), 3.92 (s, 3 H, NC*H*$_3$), 6.95 (d, *J* = 8.8 Hz, 2 H, 3′,5′-H), 7.04 (d, *J* = 16.4 Hz, 1 H, α-H), 7.42–7.45 (m, 1 H, 6-H), 7.44 (d, *J* = 8.8 Hz, 2 H, 2′,6′-H), 7.65 (d, *J* = 16.4 Hz, 1 H, β-H), 7.70 (d, *J* = 8.4 Hz, 1 H, 8-H), 7.76 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H, 7-H), 8.29 (dd, *J* = 8.1, 1.5 Hz, 1 H, 5-H), 8.39 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ_C = 40.4 (N*C*H$_3$), 55.1 (O*C*H$_3$), 114.2 (C-3′,5′), 116.8 (C-8), 117.1 (C-3), 121.1 (C-α), 123.6 (C-6), 125.0 (C-5), 126.1 (C-4a), 126.4 (C-β), 127.0 (C-2′,6′), 130.8 (C-1′), 131.7 (C-7), 139.2 (C-8a), 143.6 (C-2), 158.5 (C-4′), 174.6 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 292 (100) [M + H]$^+$, 330 (2) [M + K]$^+$. HRMS (ESI$^+$): calcd. for $C_{19}H_{18}NO_2$ [M + H]$^+$ 292.1338; found 292.1327.

(*E*)-3-[2-(4-Chlorophenyl)vinyl]-1-methylquinolin-4(1*H*)-one (3c): Yellow solid (42.2 mg, 51 %). M.p. 174–175 °C. ^{1}H NMR (300.13 MHz, [D$_6$]DMSO): δ_H = 3.92 (s, 3 H, NC*H*$_3$), 7.18 (d, *J* = 16.4 Hz, 1 H, α-H), 7.42 (d, *J* = 8.6 Hz, 2 H, 3′,5′-H), 7.46 (ddd, *J* = 8.1, 6.7, 1.5 Hz, 1 H, 6-H), 7.52 (d, *J* = 8.6 Hz, 2 H, 2′,6′-H), 7.72 (d, *J* = 7.6 Hz, 1 H, 8-H), 7.74 (d, *J* = 16.4 Hz, 1 H, β-H), 7.76 (ddd, *J* = 7.6, 6.7, 1.5 Hz, 1 H, 7-H), 8.30 (dd, *J* = 8.1, 1.5 Hz, 1 H, 5-H), 8.43 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ_C = 40.5 (N*C*H$_3$), 116.4 (C-3), 116.8 (C-8), 123.8 (C-6), 124.5 (C-α), 125.3 (C-β), 125.9 (C-5), 126.1 (C-4a), 127.3 (C-2′,6′), 128.7 (C-3′,5′), 131.0 (C-4′), 131.9 (C-7), 137.2 (C-1′), 139.2 (C-8a), 144.6 (C-2), 174.6 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 296 (^{35}Cl, 100) [M + H]$^+$, 298 (^{37}Cl, 32) [M + H]$^+$, 318 (^{35}Cl, 6) [M + Na]$^+$, 334 (^{35}Cl, 8) [M + K]$^+$. HRMS (ESI$^+$): calcd. for $C_{18}H_{15}{}^{35}ClNO$ [M + H]$^+$ 296.0842; found 296.0835; calcd. for $C_{18}H_{15}{}^{37}ClNO$ [M + H]$^+$ 298.0842; found 298.0801.

(*E*)-3-[2-(4-Bromophenyl)vinyl]-1-methylquinolin-4(1*H*)-one (3d): White solid (91.4 mg, 96 %). M.p. 186–188 °C. ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ_H = 3.92 (s, 3 H, NC*H*$_3$), 7.20 (d, *J* = 16.2 Hz, 1 H, α-H), 7.44–7.47 (m, 1 H, 6-H), 7.46 (d, *J* = 8.5 Hz, 2 H, 2′,6′-H), 7.55 (d, *J* = 8.5 Hz, 2 H, 3′,5′-H), 7.72 (d, *J* = 16.2 Hz, 1 H, β-H), 7.73 (d, *J* = 6.9 Hz, 1 H, 8-H), 7.77 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1 H, 7-H), 8.30 (dd, *J* = 8.0, 1.4 Hz, 1 H, 5-H), 8.43 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ_C = 40.5 (N*C*H$_3$), 116.4 (C-3), 116.9 (C-8), 119.6 (C-4′), 123.8 (C-6), 124.6 (C-α), 125.4 (C-β), 126.0 (C-5), 126.2 (C-4a), 127.7 (C-2′,6′), 131.6 (C-3′,5′), 131.9 (C-7), 137.6 (C-1′), 139.2 (C-8a), 144.7 (C-2), 174.6 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 340 (^{79}Br, 100) [M + H]$^+$, 342 (^{81}Br, 98) [M + H]$^+$, 362 (^{79}Br, 12) [M + Na]$^+$, 364 (^{81}Br, 10) [M + Na]$^+$. HRMS (ESI$^+$): calcd. for $C_{18}H_{15}{}^{79}BrNO$ [M + H]$^+$ 340.0337; found 340.0331; calcd. for $C_{18}H_{15}{}^{81}BrNO$ [M + H]$^+$ 342.0337; found 342.0305.

(*E*)-3-[2-(4-Fluorophenyl)vinyl]-1-methylquinolin-4(1*H*)-one (3e): Yellow solid (36.8 mg, 47 %). M.p. 164–165 °C. ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ_H = 3.92 (s, 3 H, NC*H*$_3$), 7.12 (d, *J* = 16.4 Hz, 1 H, α-H), 7.19 (t, *J* = 8.8 Hz, 2 H, 3′,5′-H), 7.45 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1 H, 6-H), 7.54 (dd, *J* = 8.8, 5.6 Hz, 2 H, 2′,6′-H), 7.73 (d, *J* = 16.4 Hz, 1 H, β-H), 7.71–7.73 (m, 1 H, 8-H), 7.77 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1 H, 7-H), 8.30 (dd, *J* = 8.0, 1.4 Hz, 1 H, 5-H), 8.41 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ_C = 40.5 (N*C*H$_3$), 115.5 (C-3′,5′, *J* = 21.4 Hz), 116.6 (C-3), 116.9 (C-8), 123.5 (C-α), 123.8 (C-6), 125.6 (C-β), 126.0 (C-5), 126.2 (C-4a), 127.6 (C-2′,6′, *J* = 7.6 Hz), 131.9 (C-7), 134.8 (C-1′), 139.3 (C-8a), 144.3 (C-2), 161.3 (C-4′, *J* = 242.7 Hz), 174.7 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 280 (100) [M + H]$^+$, 302 (18) [M + Na]$^+$, 318 (2) [M + K]$^+$. HRMS (ESI$^+$): calcd. for $C_{18}H_{15}FNO$ [M + H]$^+$ 280.1138; found 280.1129.

(*E*)-1-Methyl-3-[2-(4-nitrophenyl)vinyl]quinolin-4(1*H*)-one (3f): Orange solid (66.9 mg, 78 %). M.p. 227–228 °C. ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ_H = 3.94 (s, 3 H, NC*H*$_3$), 7.43 (d, *J* = 16.5 Hz, 1 H, α-H), 7.49 (ddd, *J* = 7.7, 7.1, 1.0 Hz, 1 H, 6-H), 7.75 (d, *J* = 8.8 Hz, 2 H, 2′,6′-H), 7.75 (d, *J* = 8.6 Hz, 1 H, 8-H), 7.80 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1 H, 7-H), 7.94 (d, *J* = 16.5 Hz, 1 H, β-H), 8.22 (d, *J* = 8.8 Hz, 2 H, 3′,5′-H), 8.32 (dd, *J* = 7.7, 1.5 Hz, 1 H, 5-H), 8.52 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ_C = 40.7 (N*C*H$_3$), 115.9 (C-3), 117.1 (C-8), 124.20 and 124.22 (C-6, C-3′,5′), 124.4 (C-β), 126.0 (C-5), 126.3 (C-4a), 126.4 (C-2′,6′), 128.9 (C-α), 132.2 (C-7), 139.2 (C-8a), 145.5 (C-4′), 145.6 (C-1′), 146.1 (C-2), 174.8 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 307 (100) [M + H]$^+$, 329 (12) [M + Na]$^+$. HRMS (ESI$^+$): calcd. for $C_{18}H_{15}N_2O_3$ [M + H]$^+$ 307.1083; found 307.1076.

Methyl (*E*)-4-[2-(1-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)vinyl]benzoate (3g): White solid (32.2 mg, 36 %). M.p. 110–111 °C. ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ_H = 2.28 (s, 3 H, CO_2CH_3), 3.93 (s, 3 H, NC*H*$_3$), 7.13 (d, *J* = 8.6 Hz, 2 H, 3′,5′-H), 7.15 (d, *J* = 16.4 Hz, 1 H, α-H), 7.46 (dt, *J* = 7.7, 1.0 Hz, 1 H, 6-H), 7.53 (d, *J* = 8.6 Hz, 2 H, 2′,6′-H), 7.72 (d, *J* = 7.7 Hz, 1 H, 8-H), 7.74 (d, *J* = 16.4 Hz, 1 H, β-H), 7.76–7.81 (m, 1 H, 7-H), 8.30 (dd, *J* = 7.7, 1.4 Hz, 1 H, 5-H), 8.43 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ_C = 20.9 (CO_2CH_3) 40.5 (N*C*H$_3$), 116.6 (C-3), 116.9 (C-8), 122.2 (C-3′,5′), 123.7 (C-α), 123.8 (C-6), 124.4 (C-4a), 125.7 (C-β), 126.0 (C-5), 126.6 (C-2′,6′), 131.9 (C-7), 135.9 (C-1′), 139.3 (C-8a), 144.4 (C-2), 149.3 (C-4′), 169.3 (CO_2CH_3), 174.6 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 320 (100) [M + H]$^+$, 342 (8) [M + Na]$^+$, 358 (3) [M + K]$^+$. HRMS (ESI$^+$): calcd. for $C_{20}H_{18}NO_3$ [M + H]$^+$ 320.1287; found 320.1277.

(*E*)-1-Methyl-3-[2-(3-nitrophenyl)vinyl]quinolin-4(1*H*)-one (3h): Dark yellow solid (82.3 mg, 96 %). M.p. 220–221 °C. ^{1}H NMR (300.13 MHz, [D$_6$]DMSO): δ_H = 3.93 (s, 3 H, NC*H*$_3$), 7.36 (d, *J* = 16.2 Hz, 1 H, α-H), 7.48 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 1 H, 6-H), 7.65 (t, *J* = 8.0 Hz, 1 H, 5′-H), 7.73 (dd, *J* = 8.5, 1.4 Hz, 1 H, 8-H), 7.79 (ddd, *J* = 8.5, 6.7, 1.6 Hz, 1 H, 7-H), 7.94 (d, *J* = 8.0 Hz, 1 H, 6′-H), 7.94 (d, *J* = 16.2 Hz, 1 H, β-H), 8.06 (ddd, *J* = 8.0, 2.1, 0.8 Hz, 1 H, 4′-H), 8.32 (d, *J* = 2.1 Hz, 1 H, 2′-H), 8.32 (dd, *J* = 8.0, 1.6 Hz, 1 H, 5-H), 8.50 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ_C = 40.6 (N*C*H$_3$), 115.9 (C-3), 116.9 (C-8), 116.6 (C-3), 119.4 (C-2′), 121.1 (C-4′), 124.3 (C-6), 126.0 (C-β), 126.3 (C-5), 126.8 (C-4a), 126.9 (C-α), 130.3 (C-5′), 132.0 (C-7), 132.2 (C-6), 139.2 (C-8a), 140.3 (C-1′), 145.6 (C-2), 148.4 (C-3′), 174.7 (C-4) ppm. MS (ESI$^+$): *m*/*z* (%) = 307 (100) [M + H]$^+$, 329 (16) [M + Na]$^+$. HRMS (ESI$^+$): calcd. for $C_{18}H_{15}N_2O_3$ [M + H]$^+$ 307.1083; found 307.1073.

(*E*)-3-[2-(3,4-Dimethoxyphenyl)vinyl]-1-methylquinolin-4(1*H*)-one (3i): Yellow solid (34.2 mg, 38 %). M.p. 175–176 °C. ^{1}H NMR

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(300.13 MHz, [D$_6$]DMSO): δ_H = 3.76 (s, 4′-OCH_3), 3.82 (s, 3′-OCH_3), 3.91 (s, 3 H, NCH_3), 6.94 (d, *J* = 8.4 Hz, 1 H, 5′-H), 7.00 (dd, *J* = 8.4, 1.7 Hz, 1 H, 6′-H), 7.05 (d, *J* = 16.4 Hz, 1 H, α-H), 7.12 (d, *J* = 1.7 Hz, 1 H, 2′-H), 7.43 (ddd, *J* = 8.0, 6.7, 1.3 Hz, 1 H, 6-H), 7.66 (d, *J* = 16.4 Hz, 1 H, β-H), 7.68 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.74 (ddd, *J* = 8.1, 6.7, 1.5 Hz, 1 H, 7-H), 8.30 (dd, *J* = 8.0, 1.5 Hz, 1 H, 5-H), 8.38 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ_C = 40.4 (NCH_3), 55.4 (4′-OCH_3), 55.5 (3′-OCH_3), 108.5 (C-2′), 111.9 (C-5′), 116.8 (C-8), 117.1 (C-3), 119.0 (C-6′), 121.3 (C-α), 123.6 (C-6), 125.9 (C-5), 126.1 (C-4a), 126.9 (C-β), 131.2 (C-1′), 131.7 (C-7), 139.2 (C-8a), 143.7 (C-2), 148.2 (C-4′), 149.0 (C-3′), 174.7 (C-4) ppm. MS (ESI$^+$): *m/z* (%) = 322 (100) [M + H]$^+$, 344 (6) [M + Na]$^+$, 360 (1) [M + K]$^+$. HRMS (ESI$^+$): calcd. for $C_{20}H_{20}NO_3$ [M + H]$^+$ 322.1443; found 322.1431.

(*E*)-3-[1-(3,4-Dimethoxyphenyl)vinyl]-1-methylquinolin-4(1*H*)-one (4i): Yellow residue (18.0 mg, 20 %). ^{1}H NMR (300.13 MHz, [D$_6$]DMSO): δ_H = 3.72 (s, 3 H, 4″-OCH_3), 3.74 (s, 3 H, 3″-OCH_3), 3.87 (s, 3 H, NCH_3), 5.41 (d, *J* = 1.7 Hz, 1 H, 2′-H), 5.55 (d, *J* = 1.7 Hz, 1 H, 2′-H), 6.77 (dd, *J* = 8.3, 2.0 Hz, 1 H, 6″-H), 6.86 (d, *J* = 8.3 Hz, 1 H, 5″-H), 6.98 (d, *J* = 2.0 Hz, 1 H, 2″-H), 7.41 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1 H, 6-H), 7.69 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.77 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1 H, 7-H), 8.00 (s, 1 H, 2-H), 8.18 (dd, *J* = 8.0, 1.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ_C = 40.3 (NCH_3), 55.5 (2 × OCH_3), 110.2 (C-2″), 111.3 (C-5″), 114.2 (C-2′), 116.7 (C-8), 119.3 (C-6″), 121.3 (C-3), 123.4 (C-6), 126.0 (C-5), 126.3 (C-4a), 131.9 (C-7), 133.4 (C-1″), 140.2 (C-8a), 144.2 (C-2), 144.4 (C-1′), 148.4 (C-4″), 148.5 (C-3″), 174.4 (C-4) ppm. MS (ESI$^+$): *m/z* (%) = 322 (77) [M + H]$^+$, 344 (100) [M + Na]$^+$. HRMS (ESI$^+$): calcd. for $C_{20}H_{20}NO_3$ [M + H]$^+$ 322.1434; found 322.1434.

(*E*)-1-Methyl-3-(1-phenylprop-1-en-2-yl)quinolin-4(1*H*)-one (3j): Yellow solid (29.3 mg, 38 %). M.p. 184–186 °C. ^{1}H NMR (300.13 MHz, [D$_6$]DMSO), signals of the (*E*) isomer: δ_H = 2.233 (s, 3 H, 1′-CH_3), 3.93 (s, 3 H, NCH_3), 6.83 (s, 1 H, 3′-H), 7.25–7.33 (m, 1 H, 4″-H), 7.38 (d, *J* = 7.4 Hz, 2 H, 3″,5″-H), 7.48 (ddd, *J* = 7.9, 6.7, 1.1 Hz, 1 H, 6-H), 7.54 (d, *J* = 7.4 Hz, 2 H, 2″,6″-H), 7.70 (d, *J* = 8.4 Hz, 1 H, 8-H), 7.78 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1 H, 7-H), 8.18 (s, 1 H, 2-H), 8.25 (dd, *J* = 7.9, 1.4 Hz, 1 H, 5-H); signals of the (*Z*) isomer: δ_H = 2.229 (s, 3 H, 1′-CH_3), 3.87 (s, 3 H, NCH_3), 6.829 (s, 1 H, 3′-H), 7.20–7.25 (m, 1 H, 4″-H), 7.37–7.40 (m, 2 H, 3″,5″-H), 7.39 (m, 1 H, 6-H), 7.53–7.56 (m, 2 H, 2″,6″-H), 7.69–7.80 (m, 2 H, 7,8-H), 8.21(dd, *J* = 7.9, 1.4 Hz, 1 H, 5-H), 8.65 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO), signals of the (*E*) isomer: δ_C = 17.4 (C-1′), 25.1 (C-2′), 40.3 (NCH_3), 116.8 (C-8), 117.8 (C-4a), 121.2 (C-3′), 123.5 (C-6) 125.6 (C-2″,6″), 125.8 (C-5), 127.0 (C-4″), 128.4 (C-3″,5″), 131.9 (C-7), 139.8 (C-8a), 143.3 (C-1″), 144.0 (C-2), 175.2 (C-4); signals of the (*Z*) isomer: δ_C = 17.4 (C-1′), 26.3 (C-2′), 40.3 (NCH_3), 117.0 (C-8), 117.8 (C-4a), 121.2 (C-3′), 124.4 (C-6) 125.6 (C-2″,6″), 126.11 (C-5), 127.9 (C-4″), 128.6 (C-3″,5″), 132.2 (C-7), 139.8 (C-8a), 143.3 (C-1″), 149.5 (C-2), 175.2 (C-4) ppm. MS (ESI$^+$): *m/z* (%) = 276 (100) [M + H]$^+$, 298 (10) [M + Na]$^+$. HRMS (ESI$^+$): calcd. for $C_{19}H_{18}NO$ [M + H]$^+$ 276.1388; found 276.1379.

General Procedure for the Heck Cross-Coupling Reaction of 3-Iodo-1-methylquinolin-4(1*H*)-one 1 with Butyl Acrylate 5: The ohmic heating reactor (10 mL) was charged with 3-iodo-1-methylquinolin-4(1*H*)-one (**1**; 60.0 mg, 0.21 mmol), butyl acrylate (**5**; 0.06 mL, 0.42 mmol), K_2CO_3 (29.1 mg, 0.21 mmol), TBAB (6.79 mg, 0.021 mmol), Pd(OAc)$_2$ (2.36 mg, 0.010 mmol), and H_2O (4 mL). The reaction mixture was heated to reflux and stirred for 45 min. Then, the aqueous mixture was extracted with ethyl acetate (4 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. Expected butyl (*E*)-3-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)acrylate (**6**) was isolated after TLC (ethyl acetate/hexane, 3:2).

Butyl (*E*)-3-(1-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)acrylate (6): White solid (31.2 mg, 52 %). M.p. 139–140 °C. ^{1}H NMR (300.13 MHz, [D$_6$]DMSO): δ_H = 0.92 (t, *J* = 7.4 Hz, 3 H, -OCH$_2$CH$_2$CH$_2$CH_3), 1.38 (m, 2 H, OCH$_2$CH$_2$CH_2CH$_3$), 1.62 (m, 2 H, OCH$_2$CH_2CH$_2$CH$_3$), 3.91 (s, 3 H, NCH_3), 4.12 (t, *J* = 6.9 Hz, 2 H, OCH_2CH$_2$CH$_2$CH$_3$), 7.16 (d, *J* = 15.8 Hz, 1 H, β-H), 7.50 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H, 6-H), 7.57 (d, *J* = 15.8 Hz, 1 H, α-H), 7.74 (dd, *J* = 8.2 Hz, 1 H, 8-H), 7.81 (ddd, *J* = 8.2, 6.8, 1.6 Hz, 1 H, 7-H), 8.28 (dd, *J* = 8.0, 1.6 Hz, 1 H, 5-H), 8.63 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ_C = 13.6 (OCH$_2$CH$_2$CH$_2$CH$_3$), 18.8 (OCH$_2$CH$_2$CH$_2$CH$_3$), 40.7 (NCH_3), 63.3 (OCH$_2$CH$_2$CH$_2$CH$_3$), 113.8 (C-3), 115.4 (C-β), 117.2 (C-8), 124.6 (C-6), 126.0 (C-5), 126.5 (C-4a), 132.5 (C-7), 139.3 (C-8a), 140.0 (C-α), 148. 6 (C-2), 167.5 (C=O ester), 174.9 (C-4) ppm. MS (ESI$^+$): *m/z* (%) = 286 (100) [M + H]$^+$, 308 (38) [M + Na]$^+$, 324 (7) [M + K]$^+$. HRMS (ESI$^+$): calcd. for $C_{17}H_{20}NO_3$ [M + H]$^+$ 286.1443; found 286.1437.

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