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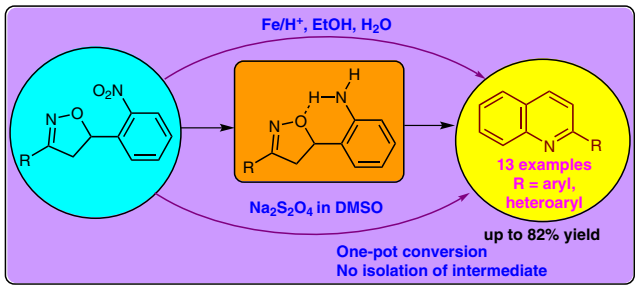
A Novel Route to 2-Arylquinolines: Reductive Cleavage of 2′-Nitroaryl-Δ²-isoxazolines

Prashantha Kamath[a]
Russell C. Viner[b]
Stephen C. Smith[b]
Mukul Lal[*a]

[a] Syngenta Biosciences Pvt. Ltd., Santa Monica Works, Corlim, Ilhas, Goa-403110, India
[b] Syngenta Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK
mukul.lal@syngenta.com

The article is dedicated to Prof. Dr. Michael Schmittel on the occasion of his 60th birthday.



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Abstract A novel synthetic route for the synthesis of quinolines starting from Δ²-isoxazolines under reductive conditions is reported. The reductive cyclization to quinolines is achieved under both metal and metal-free conditions. The reaction proceeds via an intramolecular N–H···O hydrogen bond intermediate, accelerating the reductive cleavage 1000-fold (DFT calculations) in comparison with non-hydrogen bonded system.

Key words heterocycles, cyclization, reduction, isoxazoline, quinolines

Δ²-Isoxazolines and quinolines constitute classes of heterocycles having diverse applications, including agrochemicals, drugs, dyes, rubber chemicals, flavoring agents, and in materials science.[1–12] Δ²-Isoxazolines can be accessed by a variety of methods, notably the [3+2] cycloaddition between nitrile oxides and unsaturated systems.[13,14] Their ease of synthesis, stability and ability to undergo an array of further transformations render them valuable intermediates in organic synthesis[15,16] and prompted us to investigate the potential application of these substrates to access quinolines via a reductive O–N bond cleavage.[17,18] It was hypothesized that a suitably placed nitro group in the substrates would not only be reduced to an amine but also accelerate the cyclization into a quinoline with concomitant O–N bond cleavage (Figure 1).[19]

To assess the postulated route, a range of 2′-nitroaryl-Δ²-isoxazolines **1a–m** were synthesized in good to excellent yields (70–90%) via the [3+2] cycloaddition route using the corresponding nitrile oxide and the requisite styrene (Table 1).[20–23]

To test the approach, conventional nitro group reducing agents such as iron, zinc, nickel(II) acetate and tin(II) chloride with or without additives were tested on the model substrate **1a** (Scheme 1).[24] Reductive cyclization when carried out with four equivalents of iron–ammonium chloride (1:1) in an ethanol–water mixture as the solvent did not yield the desired product at room temperature. However, when the reaction mixture was warmed to 50 °C, a clean formation of **2a** was noted. The formation of the desired product **3a** was achieved with a further rise in the reaction temperature to 80 °C, albeit with a low conversion of 10%. When the iron–ammonium chloride quantity was doubled, a complete conversion of **1a** into **3a** was observed with a yield of 74% of the desired product (Table 1, see the Supporting Information for optimization details).

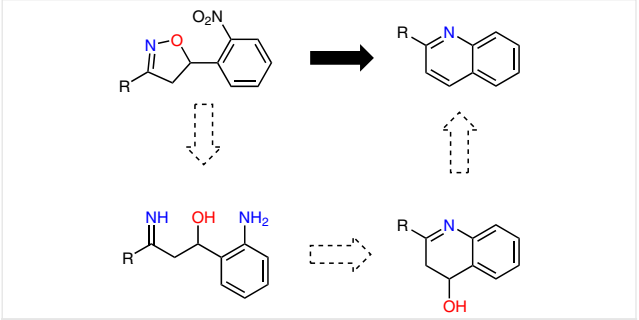
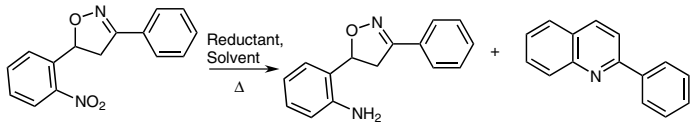


Figure 1 Conversion of 2′-nitroaryl-Δ²-isoxazolines into 2-arylquinolines

The reductive cyclization, when carried out with iron as reductant in acetic acid, resulted in complete conversion of the starting material within one hour without compromising the yield.



Scheme 1 Conversion of **1a** into **2a** and **3a** in the presence of various reducing agents

Replacement of the reductant with zinc in acetic acid or tin(II) chloride in ethanol gave similar conversions of **1a** into **3a**. Reductive cyclization with freshly prepared nickel boride gave **2a** as the sole product, despite attempts to force the reaction further by increasing the concentration of the reductant or the reaction temperature.

In order to test the generality of the reaction, a variety of 3,5-disubstituted Δ^2-isoxazoline derivatives[25] **1a–m** were subjected to iron (8.0 equiv) and ammonium chloride (8.0 equiv) in a 1:1 ethanol–water mixture as the solvent at 80 °C (Table 1). Irrespective of the substitution pattern, a consistently good yield of the corresponding quinoline **3** was obtained (72–82% yield),[26] suggesting little or no influence of the substituent in position 3 of the isoxazolines on the overall reaction outcome.

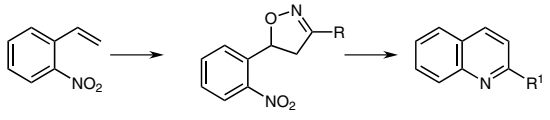
While the methodology worked as anticipated, the formation of **2a** suggested that intramolecular N–H···O hydrogen bonding might exist and that it could influence the reductive cyclization described in Scheme 1. To establish this, solution studies of **2a**, such as dilution and solvent-dependence experiments, were performed using ^{1}H NMR spectroscopy. Interestingly, in **2a**, a single peak was observed for the NH_2 protons, despite variations in the solvent polarity from non-polar (toluene) to aprotic polar (DMSO).[27] As anticipated, a downfield shift in the ^{1}H NMR for the NH_2 protons was observed with an increasing solvent polarity parameter ($E^{N/T}$) suggesting an enhanced interaction of the amine protons with the solvent and thereby a weakening of the intramolecular hydrogen bonding.

A ^{1}H NMR dilution experiment with **2a** had no influence on the NH_2 protons over a concentration range of 0.210 M to 0.002 M, demonstrating strong N–H···O type intramolecular hydrogen bonding at room temperature. In contrast, a dilution experiment with **2n**, a *para*-substituted aryl amine (control), showed a complete disappearance of NH_2 protons under similar concentrations.

Having established the presence of intramolecular N–H···O hydrogen bonding in solution for intermediate **2a**, it was hypothesized that the reductive cyclization from **1a** into **3a** could be carried out under milder conditions to take advantage of potential activation and, additionally, develop metal-free conditions for the reductive cyclization.

Dithionite is a known reductant and forms the sulfur dioxide radical anion during the process of reduction, acting as a source of electrons.[28] While literature precedence for nitro group reductions with sodium dithionite is well documented, there is no precedent for the reductive cleavage of an O–N bond in isoxazolines.[29,30] To test this, **1a** was initially treated with sodium dithionite (4.0 equiv) in ethanol as the solvent at 80 °C. No conversion was observed, but this appeared to be due to the heterogeneous reaction conditions. To circumvent this, a 50% aqueous solution of ethanol in water was used as the solvent. This resulted in complete conversion of **1a** into **2a**. When the reaction was extended by an additional 6 hours, 10% formation of **3a** was observed. The conversion was improved to 50% by further increasing the reductant quantity from 4.0 to 6.0 equivalents.

Table 1 Substrate Scope for the Synthesis of Isoxazolines **1**[a] and Quinolines **3**[b]

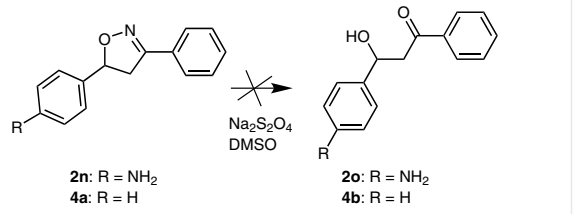


Entry	R	Yield (%) of **1**	R^1	Yield (%) of **3**[c]
a	C_6H_5	81	C_6H_5	74 (70)
b	4-BrC_6H_4	88	4-BrC_6H_4	80
c	4-Cl-2-FC_6H_3	84	4-Cl-2-FC_6H_3	80
d	4-MeOC_6H_4	79	4-MeOC_6H_4	80 (55)
e	2-thienyl	70	2-thienyl	77
f	2-bromopyridyl	90	2-bromopyridyl	78 (69)
g	2-O_2NC_6H_4	77	2-H_2NC_6H_4	72 (66)
h	3-Me-4-*t*-BuO_2CC_6H_3	82	3-Me-4-*t*-BuO_2CC_6H_3	82
i	2-Cl-5-O_2NC_6H_3	85	2-Cl-5-H_2NC_6H_3	74
j	3-pyridyl	70	3-pyridyl	72 (65)
k	2-Br-4-ClC_6H_3	82	2-Br-4-ClC_6H_3	82
l	2,4,6-$F_3C_6H_2$	90	2,4,6-$F_3C_6H_2$	81 (83)
m	4-FC_6H_4	89	4-FC_6H_4	81 (76)

[a] Reaction conditions: 1-Nitro-2-vinylbenzene (1.10 mmol), oxime (1.00 mmol), NCS (1.10 mmol), Et_3N (1.00 mmol) in DMF (3.0 mL).
[b] Reaction condition: Method 1: **1**(1.00 mmol), Fe (8.00 mmol), EtOH (7.0 mL), NH_4Cl (8.00 mmol) in H_2O (7.0 mL) at 80 °C for 6 h. Method 2: **1** (1.00 mmol), $Na_2S_2O_4$ 6.00 mmol) in DMSO (7.0 mL) at 100 °C for 3–5 h.
[c] Yields in parentheses correspond to the yield of **3** using method 2.

Further examination of the literature indicated the formation of *N*-substituted sulfamic acid type intermediates during the reduction processes using dithionite.[31] The formation of such intermediates could impact the overall reduction process; therefore addition of base was anticipated to circumvent this. Hence, addition of a base such as potassium carbonate in equimolar concentration was attempted and to our satisfaction led to complete conversion into the desired product **3a**.

Thus, the reduction of **1a** was carried out in an ethanol–water mixture (1:1) with sodium dithionite (6.0 equiv) and potassium carbonate (6.0 equiv) resulting in the clean conversion of **1a** into **3a** within 12 hours (70% yield).

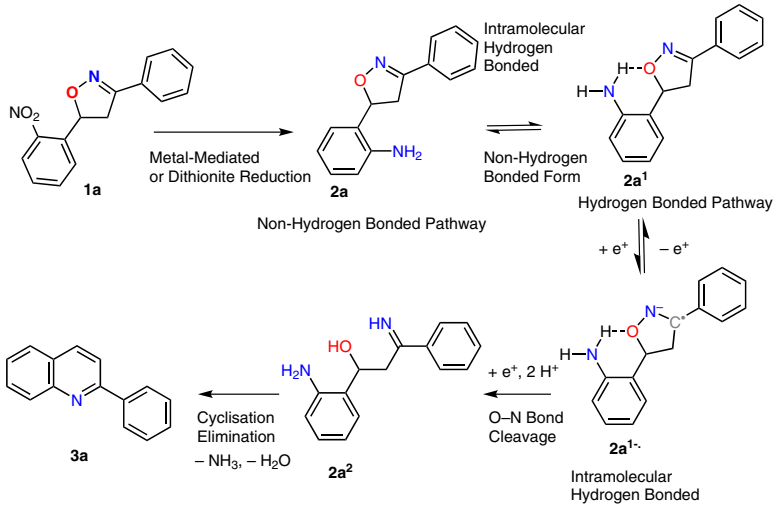


Scheme 2 Control experiments with **2n** and **4a** using method 2

Furthermore, when the reaction solvent was switched from the ethanol–water mixture to DMSO, the reaction time decreased from 12 hours to 3 hours. Interestingly, when the reductive cyclization of **1a** was carried out with sodium dithionite (6.0 equiv) in DMSO without potassium carbonate, the quinoline product **3a** was still formed with similar efficacy as before, which could be due to the increased availability and/or stability of the sulfur dioxide radical anion in DMSO.[32] Further control experiments were performed with **2n** (Scheme 2) as a model compound in which the intermediate hydrogen bond donor is remotely placed (*p*-NH_2), and **4a** (Scheme 2) which was devoid of any hydrogen bond donor group. In both cases starting material was recovered (90–95%) with little decomposition, indicating the importance of the hydrogen bond for activating the O–N bond toward reduction. Heating **2a** in DMSO at elevated temperatures up to 130 °C without dithionite did not lead to the formation of **3a**, showing that dithionite was required for the reductive ring opening of the isoxazoline O–N bond. To check the generality of the reaction, Δ^2-isoxazolines (**1a**, **1d**, **1f**, **1g**, **1j**, **1i** and **1m**) were treated under the optimized conditions to give the desired substituted quinolines (**3a**, **3d**, **3f**, **3g**, **3j**, **3i** and **3m**) in reasonable yields (50–70%).[32]

As previously stated, under certain reaction conditions **2a** was converted cleanly into **3a**, whereas under the same conditions the *p*-amino compound **2n** was unreactive. This suggests that the *o*-amino group in **2a** is facilitating the reductive cleavage of the Δ^2-isoxazoline ring. To gain further insight we carried out DFT calculations (B3LYP/6-31G** level of theory) with full geometry optimization (see the Supporting Information) of **2a** as well as **2n** (a molecule with a *p*-amino group). Indeed, the optimized structure of **2a** suggests the existence of an intramolecular N–H···O hydrogen bond. The *o*-amino group was found to stabilize the radical anion by 17.2 kJ/mol (compared to a *p*-amino group) equating to an acceleration in the rate of reaction by a factor of approximately 1000. This is consistent with the experimental observation that the *o*-amino group is required for the reductive cleavage of the Δ^2-isoxazoline ring.

From the experimental observations and theoretical calculations, a distinct mechanism appears to be operative during the reductive cyclization of 2′-nitroaryl-Δ^2-isoxazolines into 2-arylquinolines, and is summarized in Scheme 3. In the presence of a suitable reducing agent, the initial step is the reduction of the *o*-nitro group in **1a** into the amine



Scheme 3 Proposed reaction mechanism for the reductive cyclization of 2′-nitroaryl-Δ^2-isoxazolines to 2-arylquinolines

intermediate **2a** irrespective of the reducing agent used. The amine intermediate **2a** thus equilibrates to the favored intramolecular hydrogen bonded form **2a**[1]. The latter, in the presence of a reducing agent, accepts a further electron to form the corresponding radical anion **2a**[1-] which can rapidly lead to the formation of **3a** via O–N bond cleavage (Scheme 3). This could be the predominant pathway for the isoxazoline derivatives of type **2a**–**m** having an *o*-amino group. However, isoxazolines devoid of an *o*-amino group such as **2n** and **4a** might undergo non-hydrogen bonded O–N bond cleavage under iron-mediated reducing conditions to form β-hydroxy ketones.

In conclusion, the work demonstrates a novel heterocycle–heterocycle interconversion methodology for accessing quinolines from 2′-nitroaryl-Δ^2-isoxazolines. The methodology has been exemplified under a variety of conditions, including transition-metal reagents (iron, zinc and tin(II) chloride) as well as metal-free conditions (sodium dithionite, with or without potassium carbonate). A variety of 2-arylquinolines were obtained in good yields (50–80%) using this methodology. The ease of isolation of the product under dithionite-mediated reducing conditions makes the methodology attractive compared to traditional methods involving transition metals. The confirmed presence of an intramolecular H-bond to the isoxazoline in intermediate **2a** appears to activate the O–N bond of Δ^2-isoxazolines and accelerates the rate of the reaction 1000-fold towards reductive cyclization. The methodology also demonstrates the first use of dithionite in the reductive ring opening of isoxazolines. The methodology is being extended to the synthesis of other heterocycles in our laboratory.

Acknowledgment

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Supporting Information

Supporting Information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588751.

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(25) **2′-Nitroaryl-Δ^2-isoxazoline Derivatives 1a–m: General Procedure**
To a solution of the oxime (1.00 mmol, 1.0 equiv) in DMF (2.0 mL) at r.t. was added *N*-chlorosuccinimide (1.10 mmol, 1.10 equiv) and the mixture was stirred for 60 min. To the reaction mixture was added the alkene in one portion (1.10 mmol, 1.1 equiv) followed by a solution of triethylamine (1.00 mmol, 1.00 equiv) in DMF (1.0 mL). After complete addition, the reaction mixture was stirred at 23–25 °C until complete conversion of the *in situ* formed chlorooxime intermediate (reaction was monitored by TLC). After complete conversion, the reaction was poured into cold water (30.0 mL) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (3 × 20.0 mL), the combined organic layers were washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product which was purified by flash chromatography.
3,5-Bis(2-nitrophenyl)-4,5-dihydroisoxazole (1g)
White solid; yield: 241 mg (77%); mp 120–121 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (dd, *J* = 8.3, 1.3 Hz, 2 H), 8.07 (dd, *J* = 8.0, 1.3 Hz, 2 H), 7.91 (dd, *J* = 7.9, 1.4 Hz, 2 H), 7.69–7.80 (m, 4

H), 7.52–7.65 (m, 6 H), 6.42 (d, *J* = 6.3 Hz, 1 H), 6.39 (d, *J* = 6.3 Hz, 1 H), 4.04 (d, *J* = 6.0 Hz, 1 H), 3.27 (d, *J* = 6.3 Hz, 1 H), 3.22 (d, *J* = 6.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 154.1, 145.4, 142.2, 136.3, 133.5, 132.6, 130.0, 129.9, 128.0, 127.0, 124.1, 124.0, 123.9, 78.7, 45.2. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_{11}N_3O_5$: 313.0698; found: 313.0698.

***tert*-Butyl 2-methyl-4-[5-(2-nitrophenyl)-4,5-dihydroisoxazol-3-yl]benzoate (1h)**

White solid; yield: 313 mg (82%); mp 167–168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.83–7.87 (m, 2 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.49–7.54 (m, 3 H), 4.15 (dd, *J* = 17.3, 11.3 Hz, 1 H), 3.26 (dd, *J* = 17.3, 6.8 Hz, 1 H), 2.58 (s, 3 H), 1.57–1.62 (s, 9 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 166.5, 155.7, 139.8, 137.7, 134.5, 133.4, 131.4, 130.7, 129.7, 128.8, 127.6, 125.2, 123.9, 81.6, 79.3, 43.9, 28.2, 21.7. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{21}H_{22}N_2O_5$: 382.1528; found: 382.1525.

2-Arylquinoline Derivatives 3; General Procedure 1

To a solution of Δ^2-isoxazoline derivative **1** (1.00 mmol, 1.0 equiv) in ethanol (7.0 mL) at 25 °C were added iron powder (8.00 mmol, 8.0 equiv), ammonium chloride (8.00 mmol, 8.0 equiv) and water (7.0 mL). The resulting suspension was stirred at 80 °C for 6 hours and monitored by TLC and LC-MS. The reaction mixture was allowed to cool to 25 °C, and filtered through a bed of Celite®. The filtrate was distilled under reduced pressure and the resulting aqueous phase was extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with water (5.0 mL) followed by brine (5.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product which was purified by column chromatography to yield pure **3**.

2-(4-Chloro-2-fluorophenyl)quinoline (3c)

White solid; yield: 206 mg (80%); mp 85–86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (s, 2 H), 8.20–8.25 (m, 7 H), 8.15 (s, 1 H), 8.13 (s, 2 H), 8.11 (s, 1 H), 7.86–7.90 (m, 9 H), 7.77 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 5 H), 7.59 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 5 H), 7.32–7.35 (m, 5 H), 7.27 (s, 6 H), 7.24 (d, *J* = 2.0 Hz, 2 H), 1.72 (br s, 7 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 161.8–159.3 (d, *J* = 254 Hz, 1 C), 132.5, 130.0, 129.5, 128.5, 127.5, 127.3, 127.0, 125.2, 124.3, 122.2, 122.1, 121.5, 117.2, 116.9. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_9ClFN$: 257.0407; found: 257.0401.

4-Chloro-3-(2-quinolyl)aniline (3i)

Off-white gum; yield: 188 mg (74%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18–8.23 (m, *J* = 8.5 Hz, 2 H), 7.86 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.69–7.78 (m, 2 H), 7.57 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1 H), 7.20–7.28 (m, 1 H), 7.02 (d, *J* = 3.0 Hz, 1 H), 6.68 (dd, *J* = 8.5, 2.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 157.5, 147.6, 145.6, 139.6, 136.0, 130.8, 129.9, 129.3, 127.6, 127.2, 126.9, 123.0, 121.2, 118.0, 116.9. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_{11}ClN_2$: 254.0610; found: 254.0611.

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(32) **2-Arylquinoline Derivatives 3; General Procedure 2**

To a solution of 2′-nitroaryl-Δ^2-isoxazoline **1** (1.00 mmol, 1.0 equiv) in DMSO (7.0 mL) was added sodium dithionite (6.00 mmol, 6.0 equiv) at r.t. The suspension was warmed to 100 °C and stirred for 3–5 h. The reaction was monitored by TLC and LC-MS and, after complete conversion, the reaction mixture was cooled to 25 °C. The reaction mixture was poured into an icecold solution of sodium hydroxide and stirred for 10 min. The aqueous phase was extracted with diethyl ether (3 × 10.0 mL) and the combined organic layers were washed with water (10.0 mL) followed by brine (10.0 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give the crude product which was purified by flash chromatography.

2-(2,4,6-Trifluorophenyl)quinoline (3l)

White solid; yield: 137 mg (53%); mp 97–98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (d, *J* = 8.2 Hz, 1 H), 8.19 (d, *J* = 8.2 Hz, 1 H), 7.88 (d, *J* = 8.3 Hz, 1 H), 7.77 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 8.5 Hz, 1 H), 6.83 (t, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 164.1–159.5 (m, 3 C), 149.1, 148.2, 136.5, 130.0, 129.7, 127.6, 127.3, 127.1, 123.2, 101.0–100.4 (m, 2 C). HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_8F_3N$: 259.0608; found: 259.0608.