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Radical Rearrangement of Aryl/Alkylidene Malononitriles *via* Aza Michael Addition/Decynoformylation/Addition Sequence: An Access to α-Aminonitriles and α-Aminoamides

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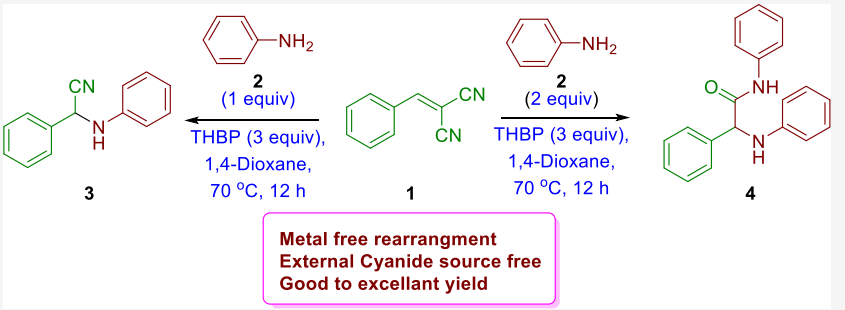

ABSTRACT: An efficient, safe, and environmentally friendly tertiary butyl hydrogen peroxide (TBHP)-mediated rearrangement of aryl/alkylidene malononitrile with anilines has been developed with *in situ* generation of HCN as the cyanide source for the synthesis of substituted α-aminonitriles and α-aminoamide. A diverse set of α-aminonitriles and α-aminoamides was efficiently synthesized in good to excellent yields. This method features a broad substrate scope and good functional group tolerance, and the *in situ*-generated HCN bypasses the use of an external cyanide source.

INTRODUCTION

α-Aminonitriles are important precursors for the synthesis of natural and unnatural amino acids,[1a,b] biologically active drug molecules such as saframycin A[1c] and phthalascidin,[1d] nitrogen-containing heterocycles,[2] amino alcoholss,[3] and pharmaceutical intermediates.[4] The α-amino amide and their analogues have gained attention because of their importance in pharmaceutical compounds (*e.g.*, ampicillin, cefachlor, and teneligliptin) and utility in natural product synthesis such as vancomycin and related glycopeptides (Figure 1).[5] In 1850, Adolph Strecker, for the first time, described the synthesis of α-aminonitriles in his popular three-component reaction of aldehydes, amines, and hydrogen cyanide.[6] Over the succeeding decades, significant modifications have been reported using different cyanide sources such as TMSCN,[7a] Et_2AlCN,[7b] ethyl cyanoformate,[7c] acetone cyanohydrin,[7d] and Bu_3SnCN[7e] under various reaction conditions. Additionally, various catalysts such as $La(O\text{-}iPr)_3$,[8a] $InCl_3$,[8b] $BiCl_3$,[8c] $NiCl_2$,[8d] $RuCl_3$,[8e] $Cu(OTf)_2$,[8f] sulfonium salts,[8g] indium MOF,[8h] MCM-41 mesoporous silica,[8i] chitosan-(biopolymer catalyst),[8j] organocatalysts,[9] Lewis bases such as Et_3N,[8f] and even montmorillonite KSF_6[7a] and iodine[10] were successfully used for the synthesis of α-aminonitriles (Scheme 1). Recently, the catalytic enantioselective Strecker reaction (cyanation of imines) has been established for the asymmetric synthesis of α-aminonitriles.[11] In previous decades, few methods were reported for the synthesis of α-aminoamides through tantalum−imine complexes with isocyanates,[12a] from disulfonyloxiranes,[12b] with arylboronic acid *via* imino amides.[12c]

However, most of these transformations over-relied on the use of different cyanide sources and metal catalysts. These traditional methods require toxic reagents and unavoidable generation of toxic byproducts. In contrast, environmentally

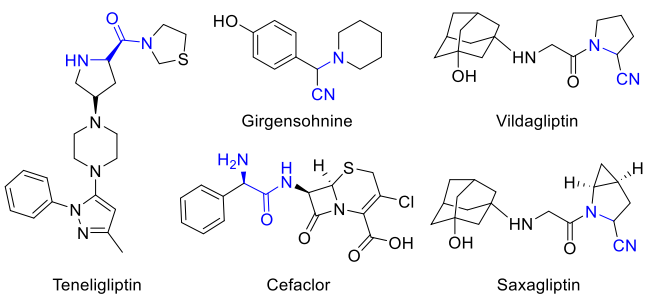

Figure 1. Natural products having α-aminonitriles and α-aminoamides.

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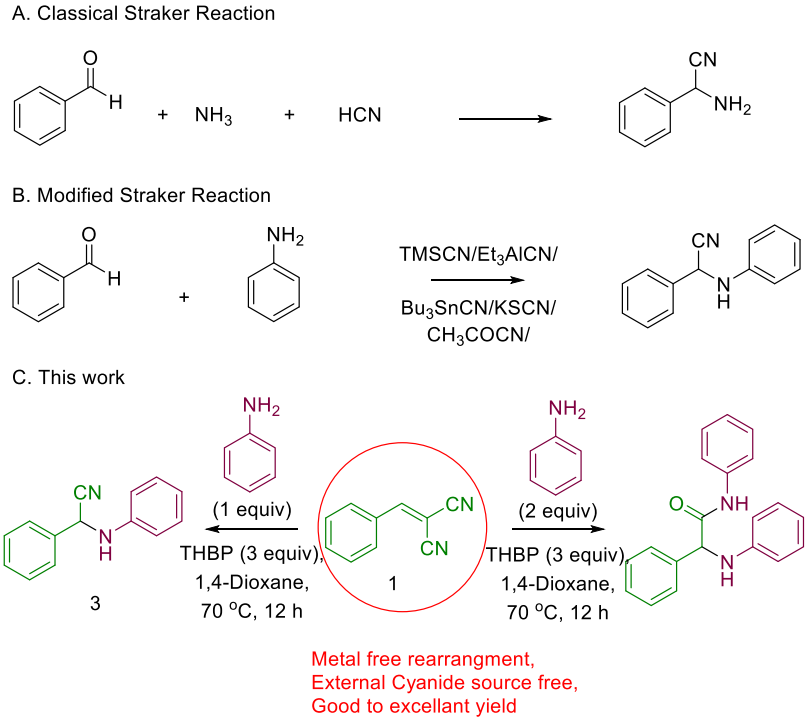
Scheme 1. Strategies for the Synthesis of α-Aminonitriles



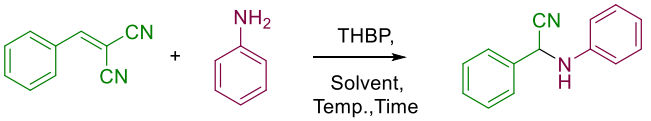
benign, safe, efficient, and metal-free methods using simple and safe reagents are desirable and need to be developed.

In our previous report, we have shown the efficient synthesis[13] of aryl/alkylidene malononitrile and its further use as a diene for cycloaddition reaction[14] and for the synthesis of 2-cyanoacrylamides and 3-substituted azetidine-2,4-diones.[15] These findings prompted us to investigate the further applicability of the aryl/alkylidene malononitrile to the synthesis of substituted α-aminonitriles. Continuing with our efforts toward the development of metal-free methodologies,[16] herein, we have developed TBHP-mediated rearrangement of aryl/alkylidene malononitrile for the synthesis of α-aminonitriles and α-aminoamide.

RESULTS AND DISCUSSION

We began with optimization using 2-benzylidene malononitrile **1a**, tertiary butyl hydrogen peroxide (TBHP, 5−6 M in decane), and anilines as a nucleophile. When 2-benzylidene malononitrile (**1a**, 1 equiv) as the substrate, aniline (**2a**), TBHP (2 equiv), and DMF as a solvent were heated for 12 h at 100 °C, however, the product **3a** was obtained only in a trace amount (Table 1, entry 1). An expected product was obtained in 32 and 41% yield with the change in solvent and temperature (Table 1, entries 2, 3). Significant improvement up to 68% yield of α-aminonitriles was observed when the toluene was replaced with 1,4-dioxane and TBHP (2 equiv) and heated at 70 °C for 12 h. The yield of a product further improved to 86% with 3 equivalents of TBHP in 1,4-dioxane at 70 °C for 12 h (Table 1, entry 4). However, the α-aminonitriles were obtained up to 86% yield, even after an intensive screening of reaction conditions such as variation in equivalents of the oxidant, time, and different polar solvents such as acetonitrile, DMF, and THF (Table 1, entries 5−10). Surprisingly, when the reaction was carried out between 1 equiv arylidene malononitrile (**1**) and 2 equivalents of aniline (**2**) under the optimized reaction conditions for α-aminonitriles, we observed the formation of α-aminonitriles (**3**) in a trace amount and α-aminoamide (**4**) as a major product (Table 1, entry 11).

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	oxidant (equiv)	solvent	time (h)	temp. (°C)	yield[b] (%)
1	TBHP (2.0)	DMF	12	100	trace
2	TBHP (2.0)	toluene	12	100	32
2	TBHP (2.0)	toluene	12	70	41
3	TBHP (2.0)	1,4-dioxane	12	70	68
4	TBHP (3.0)	1,4-dioxane	12	70	86
5	TBHP (4.0)	1 4-dioxane	12	70	83
6	TBHP (3.0)	1,4-dioxane	24	70	58
7	TBHP (3.0)	THF	12	70	NR
8	TBHP (3.0)	MeCN	12	70	NR
9	DTBP (3.0)	1,4-dioxane	12	70	NR
10	H_2O_2 (3.0)	1,4-dioxane	12	70	NR
11[c]	TBHP (3.0)	1,4-dioxane	12	70	trace[d]

[a]Reaction condition: **1a** (1 equiv), **2a** (1 equiv), and TBHP (3 equiv) in 1,4-dioxane at 70 °C in an oil bath for 12 h. [b]Isolated yields, NR: No reaction. [c]2 equiv of aniline (**1**). [d]α-aminoamide (**4**) major product.

Having optimized the reaction conditions in hand, scope and limitation of aryl/alkylidene malononitriles and aniline were investigated, as shown in Scheme 2. Generally, electron-donating and -withdrawing group substitutions on aryl/alkylidene malononitriles moieties effect reaction efficiency. Similarly, the reaction was sensitive for electronic properties of the substitution on anilines. The substrates having donating substitution on aryl/alkylidene malononitriles offered α-aminonitriles (**3f−g**, **3i−j**, and **3l**, 76−84%) in good to excellent yield and withdrawing substitution on arylidene malononitriles offered α-aminonitriles (**3h**, and **3k**, 69−73%) in moderate to

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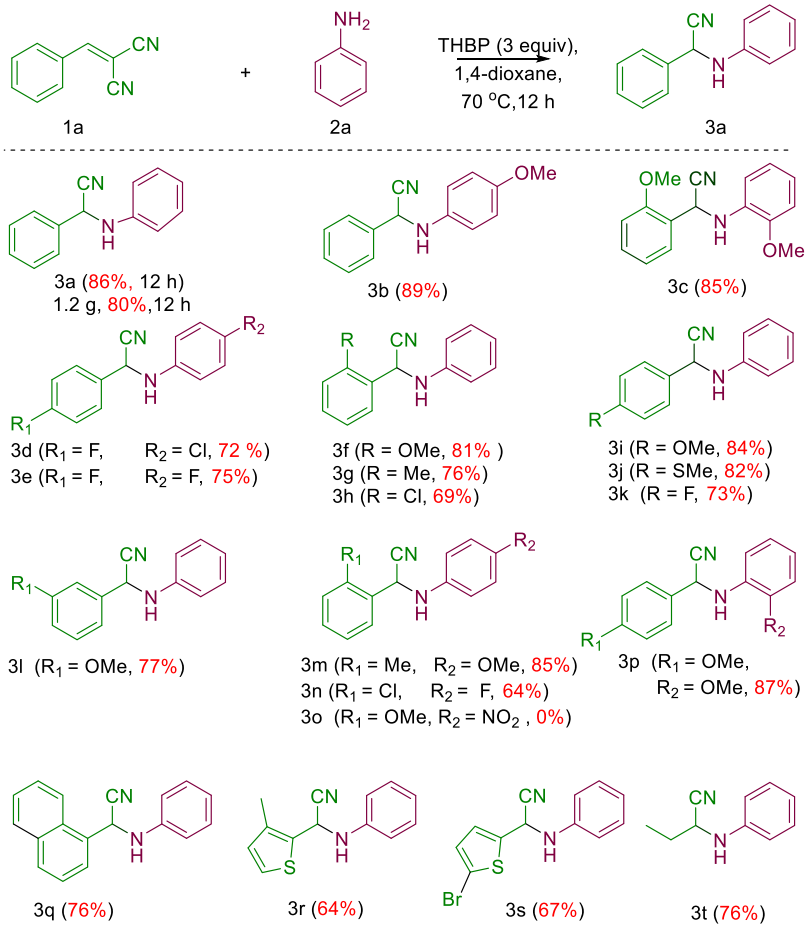
Scheme 2. Substrate Scope for α-Aminonitriles[a]



[a]Reaction condition: **1a** (1 equiv), **2a** (1 equiv), and TBHP (3 equiv, 5−6 M in decane) in 1,4-dioxane at 70 °C in an oil bath for 12 h.

good yield. Notably, the α-aminonitriles (**3b**, 89%) were obtained in excellent yield, when electron-rich anilines were used. As substrates bearing both electron-donating groups (**3c**, **3m**, and **3p**, 85−87%) and electron-withdrawing groups (**3d−e** and **3n**, 64−75%), without substitution on arylidene malononitriles and aniline, gave desired product **3a** in 86% yield in millimolar scale and 1.2 gm, 80% yield in gram-scale synthesis. It is noteworthy to mention that sterically hindered substrates with the substitution at ortho position underwent radical rearrangement very smoothly and gave the desired product α-aminonitriles in good yields (**3c**, **3m−n**, and **3p−q**). The nitro-substituted aniline with substituted arylidene malononitriles was unable to give the desired product (**3o**, 0%) under the optimized reaction condition. After successful screening of arylidene malononitriles, for the scope of the reaction to be developed, various heterocyclic arylidene malononitriles were also investigated for synthesis of heterocyclic α-aminonitriles, and the results are summarized in Scheme 2. To our delight, the optimized reaction condition works well with heterocyclic and alkylidene malononitriles and furnished heterocyclic (**3r−s**) and aliphatic α-aminonitriles (**3t**) in good to excellent yield of the product. Fortunately, some arylidene malononitriles also favored the optimized reaction condition (Table 1, entry 10) and afforded the corresponding α-aminoamide products in good yields (**4a−e**, Scheme 3). The nitro-substituted arylidene malononitrile with *p*-toluidine (2 equiv) was unable to give the desired product (**4f**, Scheme 3) under the optimized reaction condition.

Based on the previously reported reactions,[17] a plausible reaction mechanism was proposed for synthesis of α-aminonitriles (**3**) (Scheme 4). First, the reaction was initiated with 1,4-addition of aniline on arylidene malononitrile to form intermediate **I**. Under heating conditions, homolytic cleavage of TBHP generates the tertiary butoxide radical. Tertiary butoxide radical species then abstract a hydrogen from the α-position of dicyanide to generate radical intermediates **II**, which preferentially react with the tertiary butyl peroxide radical (formed from 2 mol of TBHP), leading to the intermediate **III**.[17a] The tertiary butyl peroxide intermediate **III** was reduced to cyanohydrin intermediate **IV**. Subsequently, the elimination of hydrogen cyanide from cyanohydrin intermediate **IV** formed aryl amino acetyl-cyanide intermediate **V**. As reported, elimination of formyl cyanide from intermediate **V** generated imine intermediate **VI** (confirmed by NMR). Finally, the addition of HCN across imine gave the desired product α-aminonitriles (**3**). Possibly, α-aminoamide (**4**) could be formed from reaction of excess aniline (**1**) with the nitrile group of α-aminonitriles (**3**) through intermediate **VIII**. The homolytic cleavage of 3 mol of TBHP will generate 2 mol of hydroxy radicals. Subsequently, these hydroxy radicals quenched with 1,4-dioxane (used as a solvent) formed intermediates S_1 and S_2.[17c]

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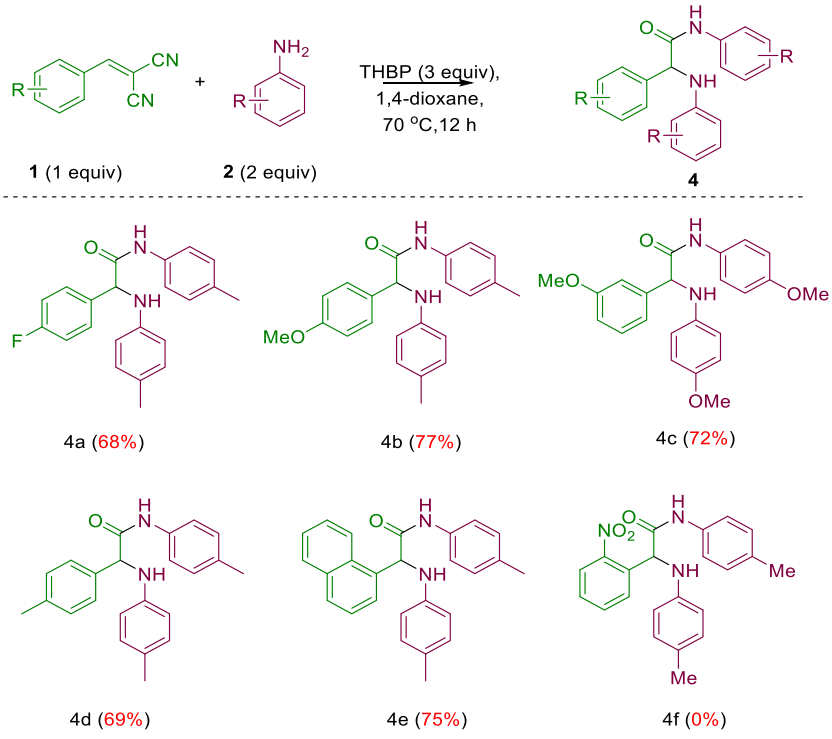
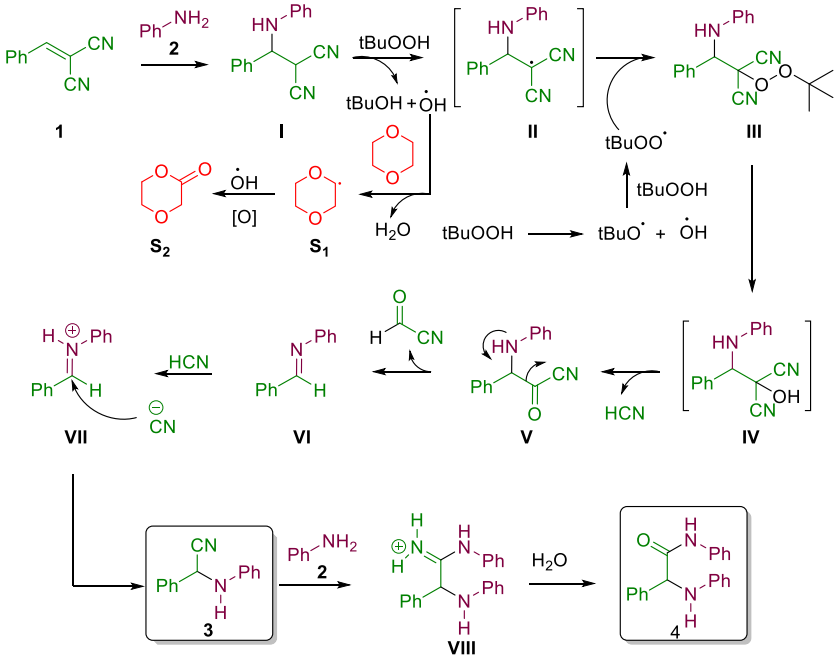
Scheme 3. Substrate Scope for α-Aminoamide[a]



[a]Reaction condition: **1** (1 equiv), **2** (2 equiv), and TBHP (3 equiv, 5−6 M in decane) in 1,4-dioxane at 70 °C in an oil bath for 12 h.

Scheme 4. Plausible Reaction Mechanism



CONCLUSIONS

We have developed a safe, efficient, metal-free, and external cyanide source-free method for synthesis of substituted α-aminonitriles (**3**) and α-aminoamide (**4**) in good to excellent yields from the simple starting material. The simple starting material, without the use of any cyanide source, inexpensive reagents, high yields, good functional group tolerance, and the value of products, makes this protocol useful for organic synthesis and medicinal chemistry as well.

EXPERIMENTAL SECTION

General Procedure. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker advance 500 (^{1}H:500 MHz, ^{13}C:125 MHz) or Bruker advance 400 (^{1}H:400 MHz, ^{13}C:100 MHz) or Bruker advance 200 (^{1}H:200 MHz, ^{13}C:50 MHz) unless otherwise mentioned. Spectrometers used $CDCl_3$ with the residual undeuterated solvent

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($CDCl_3$, 7s.26/77.00) as an internal standard. Deuterated solvent $CDCl_3$ + CCl_4 (70:30) was also used as an internal standard, and the singlet at 96.1 ppm in $^{13}C\{^1H\}$ NMR corresponds to carbon of CCl_4. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiple, and br = broad. Chemical shifts are reported in ppm and referenced to the residual solvent peak or TMS. Coupling constants are reported in Hertz. High-resolution mass spectra (HRMS) for all compounds were recorded using an ESI^+ method and Orbitrap mass analyzer (Thermo Scientific Q-Exactive, Accela 1250 pump).

General Procedure for Synthesis of Aryl/Alkylidene Malononitrile (1). To a solution of benzaldehyde (1 equiv) and malononitrile (1.5 equiv) in CH_2Cl_2 (15 mL) was added K_2CO_3 (0.5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of reaction (monitored by TLC), the solvent was evaporated under reduced pressure. The crude was quenched with ice cold water and extracted with EtOAc (10 mL* 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography using 100−200 mesh silica gel, and 10% ethyl acetate in petroleum ether as an eluting solvent offered cyanoacrylates.

General Procedure for Synthesis of α-Amino Nitrile (3). The substituted aryl/alkylidene malononitrile (1 equiv), substituted aniline (1 equiv), and tertiary butyl hydrogen peroxide (3 equiv, 5−6 M in decane) were added in 1,4-dioxane as a solvent (1 mL). The reaction mixture was stirred to heat and reflux at 70 °C in an oil bath for 12 h. After completion of reaction (monitored by TLC), crude was quenched with ice cold water and extracted with EtOAc (10 mL* 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography using 100−200 mesh silica gel, and 5% ethyl acetate in petroleum ether as an eluting solvent offered α-amino nitrile.

General Procedure for Synthesis of α-Amino Acetamide (4). The substituted aryl/alkylidene malononitrile (1 equiv), substituted aniline (2 equiv), and tertiary butyl hydrogen peroxide (3 equiv, 5−6 M in decane) were added in 1,4-dioxane as a solvent (1 mL). The reaction mixture was stirred to heat and reflux at 70 °C in an oil bath for 12 h. After completion of reaction (monitored by TLC), the crude was quenched with ice cold water and extracted with EtOAc (10 mL* 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography using 100−200 mesh silica gel, and 5% ethyl acetate in petroleum ether as an eluting solvent offered α-aminoamide.

Procedure for Gram-Scale Synthesis of 2-Phenyl-2-(phenylamino) Acetonitrile (3a). 2-Benzylidenemalononitrile (1.11 gm, 7.2 mmol), aniline (0.67 gm, 7.2 mmol), and TBHP (4.3 mL, 21.6 mmol, 5−6 M in decane) were added in 1,4-dioxane (10 mL) as a solvent. The reaction mixture was stirred to heat and reflux at 70 °C in an oil bath for 12 h. After completion of reaction (monitored by TLC), crude was quenched with ice cold water and extracted with EtOAc (30 mL* 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography using 100−200 mesh silica gel, and 5% ethyl acetate in petroleum ether as an eluting solvent offered 2-phenyl-2-(phenylamino) acetonitrile (**3a**) (1.2 gm, 80% yield) as a yellow solid.

*2-Phenyl-2-(phenylamino)acetonitrile (**3a**).*[18a] Yield: 110 mg, 86% and 1.2 g, 80%; yellow solid; mp 80−82 °C; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.77−7.62 (m, 2H), 7.61−7.47 (m, 3H), 7.43−7.29 (m, 2H), 7.05−6.93 (m, 1H), 6.85 (d, J = 7.7 Hz, 2H), 5.51 (d, J = 8.0 Hz, 1H), 4.09 (d, J = 7.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$ + CCl_4): δ 144.7, 134.1, 129.6, 129.6, 129.4, 127.3, 120.4, 118.0, 114.2, 50.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{13}N_2$, 209.1073; found, 209.1075.

*2-((4-Methoxyphenyl) amino)-2-phenylacetonitrile (**3b**).*[18a] Yield: 92 mg, 89%; yellow solid; mp 63−65 °C; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.43−7.55 (m, 2H), 7.30 (s, 1H), 7.22 (s, 1H), 6.87−6.99 (m, 3H), 6.69−6.80 (m, 2H), 5.34 (d, J = 8.2 Hz, 1H), 3.90−4.01 (1H, m), 3.83 (3H, s); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$ + CCl_4): δ 160.5, 144.8, 133.4, 129.6, 128.6, 126.1, 120.3, 114.7, 114.2, 55.3, 49.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}ON_2$, 239.1179; found, 239.1180.

*2-(2-Methoxyphenyl)-2-((2-methoxyphenyl)amino) Acetonitrile (**3c**).* Yield: 73 mg, 85%; yellow solid; mp 94−96 °C; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.55 (dd, J = 7.5, 1.6 Hz, 1H), 7.40 (td, J = 7.9, 1.6 Hz, 1H), 7.02−7.09 (m, 1H), 6.88−7.01 (m, 2H), 6.76−6.86 (m, 3H), 5.62 (d, J = 5.9 Hz, 1H), 4.82 (d, J = 8.4 Hz, 1H) 3.93 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$ + CCl_4): δ 156.8, 147.6, 134.9, 130.8, 128.7, 122.8, 121.3, 121.2, 119.3, 118.5, 111.8, 111.3, 110.0, 55.7, 55.5, 45.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}O_2N_2$ 269.1285; found, 269.1284.

*2-((4-Chlorophenyl)amino)-2-(4-fluorophenyl) Acetonitrile (**3d**).*[7a] Yield: 25 mg, 72%; yellow solid; mp 95−97 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.59 (dd, J = 8.8, 5.0 Hz, 2H), 7.21−7.28 (m, 2H), 7.14−7.19 (m, 2H), 6.69−6.73 (m, 2H), 5.39 (d, J = 7.6 Hz, 1H), 4.08 (d, J = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 164.6, 162.2, 143.1, 129.6, 129.4, 129.4, 129.3, 129.2, 125.5, 117.8, 116.7, 116.4, 115.6, 49.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{11}N_2ClF$, 261.0589; found, 261.0589.

*2-(4-Fluorophenyl)-2-((4-fluorophenyl) Amino) Acetonitrile (**3e**).*[18d] Yield: 51 mg, 75%; white solid; mp 116−118 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.51−7.66 (m, 2H), 7.17 (t, J = 8.4 Hz, 2H), 6.92−7.04 (m, 2H), 6.71−6.78 (m, 2H), 5.36 (d, J = 8.4 Hz, 1H), 3.94 (d, J = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 164.2, 161.7, 158.4, 156.0, 140.4, 129.3, 128.8, 117.6, 116.2, 116.0, 116.0, 115.8, 115.6, 115.5, 50.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{11}N_2F_2$, 245.0885; found, 245.0885.

*2-(2-Methoxyphenyl)-2-(phenylamino) Acetonitrile (**3f**).*[18b] Yield: 74 mg, 81%; yellow gummy oil; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.49 (dd, J = 1.6, 7.6 Hz, 1H), 7.44−7.32 (m, 1H), 7.29−7.19 (m, 2H), 7.07−7.00 (m, 1H), 7.00−6.93 (m, 1H), 6.91−6.80 (m, 1H), 6.79−6.72 (m, 2H), 5.55 (br s, 1H), 4.35−4.17 (m, 1H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$ + CCl_4): δ 156.7, 145.0, 130.9, 129.4, 128.8, 122.6, 121.2, 120.0, 118.4, 114.3, 111.4, 55.7, 45.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}ON_2$, 239.1179; found, 239.1177.

*2-(Phenylamino)-2-(o-tolyl) Acetonitrile (**3g**).*[18f] Yield: 34 mg, 76%; yellow solid; mp 107−109 °C; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.73 (d, J = 7.2 Hz, 1H), 7.40−7.33 (m, 2H), 7.33−7.27 (m, 3H), 6.92 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 8.0 Hz, 2H), 5.49 (d, J = 8.0 Hz, 1H), 3.86 (d, J = 8.0 Hz, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$ + CCl_4): δ 144.8, 136.4, 132.2, 131.3, 129.7, 129.6, 127.6, 127.0, 120.2, 118.2, 113.9, 48.1, 18.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}N_2$, 223.1230; found, 223.1230.

*2-(2-Chlorophenyl)-2-(phenylamino)acetonitrile (**3h**).*[18b] Yield: 57 mg, 69%; yellow solid; mp 67−70 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70−7.80 (m, 1H), 7.45−7.55 (m, 1H), 7.36−7.45 (m, 2H), 7.24−7.36 (m, 2H), 6.93 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.6 Hz, 2H), 5.75 (d, J = 8.4 Hz, 1H), 4.09 (d, J = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.5, 133.5, 131.7, 131.0, 130.4, 129.5, 129.0, 127.8, 120.4, 117.7, 114.2, 48.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{12}N_2Cl$, 243.0684; found, 243.0686.

*2-(4-Methoxyphenyl)-2-(phenylamino)acetonitrile (**3i**).*[18a] Yield: 45 mg, 84%; yellow Solid: 94−95 °C; ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.52 (d, J = 8.5 Hz, 2H), 7.33−7.28 (m, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.95−6.87 (m, 1H), 6.79 (d, J = 7.9 Hz, 2H), 5.38 (d, J = 7.9 Hz, 1H), 3.97 (d, J = 7.3 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$ + CCl_4): δ 160.5, 144.8, 133.4, 129.6, 128.6, 126.1, 120.3, 118.3, 115.2, 114.7, 114.2, 55.3, 49.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}N_2O$, 239.1179; found, 239.1181.

*2-(4-(Methylthio)phenyl)-2-(phenylamino) Acetonitrile (**3j**).* Yield: 84 mg, 82%; yellow solid; mp 104−105 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.2 Hz, 2H), 7.28−7.31 (m, 1H), 7.28 (s, 1H), 7.22−7.26 (m, 2H), 6.86−6.92 (m, 1H), 6.75 (dd, J = 8.7, 0.9 Hz, 2H), 5.37 (d, J = 8.2 Hz, 1H), 3.99 (d, J = 8.2 Hz, 1H), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.6, 140.8, 130.3, 129.6, 127.6, 126.7,

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120.3, 118.1, 114.2, 49.8, 15.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{15}N_2S$, 255.0950; found, 255.0950.

*2-(4-Fluorophenyl)-2-(phenylamino) Acetonitrile (**3k**).*[18a] Yield: 50 mg, 73%; yellow solid; mp 108−110 °C; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.68−7.57 (m, 2H), 7.48 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.34−7.28 (m, 1H), 7.26−7.18 (m, 1H), 6.97−6.85 (m, 1H), 6.78 (d, J = 7.6 Hz, 2H), 5.44 (d, J = 8.3 Hz, 1H), 4.01 (d, J = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 160.6, 144.7, 134.1, 129.6, 129.4, 127.3, 120.4, 114.2, 50.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}N_2F$, 227.0979; found, 227.0978.

*2-(3-Methoxyphenyl)-2-(phenylamino)acetonitrile (**3l**).*[18e] Yield: 55 mg, 77%; yellow solid; mp 95−96 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33−7.39 (m, 1H), 7.22−7.30 (m, 2H), 7.07−7.21 (m, 2H), 6.85−7.01 (m, 2H), 6.77 (d, J = 9.2 Hz, 2H), 5.39 (d, J = 8.4 Hz, 1H), 4.08 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ 159.9, 144.3, 135.0, 130.0, 129.2, 120.0, 119.0, 117.8, 113.7, 114.7, 112.4, 55.1, 49.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{15}ON_2$, 239.1179; found, 239.1178.

*2-((4-Methoxyphenyl)amino)-2-(o-tolyl) Acetonitrile (**3m**).* Yield: 74 mg, 85%; yellow solid; mp 102−105 °C; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.66−7.74 (m, 1H), 7.30−7.37 (m, 2H), 7.27 (d, J = 4.9 Hz, 2H), 6.82−6.92 (m, 2H), 6.73−6.82 (m, 2H), 5.40 (br s, 1H), 3.79 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 154.2, 138.8, 136.5, 132.4, 131.3, 129.7, 127.6, 126.9, 116.0, 115.1, 55.6, 49.5, 18.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}ON_2$, 253.1335; found, 253.1335.

*2-(2-Chlorophenyl)-2-((4-fluorophenyl) amino) Acetonitrile (**3n**).*[18g] Yield: 50 mg, 64%; yellow solid; mp 97−98 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71−7.76 (m, 1H), 7.47−7.52 (m, 1H), 7.39−7.44 (m, 2H), 7.22−7.27 (m, 1H), 7.11 (t, J = 8.8 Hz, 1H), 6.97−7.01 (m, 1H), 6.76−6.79 (m, 1H), 5.66 (d, J = 8.4 Hz, 1H), 3.95 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ 156.7, 140.8, 133.5, 131.5, 131.1, 130.5, 129.0, 127.8, 116.3, 116.0, 116.0, 49.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2ClF$, 261.0589; found, 261.0587.

*2-(4-Methoxyphenyl)-2-((2-methoxyphenyl) amino) Acetonitrile (**3p**).* Yield: 34 mg, 87%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.55 (dd, J = 7.6, 1.4 Hz, 1H), 7.35−7.47 (m, 1H), 7.03−7.11 (m, 1H), 6.89−7.03 (m, 2H), 6.76−6.87 (m, 3H), 5.63 (d, J = 6.4 Hz, 1H), 4.82 (br s, 1H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 156.8, 147.9, 134.9, 130.8, 128.7, 122.8, 121.3, 121.2, 119.3, 118.5, 111.8, 111.3, 110.0, 55.8, 55.5, 45.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2$, 269.1285; found, 269.1285.

*2-(Naphthalen-1-yl)-2-(phenylamino)acetonitrile (**3q**).*[18c] Yield: 24 mg, 76%; gummy oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 4H), 7.46−7.74 (m, 4H), 7.35 (t, J = 7.8 Hz, 2H), 6.77−7.11 (m, 3H), 6.05 (d, J = 7.7 Hz, 1H), 4.09 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.8, 134.0, 130.7, 129.7, 129.1, 127.5, 126.6, 126.3, 125.3, 122.8, 120.2, 113.7 48.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2$, 259.1230; found, 259.1229.

*2-(3-Methylthiophen-2-yl)-2-(phenylamino)acetonitrile (**3r**).* Yield: 80 mg, 64%; brown solid; mp 96−98 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21−7.30 (m, 3H), 6.92 (d, J = 7.4 Hz, 1H), 6.88 (d, J = 5.3 Hz, 1H), 6.79 (s, 1H), 6.75 (s, 1H), 5.52 (d, J = 7.5 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.4, 136.8, 130.9, 129.6, 125.0, 120.4, 115.1, 114.2, 44.2, 13.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_2S$, 229.0794; found, 229.0795.

*2-(5-Bromothiophen-2-yl)-2-(phenylamino)acetonitrile (**3s**).* Yield: 65 mg, 67%; brown oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27−7.34 (m, 2H), 7.15 (d, J = 3.1 Hz, 1H), 7.02 (d, J = 3.8 Hz, 1H), 6.80 (d, J = 7.6 Hz, 2H), 5.58 (d, J = 7.5 Hz, 1H), 4.22 (d, J = 9.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.0, 143.8, 138.2, 129.9, 129.6, 129.1, 127.3, 121.2, 114.8, 46.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}N_2BrS$, 292.9743; found, 292.9740.

*2-(Phenylamino) Butane Nitrile (**3t**).*[18a] Yield: 65 mg, 76%; brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.2−7.3 (m, 2H), 6.9 (tt, J = 7.4, 1.1 Hz, 1H), 6.7−6.7 (m, 2H), 4.1−4.2 (m, 1H), 3.8 (d, J = 8.9 Hz, 1H), 1.9−2.0 (m, 2H), 1.2 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 129.5, 119.9, 119.4, 114.0, 47.3, 26.9, 10.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{13}N_2$ 161.1073; found, 161.1072.

*2-(4-Fluorophenyl)-N-(p-tolyl)-2-(p-tolylamino) Acetamide (**4a**).* Yield: 55 mg, 68%; gummy liquid; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 8.8 (s, 1H), 7.4−7.5 (m, 4H), 7.0−7.1 (m, 6H), 6.6 (d, J = 8.3 Hz 2H), 4.8 (s, 1H), 4.3 (br s, 1H), 2.3 (s, 3H), 2.3 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 169.2, 144.0, 135.3, 134.7, 134.2, 130.0, 129.6, 129.5, 129.4, 129.3, 129.1, 120.4, 120.0, 116.4, 116.0, 115.5, 114.2, 64.9, 20.9, 20.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}ON_2F$, 349.1711; found, 349.1714.

*2-(4-Methoxyphenyl)-N-(p-tolyl)-2-(p-tolylamino) Acetamide (**4b**).* Yield: 64 mg, 77%; gummy liquid; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 8.8 (s, 1H), 7.4−7.5 (m, 4H), 7.0−7.2 (m, 4H), 6.9−7.0 (m, 2H), 6.6 (d, J = 8.1 Hz, 2H), 4.7 (s, 1H), 4.3 (br s, 1H), 3.8 (s, 3H), 2.3 (s, 3H), 2.3 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 169.2, 159.1, 143.6, 134.2, 133.5, 130.1, 129.3, 128.8, 128.4, 128.0, 119.3, 113.9, 113.5, 64.4, 54.6, 20.2, 19.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}O_2N_2$, 361.1911; found, 361.1922.

*2-(3-Methoxyphenyl)-N-(4-methoxyphenyl)-2-((4-methoxyphenyl) Amino) Acetamide (**4c**).* Yield: 150 mg, 72%; dark brown oil; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.3−7.5 (m, 2H), 7.1−7.2 (m, 2H), 6.9−7.0 (m, 2H), 6.8−6.9 (m, 2H), 6.7−6.8 (m, 3H), 6.6−6.7 (m, 1H), 5.3 (br s, 1H), 3.9 (d, J = 3.1 Hz, 1H), 3.8 (s, 3H), 3.8 (s, 3H), 3.7 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 160.2, 154.1, 152.8, 139.8, 138.5, 135.5, 130.3, 119.3, 116.5, 116.3, 116.2, 115.1, 115.0, 114.8, 112.7, 55.7, 55.6, 55.4, 51.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}O_4N_2$, 393.1809; found, 393.1802.

*N,2-Di-p-tolyl-2-(p-tolylamino) Acetamide (**4d**).* Yield: 63 mg, 69%; gummy liquid; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 8.7 (s, 1H), 7.4 (t, J = 8.0 Hz, 4H), 7.0−7.2 (m, 2H), 6.6 (d, J = 8.2 Hz, 2H), 4.7 (s, 1H), 4.3 (br s, 1H), 2.4 (s, 3H), 2.3 (s, 3H), 2.3 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + CCl_4): δ 169.5, 144.3, 138.4, 135.8, 134.9, 134.0, 130.0, 129.4, 129.0, 127.3, 127.1, 120.2, 119.9, 114.2, 65.4, 21.2, 20.9, 20.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}ON_2$, 345.1961; found, 345.1965.

*2-(Naphthalen-1-yl)-N-(p-tolyl)-2-(p-tolylamino)acetamide (**4e**).* Yield: 26 mg, 75%; faint brown oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.1 (s, 1H), 7.9−8.0 (m, 3H), 7.5−7.6 (m, 6H), 7.1−7.2 (m, 4H), 6.7 (d, J = 8.3 Hz, 2H), 5.6 (s, 1H), 4.3 (br s, 1H), 2.3 (s, 3H), 2.3 (s, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ 169.5, 143.9, 133.9, 129.5, 128.9, 128.8, 128.5, 126.5, 125.5, 124.9, 124.5, 119.3, 113.5, 61.7, 20.2, 19.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{25}ON_2$, 381.1961; found, 381.1969.

Imine Intermediate (VI). Yield: 8 mg, White solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.90−7.94 (m, 2H), 7.50 (d, J = 2.0 Hz, 2H), 7.49 (d, J = 1.8 Hz, 1H), 7.38−7.44 (m, 2H), 7.20−7.26 (m, 3H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ 160.5, 152.0, 136.2, 131.4, 129.1, 128.8, 128.8, 125.9, 120.9.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01358.

^{1}H and ^{13}C spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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