An efficient synthesis of 4-arylquinolin-2(1*H*)-ones and 3-alkenyl-4-arylquinolin-2(1*H*)-one using a Pd/$NiFe_2O_4$-catalyzed consecutive Heck reaction

Sanjay R. Borhade and Suresh B. Waghmode

Abstract: A convenient one-pot method for the synthesis of 4-arylquinolin-2(1*H*)-ones and 4-arylcoumarins has been described. The successive Heck reaction on substituted 2-iodoaniline and 2-iodophenol catalyzed by a Pd/nickel ferrite catalyst followed by in situ cyclization was the key step. The scope of this methodology was extended to the synthesis of bioactive 3-alkenyl derivatives of 4-arylquinolin-2(1*H*)-ones.

Key words: 4-arylquinolin-2(1*H*)-ones, Pd/nickel ferrite, Heck reaction, cross-coupling reactions, heterogeneous catalysis.

Résumé : On décrit une méthode monotope commode de synthèse des 4-arylquinoléin2(1*H*)-ones et 4-arylcoumarines. L'étape clé est une réaction successive de Heck sur une 2-iodoaniline et le 2-iodophénol, catalysée de un catalyseur de Pd/ferrite de nickel, suivie par une cyclisation in situ. On a étendu la portée de cette méthodologie à la synthèse de dérivés 3-alkényles biologiquement actifs des 4-arylquinoléin-2(1*H*)-ones.

Mots-clés : 4-arylquinoléin-2(1*H*)-ones, Pd/ferrite de nickel, réaction de Heck, réactions de couplage croisé, catalyse hétérogène.

[Traduit par la Rédaction]

Introduction

Quinolin-2(1*H*)-ones constitute the basic structural fragments of many natural and synthetic biologically active molecules. They shows antiviral, antineoplastic, anti-ischemic, antiallergic, antihypertensive, and antiulcerative activity.[1] Moreover, quinolin-2(1*H*)-ones also serve as valuable synthetic intermediates because they can be easily transformed into 2-substituted quinolines (e.g., 2-Cl, 2-OTf), which can undergo further functionalization, such as nucleophillic aromatic substitutions and Pd-catalyzed coupling reactions.[2]

In particular, functionalized 4-aryl-quinolin-2(1*H*)-ones (Fig. 1) are excellent inhibitors of acyl co-enzyme A and cholesterol acyltransferase and are potent openers of high-conductance calcium-activated K+ channels.[3,4] They also show potent antibacterial activity and inhibit the replication of human immunodeficiency virus (HIV) induced by tumor necrosis factor (TNF-α) with an IC_{50} of 2.5 μm.[5] The derivatives of 3-(quinolin-3-yl) acrylates **4** and the corresponding reduced allylic alcohols have been identified by a group from Bristol-Myers Squibb (BMS) as novel and potent maxi-K channel openers useful for the treatment of male erectile dysfunction.[3a] In addition, R 115777 (Zarnestra, **5**), an orally active antitumor agent, is currently undergoing human clinical trials.[3c–3d] Although quinolinones exhibit a wide range of biological activities, only a few methods for the synthesis of 4-arylquinolinon-2(1*H*)-ones are reported in the literature.[6] In most instances, an arylquinolin-2(1*H*)-one moiety was achieved by acid–base catalyzed cyclization of *N*-acyl-*o*-amino benzophenone or via closely related procedures.[3c–3d] However, starting materials used for the cyclization approach are mostly amino ketones, which are not readily available; furthermore, these procedures suffer from the disadvantage that the aryl ring attached to the C-4 position of quinolinon-2(1*H*)-ones has to be introduced very early in the overall synthetic scheme, which limits the further laboration of this substituent.

Several research groups have recently demonstrated the successful use of a Pd-catalyzed C–C coupling reaction for the synthesis of quinolin-2(1*H*)-one as a facile, versatile, and practical route.[7,8] Xu et al.[8b] reported a solid-phase protocol (HypoGel Br resin) for the synthesis of 4-substituted quinolinones using Pd-catalyzed Suzuki and Negishi cross-coupling reactions in 63%–90% yield within 14 h. Cacchi and co-workers[8c–8d] developed a methodology for the synthesis of 4-aryl-quinolin-2(1*H*)-ones from 2-bromocinnamides and aryl iodides through Heck reaction followed by an intramolecular Buchwald–Hartwig amination sequence. In addition to this, they also reported Heck reaction and in situ cyclization of methyl β-(*o*-acetamidophenyl)acrylates with aryl iodides for the synthesis of 4-aryl-quinolin-2(1*H*)-ones in the presence of Pd $(OAc)_2$ and KOAc in DMF at 120 °C.[8g] Kappe and co-workers[8e] reported the synthesis of functionalized 4-aryl-quinolin-2(1*H*)-ones by Suzuki coupling from 4-chloroquinoline-2(1*H*)-one and boronic acid using a microwave. Although they reported a good yield in a shorter reaction time, the use of a microwave for industrial large-scale synthesis is not viable and also the

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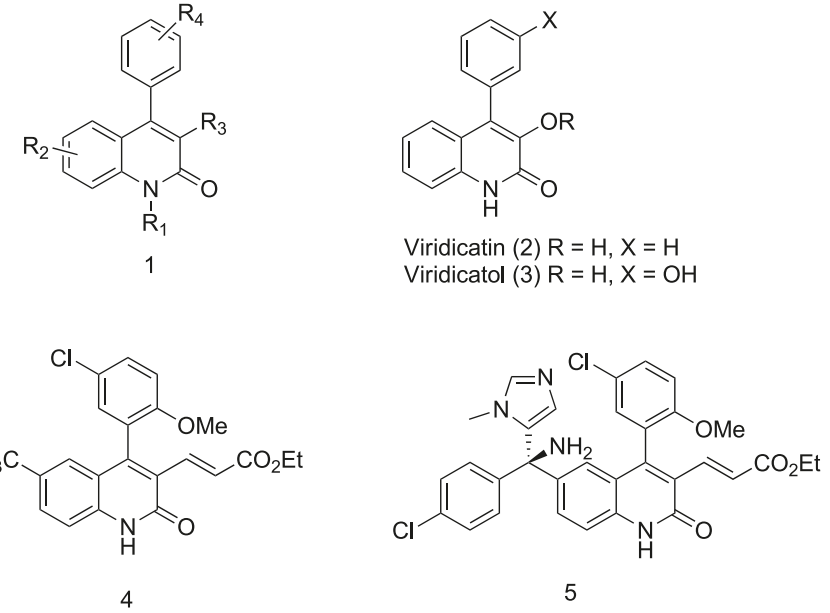
Fig. 1. Biologically active 4-arylquinolin-2(1*H*)-one derivatives.



required boronic acids are costly. More recently, Inamoto et al.[8a] reported a synthetic approach through C–H bond functionalization and intramolecular amidation sequencing in the presence of a catalytic amount of $PdCl_2$ and $Cu(OAc)_2$ under an O_2 atmosphere. Although these authors have reported moderate to good yields of 4-arylquinolin-2(1*H*)-ones, nonrecovery of the precious palladium catalyst and Pd metal contamination of the final products make these processes commercially undesirable. Our ongoing interest is towards the development of new catalyst system; recently, our group[9a,9c,9d] and Manorama and co-workers[9b] reported the filtration-free magnetically separable $Pd/NiFe_2O_4$ as an efficient and inexpensive catalyst for the Heck reaction. In light of this successful methodology, we anticipated that the C–C bond formation using the Heck reaction could lead to an efficient protocol for the synthesis of 4-arylquinolin-2(1*H*)-ones. Herein we report the novel use of Pd supported on nickel ferrite as a heterogeneous and recyclable catalyst for the synthesis of functionalized 4-arylquinolin-2(1*H*)-ones and 4-arylcoumarins in one pot. We have also demonstrated the applicability of this methodology for the synthesis of (2*E*)-ethyl-3-(4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1,2-dihydro-1-methyl-2-oxoquinolin-3-yl)acrylates in four steps.

Results and discussion

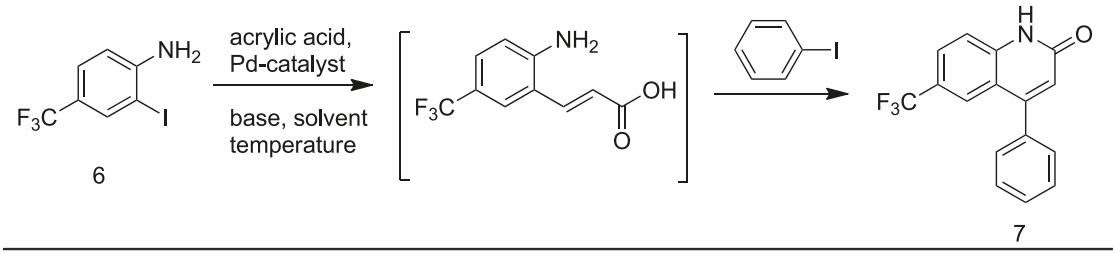
Initial studies were performed using 4-(trifluoromethyl)-2-iodoaniline, acrylic acid, and iodobenzene to determine the optimal reaction conditions. We examined various palladium sources, solvents, bases, and temperatures and the results obtained are summarized in Table 1. Amongst the different Pd sources studied, palladium acetate ($Pd(OAc)_2$), tetrakistriphenylphosphine palladium(0) ($Pd(PPh_3)_4$), and tetraamminepalladium(II) chloride ($Pd(NH_3)_4Cl_2{\cdot}H_2O$) gave good to moderate yields of corresponding 6-(trifluoromethyl)-4-phenyl-2-quinolinone products (Table 1, entries 5 and 6). However, 1,1-bis(diphenylphophino)ferrocene–dichloropalladium ($PdCl_2$(dppf)) and palladium chloride ($PdCl_2$) gave very poor yields (Table 1, entries 3 and 4). The presence of a Pd(IV) oxidation state in the sodiumhexachloropalladate tetrahydrate ($Na_2PdCl_6{\cdot}4H_2O$) would not allow the catalyzation of the Heck reaction (entry 7).

We conclude that the Pd sources having oxidation states Pd(II) and Pd(0) were catalytically active for the Heck reaction, whereas the Pd(IV) oxidation state was not active at all. In comparison with homogeneous $Pd(OAc)_2$, a slight increase in the yield was observed for the $Pd/NiFe_2O_4$ catalyst (Table 1, entries 2 and 8). Since it was easily separable from the reaction mixture by applying an external magnetic field and no product contamination with Pd metal was observed, from this point forward $Pd/NiFe_2O_4$ catalyst was used unless otherwise stated. Among the different bases studied, triethylamine (TEA) and tributylamine (TBA) were found to be the best (Table 1, entries 8 and 9). These organic bases were superior to inorganic bases such as $NaHCO_3$, NaOAc, and Na_2CO_3 (Table 1, entries 8–12).

The effect of various solvents for consecutive Heck reaction and in situ cyclization was studied and the results showed that DMF and CH_3CN gave 75% and 66% yield, respectively, after 18 h, using TEA as a base. Nonpolar solvents such as toluene and xylene were unproductive (Table 1, entries 15 and 16). Temperature studies revealed that 85 °C was enough to activate the $Pd/NiFe_2O_4$ catalyst for the Heck reaction, whereas at higher temperature (100 °C), a lower yield was observed. Various olefins such as methyl acrylate, ethyl acrylate, butyl acrylate, and acrylic acid were reacted with 4-(trifluoromethyl)-2-iodoaniline and it was found that acrylic acid gave maximum yield.

Using the optimized reaction conditions we explored the general applicability of the $Pd/NiFe_2O_4$ catalyst for the consecutive Heck reaction of different 2-iodoanilines followed by cyclization to yield corresponding 4-arylquinolin-2(1*H*)-ones (Table 2). The transformation of various substituted aryl iodides and bromides to corresponding 4-arylquinolin-2-(1*H*)-one derivatives offered moderate to good yields. Aryl iodides gave superior yields of the desired product as

Table 1. Optimization of the Heck coupling and cyclization conditions for the synthesis of 4-aryl-2-quinolin-2(1*H*)-one.



6 7

Entry	Pd source	Base	Solvent	Temp. (°C)	Yield[a]
1	—	TEA	DMF	85	—
2	$Pd(OAc)_2$	TEA	DMF	85	71
3	$PdCl_2$	TEA	DMF	85	29
4	$PdCl_2$(dppf)	TEA	DMF	85	23
5	$Pd(PPh_3)_4$	TEA	DMF	85	58
6	$Pd(NH_3)_4Cl_2{\cdot}H_2O$	TEA	DMF	85	48
7	$Na_2PdCl_6{\cdot}4H_2O$	TEA	DMF	85	—
8	$Pd/NiFe_2O_4$	TEA	DMF	85	75
9	$Pd/NiFe_2O_4$	TBA	DMF	85	72
10	$Pd/NiFe_2O_4$	NaOAc	DMF	85	8
11	$Pd/NiFe_2O_4$	$NaHCO_3$	DMF	85	12
12	$Pd/NiFe_2O_4$	Na_2CO_3	DMF	85	11
13	$Pd/NiFe_2O_4$	TEA	CH_3CN	85	69
14	$Pd/NiFe_2O_4$	TEA	DMSO	85	24
15	$Pd/NiFe_2O_4$	TEA	Xylene	85	2
16	$Pd/NiFe_2O_4$	TEA	Toluene	85	3
17	$Pd/NiFe_2O_4$	TEA	1,4-Dioxane	85	14
18	$Pd/NiFe_2O_4$	TEA	DMF	70	5
19	$Pd/NiFe_2O_4$	TEA	DMF	100	63

Note: Reaction conditions: 4-(trifluoromethyl)-2-iodoaniline (1.0 mmol), acrylic acid (1.05 mmol), Pd catalyst (2.5 mol %), base (3.25 mmol), solvent (3.0 mL) and iodobenzene (1.25 mmol) added in a second step, time 18 h. TEA, triethylamine; TBA, tributylamine.

[a]GC yields.

compared with aryl bromides. The less reactive chlorobenzene and phenylboronic acid did not couple in the second Heck reaction condition (Table 2, entries 11 and 12). The aryl iodides reacted in the second Heck coupling reaction with (*E*)-3-(2-amino-5-(trifluoromethyl)phenyl)acrylic acid containing electron-donating methoxy groups at the ortho, meta, or para positions produced the corresponding 4-arylquinolin-2-(1*H*)-one compounds **10**–**12** in 59%, 61%, and 67% yields, respectively (Table 2, entries 4–6).

We also attempted the synthesis of a biologically active flavonoid (4-aryl-2*H*-chromen-2-one, neoflavone),[10] by a similar route using 2-iodophenol and ethyl acrylates as starting materials (Table 3).

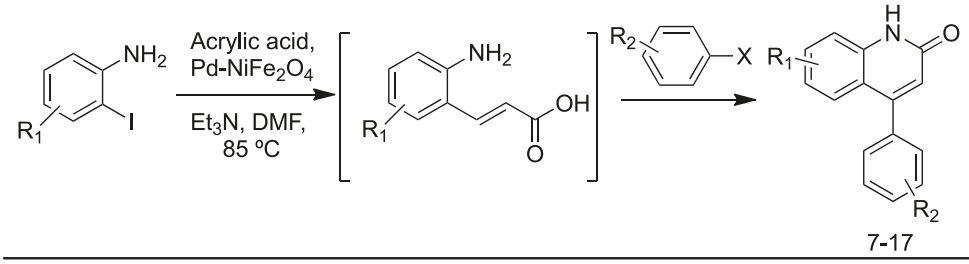
2-Iodophenol successfully reacted with ethyl acrylate and gave 96% yield of the corresponding (*E*)-3-(2-hydroxyphenyl)acrylate, but the second Heck reaction with iodobenzene and in situ cyclization was ineffective. However, after optimization of the reaction conditions we could achieve a maximum yield of up to 31% of the corresponding 4-phenyl-2*H*-chromen-2-one (Table 3, entry 1).

A hot filtration test[11] was performed to investigate Pd leaching into the reaction mixture. The test was done for the 4-(trifluoromethyl)-2-iodoaniline (Table 1, entry 8). After 18 h, the $Pd/NiFe_2O_4$ catalyst was removed from the hot reaction mixture by applying an external magnet and the clear solution was filtered to remove any dispersed particles. The filtrate was concentrated and digested in the presence of concd HNO_3 + H_2O_2. The filtrate was then diluted to 50 mL using a volumetric flask and analyzed by atomic absorption spectroscopy (AAS) analysis. The Pd content detected in the filtrate was only 2.1 ppm.

We believe that the present one-pot synthesis of 4-arylquinolin-2(1*H*)-ones proceed via the pathway shown in Scheme 1. The *trans*-2-aminocinnamic acid formed during the first Heck reaction should not cyclize without first isomerizing.[12] Oxidative addition of Pd to the aryl halide added in the second step attached to an olefinic double bond of *trans*-2-aminocinnamic acid and gave alkyl palladium species **21**. Species **21** then underwent β-hydrogen elimination to produce species **22**, which generated product **7**. Alternatively, **7** also could be formed by the route via intermediate **23** followed by the β-hydrogen elimination.

The usefulness of our methodology was extended to the synthesis of biologically important maxi-K channel opener **4** using the $Pd/NiFe_2O_4$-catalyzed Heck reaction. The synthesis of **4** has been previously described by Hewawasam et al.[3a] in 2003 starting from *N*-Boc-protected 4-(trifluoromethyl)aniline, which involves more than 10 linear steps. The key step in their synthesis was a base-catalyzed cyclization of an appropriate *N*-acyl-*O*-aminobenzophenone precursor. Kappe

Table 2. One-pot synthesis of 4-aryl-2-quinolin-2(1*H*)-one derivatives.



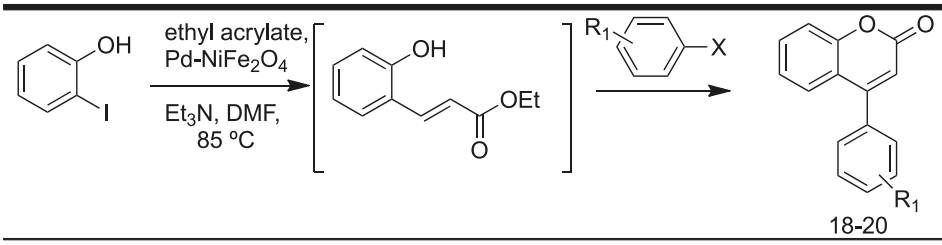
7-17

Entry	R_1	R_2	X	Yield[a]	Product
1	4-CF_3	H	I	75	**7**
2	4-CF_3	4-CH_3	I	77	**8**
3	4-CF_3	3-CH_3	I	71	**9**
4	4-CF_3	2-OCH_3	I	59	**10**
5	4-CF_3	3-OCH_3	I	61	**11**
6	4-CF_3	4-OCH_3	I	67	**12**
7	4-CF_3	H	Br	53	**7**
8	4-CF_3	4-OCH_3	Br	60	**12**
9	H	H	I	81	**13**
10	H	H	Br	47	**13**
11	H	H	Cl	—	**13**
12	H	H	$B(OH)_2$	—	**13**
13	H	3-OCH_3	I	64	**14**
14	H	4-OMe	I	65	**15**
15	H	3-CH_3	I	70	**16**
16	H	4-Me	I	67	**17**
17	H	4-OMe	Br	59	**16**

Note: Reaction conditions: substituted 2-iodoaniline (1.0 mmol), acrylic acid (1.05 mmol), triethylamine (3.25 mmol), Pd/$NiFe_2O_4$ (2.5 mol %), aryl halide (1.25 mmol), and DMF (4.0 mL) at 85 °C with a time duration of 18 h.

[a]Isolated yields after column chromatography.

Table 3. One-pot synthesis of 4-aryl-2*H*-chromen-2-one derivatives.



18-20

Entry	R_1	X	Yield[a]	Product
1	H	I	31	**18**
2	H	Br	13	**18**
3	4-CH_3	I	24	**19**
4	4-OCH_3	I	28	**20**

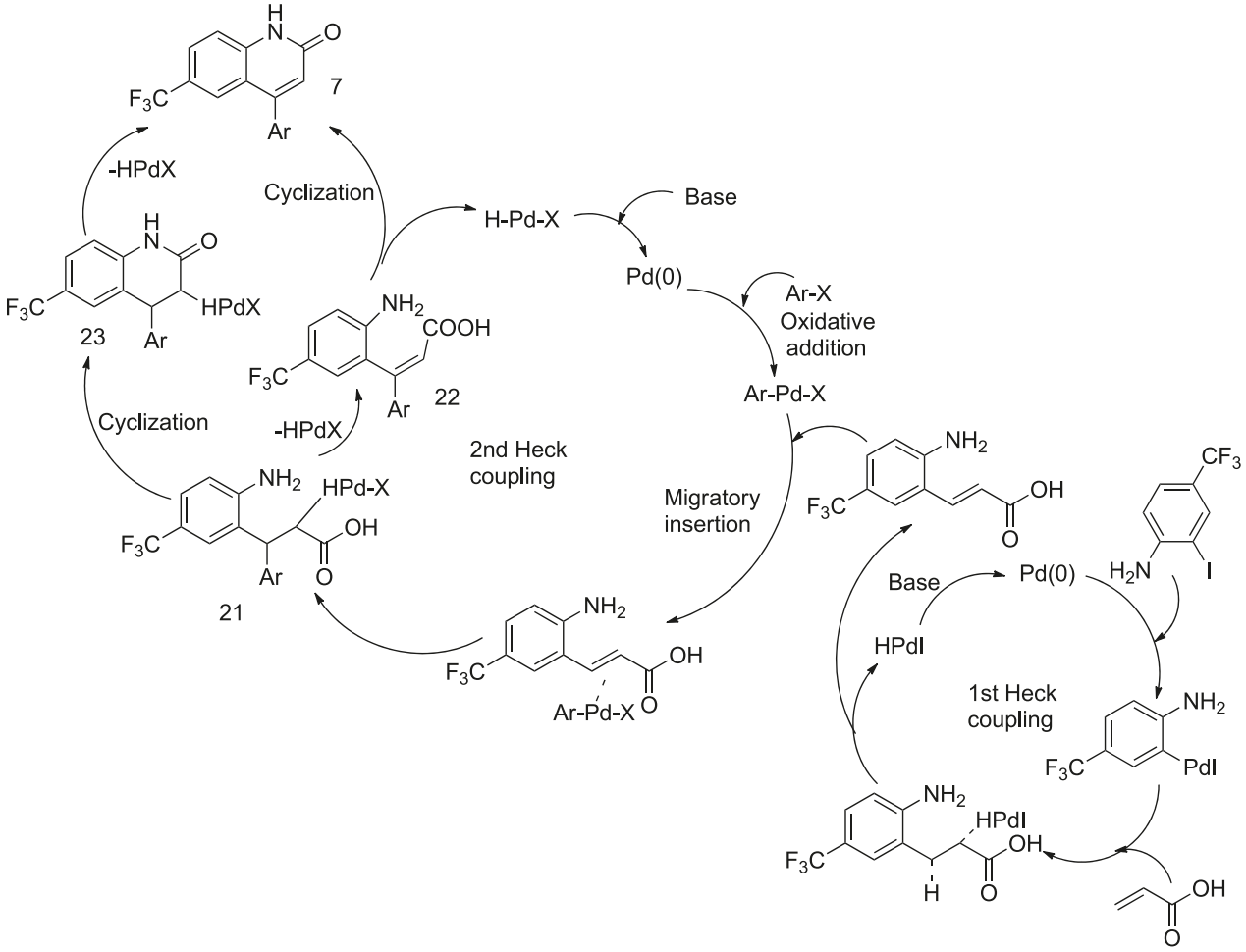
Note: Reaction conditions: 2-iodophenol (1.0 mmol), ethyl acrylate (1.05 mmol), triethylamine (3.25 mmol), Pd/$NiFe_2O_4$ (2.5 mol %), aryl halide (1.25 mmol), DMF (4.0 mL), over 18 h of heating at 85 °C.

[a]Isolated yields after column chromatography.

and co-workers[8e] reported the synthesis of **4** from *N*,*N*-bis[4-(trifluoromethyl)phenyl]malonide using Pd-catalyzed Suzuki and Heck reactions assisted by microwave, which involves six steps. Recently, Wu and co-workers[8f] also developed a general synthetic methodology for the synthesis of **4** in a combinatorial format starting from 3-bromo-4-trifloxy-quinolin-2(1*H*)-one. Although there are reported methods for the synthesis of **4**, none of the reported methods is practical, concise, or has a short synthetic route.

Our synthesis (Scheme 2) commenced with the consecutive Heck reaction of 4-(trifluoromethyl)-2-iodoaniline (**6**) with acrylic acid and 4-chloro-2-iodophenol was added in a second step in DMF at 85 °C using Pd/$NiFe_2O_4$ as the catalyst in the presence of TEA base. We observed the formation of the

Scheme 1. Catalytic cycle for the consecutive Heck reaction and cyclization step.



desired product (**24**) in 75% yield. The N- and O-methylation of **24** to **25** was carried out using methyl iodide in DMF at room temperature in the presence of K_2CO_3 base. We introduced the bromine moiety at the C-3 position of **25** by using our photochemical reaction approach with *N*-bromosuccinamide (NBS) in acetonitrile under UV irradiation.[13] The required 3-bromo product (**26**) was obtained in 78% yield. Further Heck vinylation of 3-bromoquinolinone (**26**) with ethyl acrylate in the presence of 2.5 mol% $Pd/NiFe_2O_4$ catalyst offered the target molecule **4** in its *N*-methyl-protected form, but in very poor yield (12%). To improve the yield of **4**, we varied the palladium precursor. The reaction carried out with $Pd(OAc)_2$ gave only 26% yield. To further improve the yield, the reaction was performed with $Pd(PPh_3)_4$ in an inert atmosphere, and this transformed into a 79% yield of the product **4**.[14]

Conclusion

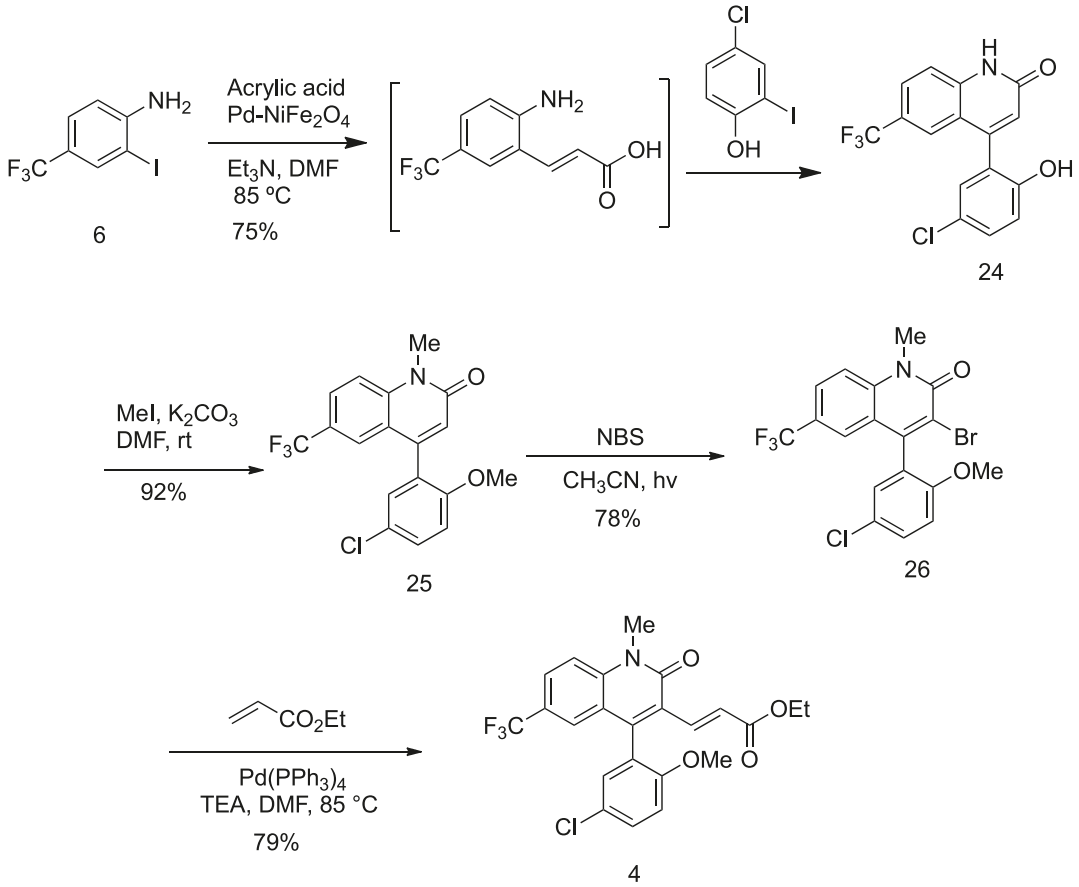
In summary, we have presented a practical useful one-pot methodology for the synthesis of various 4-arylquinolin-2(1*H*)-ones from 2-iodoanilines in good yields. The heterogeneous $Pd/NiFe_2O_4$ catalyst efficiently catalyzed the successive Heck reaction in one pot and it could be easily separated from the reaction mixture by applying an external magnetic field. The scope of this methodology was successfully applied for the synthesis of biologically active 3-alkenyl-4-aryl-2-quinolinone from 4-(trifluoromethyl)-2-iodobenzamine in four linear steps in an overall yield of 42.5%.

Experimental section

General methods

Unless otherwise stated, all experiments were performed in an ambient atmosphere. All glasswares were acid and base washed and oven-dried before use. The catalytic reactions were carried out in 25 mL two-neck round-bottomed flasks equipped with a reflux condenser in an air atmosphere. The Pd salts/complexes, reactants, and solvents were obtained from Sigma-Aldrich/Merck or Spectochem and used as received without further purification or drying. The progress of the reaction was monitored by gas chromatography (GC; HP-5890, series II, equipped with a HP-5 capillary column and an FID detector) and TLC. The products were isolated by extractive work-up using ethyl acetate and were purified using silica gel (100–200) column chromatography. The products were characterized by GC–MS (Shimadzu QP-5050, DB-5 column, and FID detector), FTIR (8400 Shimadzu), and NMR (Varian 300 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard) spectroscopies. The Pd content was detected using an atomic absorption spectrophotometer (AAS), model No. Chemito AA-201.

Scheme 2. Synthesis of the 3-alkenyl-4-aryl-2-quinolinone derivative.



*General one-pot procedure for the synthesis of 4-arylquinolin-2(1*H*)-ones (products 7–17)*

To a 25 mL two-neck round-bottomed flask attached with a reflux condenser were added 2-iodo-aniline (1 mmol), acrylic acid (1.5 mmol), triethylamine (3.25 mmol), and Pd/$NiFe_2O_4$ (2.5 mol %) in 4 mL of DMF solvent. The reaction mixture was placed in a preheated oil bath at 85 °C for 30 min. The reactions were analyzed by GC and TLC. The reaction mixture (0.25 mL) was withdrawn by using a syringe, then diluted with water (1.0 mL), and extracted with ethyl acetate (1.0 mL). The ethyl acetate layer was separated, dried over sodium sulfate, and analyzed by GC. After the complete conversion of starting material, the new substrate, aryl halide (1.25 mmol), was added and the reaction continued for a further 16 h.

After the specified time of heating, the reaction mixture was cooled to room temperature and the catalyst was separated from the reaction mixture by applying an external magnet, and the clear solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The crude product was then purified by silica gel column chromatography (hexane – ethyl acetate, 7:3). All products were analyzed and characterized by GC, GC–MS, IR, and NMR.

*General one-pot procedure for the synthesis of 4-aryl-2*H*-chromen-2-ones (products 18–20)*

To a 25 mL two-neck round-bottomed flask attached with a reflux condenser were added 2-iodophenol (1 mmol), ethyl acrylate (1.5 mmol), triethylamine (3.25 mmol), and Pd/$NiFe_2O_4$ (2.5 mol %) in 4 mL of DMF solvent. The reaction mixtures were heated at 85 °C for 30 min. The reactions were monitored by GC and TLC. The reaction mixture (0.25 mL) was withdrawn by using a syringe, then diluted with water (1.0 mL), and extracted with ethyl acetate (2 × 1.0 mL). The ethyl acetate layer was separated, dried over sodium sulfate, and analyzed by GC. After the complete conversion of starting material, the new substrate, aryl halide (1.25 mmol), was added and the reaction continued for a further 16 h.

After the specified time of heating, the reaction mixture was cooled to room temperature and the catalyst was separated from the reaction mixture by applying an external magnet, and the clear solution was extracted with ethyl acetate three times. The combined organic extracts were dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The crude product was then purified by silica gel column chromatography (hexane – ethyl acetate, 7:3). Purified products were analyzed and characterized by GC, GC–MS, IR, and NMR.

*Synthesis of 4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1-methylquinolin-2(1*H*)-one (25)*

To a solution of **24** (0.34 g, 1.0 mmol) in DMF (4.0 mL) were added methyl iodide (0.35 g, 2.2 mmol) and K_2CO_3 (0.44 g, 3.2 mmol) at ambient temperature. The reaction mixture was stirred for 3 h at room temperature and then diluted with ethyl acetate (3 × 20 mL). The organic layer was

washed with water (2 × 10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography using hexane – ethyl acetate (1:4) as the eluent to give **25** (0.36 g, 96% yield) as a white solid.

*Synthesis of 3-bromo-4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1-methyl quinolin-2(1*H*)-one (26)*

A mixture of **25** (0.37 g, 1.0 mmol) and NBS (0.35 g, 2.0 mmol) was stirred in 4 mL of acetonitrile under an N_2 atmosphere in the presence of a Philips HPL-N lamp (250 W, k_{max} = 200–600 nm) fitted with a water circulation arrangement at room temperature. After completion of the reaction (monitored by TLC and GC), the reaction mixture was quenched with cold water and extracted with ethyl acetate (3 × 25 mL). The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel (60–120 mesh) using ethyl acetate and petroleum ether (1:2) as the eluent to give **26** (0.35 g, 78% yield) as a white solid.

*Synthesis of (2*E*)-ethyl 3-(4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1,2-dihydro-1-methyl-2-oxoquinolin-3-yl) acrylate (4)*

In an oven-dried 25 mL two-neck round-bottomed flask attached with a reflux condenser were added **26** (0.44 g, 1.0 mmol), $Pd(PPh_3)_4$ (0.06 g, 5.0 mol%), ethyl acrylate (0.30 g, 3.0 mmol), triethylamine (0.25 g, 2.5 mmol), and 5.0 mL of dry DMF. The reaction mixture was then heated at 85 °C for 12 h. After the completion of reaction (monitored by TLC), the heating was discontinued and the reaction was quenched by adding ice-water (25 mL). The whitish precipitate was then extracted with ethyl acetate (3 × 25 mL). The combined organic extracts was washed with brine (30 mL), dried over Na_2SO_4, and solvent was evaporated under reduced pressure. The crude product was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate and petroleum ether (1:1) as the eluent to give **4** (0.37 g, 79% yield) as a white solid.

Characterization data for all products

*6-(Trifluoromethyl)-4-phenylquinolin-2(1*H*)-one (7)*

FTIR (KBr, cm^{-1}): 1265, 1475, 1573, 1685, 2918, 3315. ^{1}H NMR (DMSO-d_6) δ: 6.51 (s, 1H), 7.47–7.57 (m, 7H), 7.83 (d, 1H, J = 9.8 Hz), 12.20 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 116.0, 116.9, 118.0, 122.6, 123.1(q), 126.8, 128.5, 128.8, 129.1, 135.7, 139.8, 141.7, 150.9, 161.2. MS (EI): *m*/*z* 289 (M^+). Anal. calcd for $C_{16}H_{10}F_3NO$: C 66.44, H 3.48, N 4.84; found: C 66.47, H 3.95, N 4.83.

*6-(Trifluoromethyl)-4-*p*-tolylquinolin-2(1*H*)-one (8)*

FTIR (KBr, cm^{-1}): 1265, 1508, 1564, 1658, 3007, 3321. ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H), 6.39 (s, 1H), 7.28 (s, 4H), 7.45 (d, 1H, J = 8.8 Hz), 7.52 (s, 1H), 7.76 (d, 1H, J = 8.2 Hz), 12.11 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 20.7, 116.8, 118.0, 122.4, 123.1(q), 125.0, 126.7, 128.4, 129.4, 132.8, 138.7, 141.7, 150.9, 161.2, 168.7. MS (EI): *m*/*z* 303 (M^+). Anal. calcd for $C_{17}H_{12}F_3NO$: C 67.32, H 3.99, N 4.62; found: C 67.33, H 4.10, N 4.63.

*6-(Trifluoromethyl)-4-*m*-tolylquinolin-2(1*H*)-one (9)*

FTIR (KBr, cm^{-1}): 1105, 1577, 1614, 1668, 3005, 3404. ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H) 6.61 (s, 1H), 7.37–7.47 (m, 3H), 7.56 (t, 1H) 7.68 (t, 1H) 7.96 (dd, 1H, J = 8.2 and 1.7 Hz), 12.35 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 20.8, 116.9, 118.0, 121.8, 122.2, 122.5, 123.2(q), 125.6, 126.7, 128.6, 129.0, 129.7, 135.7, 138.3, 141.7, 151.0, 161.3. MS (EI): *m*/*z* 303 (M^+). Anal. calcd for $C_{17}H_{12}F_3NO$: C 67.32, H 3.99, N 4.62; found: C 67.32, H 4.08, N 4.62.

*6-(Trifluoromethyl)-4-(*o*-methoxyphenyl)quinolin-2(1*H*)-one (10)*

FTIR (neat, cm^{-1}): 1070, 1371, 1494, 1579, 1658, 3306. ^{1}H NMR (DMSO-d_6) δ: 3.72 (s, 3H), 6.97 (t, 1H, J = 7.4 Hz), 7.09 (d, 1H, J = 8.2 Hz), 7.27 (d, 1H, J = 7.4 Hz), 7.37 (t, 1H, J = 8.2 and 7.4 Hz), 7.47 (d, 1H, J = 8.5 Hz), 7.80 (d, 1H, J = 8.8 Hz), 7.90 (s, 1H), 8.13 (s, 1H), 12.17 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 55.8, 111.3, 115.6, 118.8, 120.0, 121.9, 122.3 (q), 125.1, 125.3, 126.1, 129.5, 130.7, 132.3, 138.3, 140.8, 156.9, 160.8. MS (EI): *m*/*z* 319 (M^+). Anal. calcd for $C_{17}H_{12}F_3NO_2$: C 63.95, H 3.79, N 4.39; found: C 63.97, H 3.88, N 4.62.

*6-(Trifluoromethyl)-4-(*m*-methoxyphenyl)quinolin-2(1*H*)-one (11)*

FTIR (KBr, cm^{-1}): 1074, 1319, 1473, 1568, 1674, 3007, 3147. ^{1}H NMR (DMSO-d_6) δ: 3.80 (s, 3H), 6.55 (s, 1H), 7.04–7.12 (m, 3H), 7.45–7.63 (m, 3H), 7.85 (d, 1H, J = 8.2 Hz), 12.24 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 55.6, 114.5, 115.2, 117.3, 118.4, 121.2, 123.0(q), 123.7, 127.2, 130.4, 137.5, 142.2, 151.2, 159.9, 161.7. MS (EI): *m*/*z* 319 (M^+). Anal. calcd for $C_{17}H_{12}F_3NO_2$: C 63.95, H 3.79, N 4.39; found: C 63.97, H 4.14, N 4.37.

*6-(Trifluoromethyl)-4-(*p*-methoxyphenyl)quinolin-2(1*H*)-one (12)*

FTIR (KBr, cm^{-1}): 1124, 1317, 1510, 1608, 1668, 2841, 3151. ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H), 6.48 (s, 1H), 7.13 (d, 2H, J = 7.2 Hz), 7.45 (d, 2H, J = 7.2 Hz), 7.56 (d, 1H, J = 8.3 Hz), 7.67 (s, 1H), 7.86 (d, 1H, J = 8.6 Hz), 12.19 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 55.1, 114.2, 116.8, 118.1, 121.7, 122.2, 123.1(q), 125.8, 126.7, 127.8, 130.0, 141.7, 150.6, 159.8, 161.2. MS (EI): *m*/*z* 319 (M^+). Anal. calcd for $C_{17}H_{12}F_3NO_2$: C 63.95, H 3.79, N 4.39; found: C 63.94, H 3.90, N 4.07.

*4-Phenylquinolin-2(1*H*)-one (13, 5855-57-2)[8a]*

FTIR (neat, cm^{-1}): 1072, 1265, 1433, 1496, 1568, 1654, 3306. ^{1}H NMR (DMSO-d_6) δ: 6.30 (s, 1H), 7.03–7.08 (m, 1H), 7.27–7.32 (m, 2H), 7.37–7.44 (m, 6H) 11.79 (s, 1H). MS (EI): *m*/*z* 221 (M^+).

*4-(3-Methoxyphenyl)quinolin-2(1*H*)-one (14, 65848-66-0)[8a]*

FTIR (neat, cm^{-1}): 1045, 1214, 1388, 1432, 1574, 1601, 1653, 2837, 3310. ^{1}H NMR (DMSO-d_6) δ: 3.80 (s, 3H), 6.41 (s, 1H), 7.00–7.15 (m, 4H), 7.39–7.54 (m, 4H), 11.89 (s, 1H). MS (EI): *m*/*z* 251 (M^+).

*4-(4-Methoxyphenyl)quinolin-2(1*H*)-one (15, 37118-72-2)[8a]*

FTIR (neat, cm^{-1}): 1029, 1170, 1251, 1506, 1610, 1674, 2962, 3300.^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H), 6.33 (s, 1H),

7.05–7.14 (m, 3H), 7.35–7.52 (m, 5H), 11.79 (s, 1H). MS (EI): *m/z* 251 (M^+).

4*-m-*Tolylquinolin-2(1H)-one (16, 92909-30-4)[8c]

FTIR (neat, cm^{-1}): 1038, 1160, 1271, 1385, 1432, 1547, 1606, 1654, 2836, 3316. ^1H NMR (DMSO-d_6) δ: 2.36 (s, 3H), 6.34 (s, 1H), 7.08–7.13 (m, 1H), 7.20–7.41 (m, 7H), 11.85 (s, 1H). MS (EI): *m/z* 235 (M^+).

4*-p-*Tolylquinolin-2(1H)-one (17, 106015-76-3)[8c]

FTIR (neat, cm^{-1}): 1039, 1383, 1433, 1502, 1608, 1664, 2850, 3319. ^1H NMR (DMSO-d_6) δ: 2.40 (s, 3H), 6.35 (s, 1H), 7.13 (t, 1H, J = 7.7 and 7.9 Hz), 7.35–7.41 (m, 6H), 7.52 (t, 1H, J = 7.9 and 7.2 Hz), 11.82 (s, 1H). MS (EI): *m/z* 235 (M^+).

4-Phenyl-2H-chromen-2-one (18, 15185-05-4)[10]

FTIR (neat, cm^{-1}): 1365, 1444, 1491, 1560, 1606, 1734, 3072. ^1H NMR ($CDCl_3$) δ: 6.36 (s, 1H), 7.22 (t, 1H, J = 7.7 Hz), 7.40–7.57 (m, 8H). MS (EI): *m/z* 222 (M^+).

4*-p-*Tolyl-2H-chromen-2-one (19, 76103-24-7)[10]

FTIR (neat, cm^{-1}): 1365, 1510, 1608, 1726, 3070. ^1H NMR ($CDCl_3$) δ: 2.45 (s, 3H), 6.36 (s, 1H), 7.20 (d, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 7.6 Hz), 7.34 (m, 4H), 7.54 (m, 2H). MS (EI): *m/z* 236 (M^+).

4*-(4-Methoxyphenyl)-2H-*chromen-2-one (20, 170456-76-5)[10]

FTIR (neat, cm^{-1}): 1294, 1599, 1491, 1670, 1757, 3072.^1H NMR ($CDCl_3$) δ: 3.90 (s, 3H), 6.36 (s, 1H), 7.05 (d, 2H, J = 8.5 Hz), 7.25 (t, 1H), 7.42 (m, 3H), 7.56 (t, 2H, J = 8.5 Hz). MS (EI): *m/z* 252 (M^+).

***4*-(5-Chloro-2-hydroxyphenyl)-6-(trifluoromethyl)quinolin-2 (1H)-one (24)**

FTIR (neat, cm^{-1}): 1437, 1558, 1653, 3311. ^1H NMR (DMSO-d_6) δ: 6.49 (s, 1H), 7.02 (d, 1H, J = 8.8 Hz), 7.30–7.35 (m, 3H), 7.52 (d, 1H, J = 8.8 Hz), 7.81 (d, 1H, J = 8.5 Hz), 10.11 (s, 1H), 12.2 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 116.5, 117.3, 117.9, 121.6, 122.0, 122.8, 123.6(q), 124.6, 126.4, 126.5, 129.6, 130.1, 141.1, 147.9, 153.2, 161.4. MS (EI): *m/z* 339 (M^+) 341 (M^++2). Anal. calcd for $C_{16}H_9ClF_3NO_2$: C 56.57, H 2.67, N 4.12; found: C 56.59, H 2.87, N 4.17.

***4*-(5-Chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1-methylquinolin-2(1H)-one (25)**

FTIR (neat, cm^{-1}): 1305, 1494, 1602, 1674, 2845, 3055.^1H NMR (DMSO-d_6) δ: 3.68 (s, 3H), 3.71 (s, 3H), 6.66 (s, 1H), 7.24 (s, 1H), 7.27 (d, 1H, J = 7.0 Hz), 7.40 (d, 1H, J = 2.4 Hz), 7.58 (dd, 1H, J = 8.8 and 2.4 Hz), 7.79 (d, 1H, J = 8.8 Hz), 7.94 (d, 1H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6) δ: 29.4, 55.8, 113.5, 116.4, 119.0, 122.9, 123.6, 124.7, 125.9, 126.8, 129.7, 130.5, 141.8, 146.1, 155.0, 160.5. MS (EI): *m/z* 367 (M^+), 369 (M^+ + 2). Anal. calcd for $C_{18}H_{13}ClF_3NO_2$: C 58.79, H 3.56, N 3.81; found: C 58.81, H 3.68, N 3.81.

***3*-Bromo-4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1-methylquinolin-2(1H)-one (26)**

FTIR (neat, cm^{-1}): 1120, 1311, 1491, 1654, 2848, 2941. ^1H NMR (DMSO-d_6) δ: 3.36 (s, 3H), 3.81 (s, 3H), 7.19 (s, 1H), 7.29 (d, 1H, J = 8.8 Hz), 7.35 (d, 1H, J = 2.4 Hz), 7.58 (dd, 1H, J = 2.4 and 8.8 Hz), 7.84 (d, 1H, J = 8.8 Hz), 7.97 (d, 1H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6) δ: 31.2, 56.0, 113.8, 116.7, 119.5, 121.0, 122.6, 123.0, 123.3 (q), 124.5, 126.1, 127.0, 129.1, 130.6, 140.7, 145.8, 154.5, 157.1. MS (EI): *m/z* 445 (M^+), 447 (M^+ + 2), 449 (M^+ + 4). Anal. calcd for $C_{18}H_{12}BrClF_3NO_2$: C 48.40, H 2.71, N 3.14; found: C 48.35, H 3.02, N 3.18.

(2E)-Ethyl-3-(4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1,2-dihydro-1-methyl-2-oxoquinolin-3-yl) acrylate (4)

FTIR (neat, cm^{-1}): 1132, 1286, 1371, 1494, 1620, 1662, 1695, 3111.^1H NMR ($CDCl_3$) δ: 1.25 (t, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.16 (q, 2H), 7.02 (d, 1H, J = 9.1 Hz), 7.08 (d, 1H, J = 2.4 Hz), 7.27 (s, 1H), 7.35 (d, 2H, J = 2.4 Hz), 7.58 (m, 2H), 7.80 (d, 1H, J = 9.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 14.1, 30.1, 55.9, 60.3, 112.8, 114.8, 120.0, 124.1, 124.4, 125.1, 125.3, 125.4, 125.5, 126.1, 127.5(q), 130.1, 130.8, 137.4, 141.1, 147.0, 155.0, 160.4, 167.5. MS (EI): *m/z* 465 (M^+), 467 (M^+ + 2). Anal. calcd for $C_{23}H_{19}ClF_3NO_4$: C 59.30, H 4.11, N 3.01; found: C 59.29, H 4.26, N 3.08.

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