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Sequential 1,3-Dipolar Cycloaddition of Nitrones to β-(2-Aminophenyl) α,β-Ynones and Cyclocondensation: A New Entry to the Isoxazolino[4,5-*c*]quinoline Ring

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The reaction of β-(2-aminophenyl) α,β-ynones with *N*-methyl nitrones provides a simple and efficient entry to the isoxazolino[4,5-*c*]quinoline ring system through a sequential 1,3-dipolar cycloaddition/annulation process.

Introduction

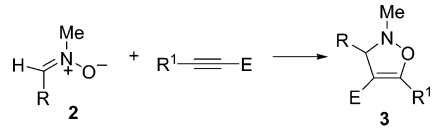
The development of one-pot transformations for building up target compounds is a challenge in organic synthesis. Performing more than one synthetic step in the same reaction vessel represents a useful tool for saving time and energy, as well as for reducing the use of organic solvents in the isolation and purification of intermediates. For these reasons, the development of new sequential reactions is by itself a considerable success en route to sustainable organic chemistry.

As part of our ongoing research activities in this field, we have investigated the sequential addition/annulation reactions of β-(2-aminophenyl) α,β-ynones **1**. These derivatives gave 2,4-disubstituted quinolines through sequential nucleophilic addition/annulation reactions[1] or sequential transition-metal-catalysed hydroarylation (hydrovinylation)/annulation processes.[2,3] Moreover, we reported that sequential [2+2] cycloaddition of cycloalkanone enamines with **1** followed by cyclocondensation afforded quinolines *cis*-fused to different-sized carbocyclic rings.[4] In a related process, the reactions of **1** with azides[1] or nitrile oxides[5] resulted in the formation of quinoline derivatives *cis*-fused to heteroaromatic triazole or isoxazole rings.

These synthetic methods can lead to the formation of polycyclic quinolines that are not otherwise easily available. We decided therefore to investigate the possibility of embedding a different pentatomic heterocyclic ring into the fused quinoline system.

Isoxazolines represent a current synthetic target[6–10] owing to their importance in medicinal chemistry. In particular, the isoxazoline nucleus represents a stable bioisosteric replacement for the amide bond, which is found in many biologically active molecules and drugs such as antibiotics.[11] On the other hand, the polycyclic quinoline ring system is also present in pharmacologically active substances.[5,12,13] Although there are various efficient procedures leading to isoxazolines, to the best of our knowledge the synthesis of isoxazolino[4,5-*c*]quinolines **4** has not been reported yet; only dehydrogenated analogues of **4**, namely isoxazolo[4,5-*c*]quinolines, have been synthesized.[5,14–16] Consequently, we focused our efforts on the development of a viable approach to the synthesis of **4**.

Nitrones are useful and versatile intermediates in organic synthesis; they behave as 1,3-dipoles in cycloaddition reactions[17] and are particularly suitable for the construction of structurally complex molecules such as nitrogen-containing biologically active compounds[18] and fused or bridged ring structures.[19] Alkynes undergo facile cycloaddition reactions with nitrones under thermal conditions to give isoxazolines and the regioselectivity is strongly affected by steric and electronic factors.[20] Monosubstituted electron-rich alkynes give 5-substituted 4-isoxazolines as the main products, whereas electron-poor monosubstituted alkynes show a strong tendency to afford 4-substituted 4-isoxazolines **3** with high regioselectivity (Scheme 1).[21] This is also the



Scheme 1.

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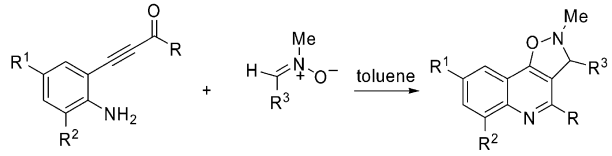
case for disubstituted alkynes such as ethyl phenylpropiolate. This inversion of regioselectivity has been rationalized by FMO theory.[22]

On the basis of this knowledge, we envisaged that the cycloaddition reaction of β-(2-aminophenyl) α,β-ynones **1** with nitrones **2** could represent a straightforward entry to polycyclic compounds **4** through a sequential one-pot protocol (see Scheme 2). Herein we report the results of this study.

Results and Discussion

The reaction between the α,β-ynone **1a** and the nitrone **2a** in toluene was chosen as a model system. As shown in Scheme 2, we observed the formation of the isoxazolino[4,5-*c*]quinoline **4a** as a single regioisomer. The effect of temperature and the amount of nitrone was briefly investigated. The use of 2 equiv. of **2a** at 110 °C is necessary to attain the best yields; a lower molar excess gave unsatisfactory results. The reaction can be also carried out at 80 °C by prolonging the reaction time but, at least in the model reaction, this resulted in lower efficiency.



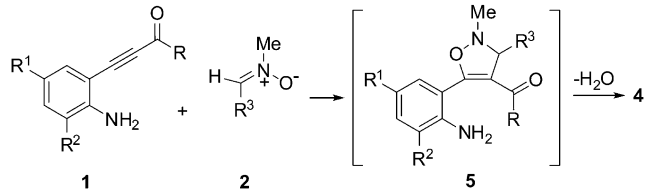
1a: R = 4-COMe-C_6H_4; $R^1 = R^2 = H$ **2a**: R^3 = *p*-tolyl **4a**

Equiv. of **2a**	*T* (°C)	Time (h)	Yield of **4a** (%)
1.3	110	3	50
2.0	110	3	78
2.0	80	24	67

Scheme 2.

The procedure was then extended to include different combinations of β-(2-aminophenyl) α,β-ynones **1a**–**g** and nitrones **2a**–**d**. The results are reported in Table 1.

The isoxazolino[4,5-*c*]quinolines **4** were isolated in moderate-to-high yields as single regioisomers. According to our previous studies,[1–5] the present process can be explained as depicted in Scheme 3: regioselective 1,3-dipolar cycloaddition of nitrones **2** to α,β-ynones **1** results in the formation of alkenes **5**, from which the quinoline nucleus is generated by condensation between the amino and carbonyl groups.



1 **2** **5**

Scheme 3.

Table 1. Synthesis of the isoxazolino[4,5-*c*]quinolines **4**.[a]

Entry	α,β-Ynone **1** R	R^1	R^2	Nitrone **2** R^3	Time [h]	Product **4**[b]	Yield (%)[c]
1	**1a**			**2b**	3	**4b**	81
2	**1a**			**2c**	3	**4c**	60
3	4-OMe-C_6H_4- **1b**	H	H	**2a**	24	**4d**	59
4	4-Cl-C_6H_4- **1c**	H	H	**2a**	7	**4e**	84
5	**1c**			**2d**	24	**4f**	43
6	**1c**			**2b**	4	**4g**	86
7	**1c**			**2c**	4	**4h**	58
8	3-CF_3-C_6H_4- **1d**	H	H	**2a**	8	**4i**	87
9	4-COOEt-C_6H_4- **1e**	H	H	**2a**	2	**4j**	50
10	4-CN-C_6H_4- **1f**	H	H	**2a**	2	**4k**	61
11	2-OMe-C_6H_4- **1g**	F	F	**2a**	5	**4l**	68

[a] Reactions were carried out on a 0.5 mmol scale in dry toluene (5 mL) with the molar ratio **1**/**2** = 1:2. [b] Racemic mixtures. [c] Isolated yields.

All compounds were identified on the basis of analytical and spectroscopic data, and proposed structures are in agreement with the experimental data of similar compounds reported in the literature. In particular, the regiochemistries of compounds **4a** and **4e** were unambiguously established by NOESY experiments and extended by analogy to the entire series. Diagnostic NOE interactions are shown in Figure 1.

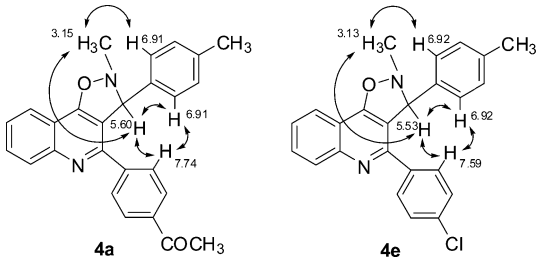


Figure 1. Diagnostic NOE interactions as well as significant proton chemical shifts for compounds **4a** and **4e**.

As shown in Table 1, the reaction tolerates various functional groups, such as the nitrile (entry 10), ester (entry 9) and keto (entries 1 and 2) groups; vinylic (entries 1, 2, 6 and 7) and heteroarylic (entry 5) substituents are also allowed on the isoxazoline moiety. Moreover the isoxazolino[4,5-*c*]-quinoline **4l**, substituted on the benzene ring of the quinoline, can also be obtained in good yield.

Conclusions

The results reported here prove that the sequential 1,3-dipolar cycloaddition/cyclocondensation reaction involving β-(2-aminophenyl) α,β-ynones **1** and *N*-methyl nitrones **2a**–**d** represents a simple and efficient entry to the isoxazolino[4,5-*c*]quinoline ring system. The procedure allows the easy assembly of a complex polycyclic structure by sequential double annulation starting from the easily available acyclic substrates. The reaction is also valuable in terms of "atom economy"[23] as the final product represents simply the sum of the reactants with the loss of a water molecule.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz in $CDCl_3$ with a Bruker AC 200 spectrometer. IR spectra were recorded with a Perkin–Elmer 683 spectrometer. Only the most significant IR absorptions are given. EI mass spectra were recorded with a Saturn 2000T GC/MS spectrometer. CHN analyses were performed with an Eager 200 analyser. The synthesis of β-(2-aminoaryl) α,β-ynones **1** has been described previously.[3] Compounds **1a**–**d** and **1g** have previously been characterized. Nitrones **2a**–**d** were obtained from *N*-methylhydroxylamine hydrochloride and the corresponding aldehydes following the procedure reported for the synthesis of *N*-(phenylmethylene)methanamine *N*-oxide.[24]

Ethyl 4-[3-(2-Aminophenyl)prop-2-ynoyl]benzoate (1e): M.p. 123–125 °C. ^{1}H NMR: δ = 8.26 (d, J = 8.6 Hz, 2 H), 8.17 (d, J = 8.6 Hz, 2 H), 7.48 (dd, J_1 = 1.6, J_2 = 8.4 Hz, 1 H), 7.31–7.22 (m, 1 H), 6.77–6.68 (m, 2 H), 4.60 (br. s, 2 H), 4.42 (q, J = 7.1 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 177.0, 165.7, 150.7, 140.0, 134.9, 133.9, 133.0, 129.8, 129.2, 118.0, 114.8, 103.4, 93.4, 92.5, 61.6, 14.3 ppm. IR (KBr): $\tilde{\nu}$ = 2150, 1730, 1640 cm^{-1}. MS (EI): *m*/*z* (%) = 293 (100) $[M]^+$. $C_{18}H_{15}NO_3$ (293.32): calcd. C 73.71, H 5.15, N 4.78; found C 73.47, H 5.13, N 4.80.

4-[3-(2-Aminophenyl)prop-2-ynoyl]benzonitrile (1f): M.p. 124–125 °C. ^{1}H NMR: δ = 8.29 (d, J = 8.3 Hz, 2 H), 7.82 (d, J = 8.3 Hz, 2 H), 7.48 (dd, J_1 = 1.3, J_2 = 8.1 Hz, 1 H), 7.34–7.25 (m, 1 H), 6.79–6.72 (m, 2 H), 4.55 (br. s, 2 H) ppm. ^{13}C NMR: δ = 175.9, 150.8, 139.9, 133.9, 133.3, 132.5, 129.7, 118.1, 117.9, 117.0, 114.9, 103.1, 93.5, 93.2 ppm.. IR (KBr): $\tilde{\nu}$ = 2200, 2150, 1630 cm^{-1}. MS (EI): *m*/*z* (%) = 246 (100) $[M]^+$. $C_{16}H_{10}N_2O$ (246.26): calcd. C 78.03, H 4.09, N 11.38; found C 78.29, H 4.09, N 11.34.

***N*-[(4-Methylphenyl)methylene]methanamine *N*-Oxide (2a):** M.p. 114–115 °C. ^{1}H NMR: δ = 8.11 (d, J = 8.2 Hz, 2 H), 7.32 (s, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 3.82 (s, 3 H), 2.36 (s, 3 H) ppm. ^{13}C NMR: δ = 140.8, 135.1, 129.1, 128.4, 127.9, 54.2, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 1590, 1410 cm^{-1}. MS (EI): *m*/*z* (%) = 149 (100) $[M]^+$. $C_9H_{11}NO$ (149.19): calcd. C 72.46, H 7.43, N 9.39; found C 72.58, H 7.42, N 9.40.

***N*-[(2*E*)-3-Phenylprop-2-enylidene]methanamine *N*-Oxide (2b):** M.p. 86–88 °C. ^{1}H NMR: δ = 7.51–7.21 (m, 7 H), 6.95 (d, J = 16.2 Hz, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR: δ = 137.7, 137.2, 135.8, 128.9, 128.6, 127.0, 118.1, 52.0 ppm. IR (KBr): $\tilde{\nu}$ = 1550, 1400 cm^{-1}. MS (EI): *m*/*z* (%) = 161 (100) $[M]^+$. $C_{10}H_{11}NO$ (161.20): calcd. C 74.51, H 6.88, N 8.69; found C 74.69, H 6.89, N 8.68.

***N*-[(2*E*)-3-(2-Furyl)prop-2-enylidene]methanamine *N*-Oxide (2c):** M.p. 128–129 °C. ^{1}H NMR: δ = 7.44 (s, 1 H), 7.23–7.17 (m, 2 H), 6.95–6.83 (m, 1 H), 6.50–6.43 (m, 2 H), 3.73 (s, 3 H) ppm. ^{13}C NMR: δ = 152.4, 143.7, 136.3, 124.0, 116.3, 112.1, 111.7, 52.2 ppm. IR (KBr): $\tilde{\nu}$ = 1610, 1570, 1390 cm^{-1}. MS (EI): *m*/*z* (%) = 151 (100) $[M]^+$. $C_9H_9NO_2$ (151.16): calcd. C 63.56, H 6.00, N 9.27; found C 63.35, H 6.01, N 9.24.

***N*-[2-Furylmethylene]methanamine *N*-Oxide (2d):** M.p. 90–91 °C. ^{1}H NMR: δ = 7.75 (d, J = 3.5 Hz, 1 H), 7.57 (s, 1 H), 7.48 (d, J = 1.4 Hz, 1 H), 6.56–6.53 (m, 1 H), 3.82 (s, 3 H) ppm. ^{13}C NMR: δ = 146.6, 143.4, 126.0, 114.9, 112.0, 52.6 ppm. IR (KBr): $\tilde{\nu}$ = 1600, 1480, 1400 cm^{-1}. MS (EI): *m*/*z* (%) = 125 (100) $[M]^+$. $C_6H_7NO_2$ (125.13): calcd. C 57.59, H 5.64, N 11.19; found C 57.69, H 5.63, N 11.17.

General Procedure for the Synthesis of Isoxazolino[4,5-*c*]quinolines 4: Nitrones **8** (1.00 mmol) were added to solutions of the β-(2-aminoaryl) α,β-ynones **1** (0.5 mmol) in dry toluene (8 mL). The mixtures were heated at reflux at 110 °C until disappearance of **1** (GC–MS and TLC analysis) and then concentrated in vacuo. The crude residues were purified by flash chromatography on silica gel (hexane/ethyl acetate mixtures as mobile phases) to yield compounds **4**.

4a: Yield 67%; 121 mg were obtained from 120 mg of **1a** and 136 mg of **2a**. Hexane/ethyl acetate, 75:25, v/v, as the mobile phase; m.p. 120–122 °C. ^{1}H NMR: δ = 8.17 (d, J = 8.5 Hz, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 2 H), 7.74 (d, J = 8.3 Hz, 2 H), 7.81–7.71 (m, 1 H), 7.57 (t, J = 7.8 Hz, 1 H), 6.96 (d, J = 8.1 Hz, 2 H), 6.89 (d, J = 8.1 Hz, 2 H), 5.56 (s, 1 H, NCH), 3.11 (s, 3 H, NCH_3), 2.57 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR: δ = 197.7, 160.4, 154.8, 149.5, 143.4, 138.1, 137.0, 130.6, 129.5, 129.3, 129.0, 128.7, 128.3, 127.5, 126.4, 121.8, 116.4, 114.9, 75.1 (CH-N), 47.1 (Me-N), 26.6, 21.0 ppm. IR (KBr): $\tilde{\nu}$ = 1670, 1590 cm^{-1}. MS (EI): *m*/*z* (%) = 394 (100) $[M]^+$, 303 (49). $C_{26}H_{22}N_2O_2$ (394.47): calcd. C 79.16, H 5.62, N 7.10; found C 78.93, H 5.60, N 7.12.

4b: Yield 81%; 163 mg were obtained from 130 mg of **1a** and 160 mg of **2b**. Hexane/ethyl acetate, 75:25, v/v, as the mobile phase; m.p. 94–96 °C.^{1}H NMR: δ = 8.17 (d, J = 8.5 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 2 H), 7.93 (d, J = 8.5 Hz, 2 H), 8.05–7.95 (m, 1 H), 7.80–7.71 (m, 1 H), 7.57 (t, J = 7.1 Hz, 1 H), 7.20–7.08 (m, 5 H), 6.31 (d, J = 15.9 Hz, 1 H), 6.05 (dd, J_1 = 15.9, J_2 = 6.8 Hz, 1 H), 5.27 (d, J = 6.8 Hz, 1 H, NCH), 3.13 (s, 3 H, NCH_3), 2.59 (s, 3 H) ppm. ^{13}C NMR: δ = 197.6, 160.2, 154.8, 149.5, 143.4, 137.2, 135.9, 133.0, 130.6, 129.4, 128.8, 128.4, 128.0, 126.5, 126.4, 125.9, 121.7, 115.3, 115.0, 73.1 (CH-N), 46.6 (Me-N), 26.6 ppm. IR (KBr): $\tilde{\nu}$ = 1680, 1620 cm^{-1}. MS (EI): m/z (%) = 406 (96) [M]$^+$, 378 (82), 208 (100). $C_{27}H_{22}N_2O_2$ (406.48): calcd. C 79.78, H 5.46, N 6.89; found C 80.00, H 5.47, N 6.86.

4c: Yield 60%; 122 mg were obtained from 135 mg of **1a** and 155 mg of **2c**. Hexane/ethyl acetate, 75:25, v/v, as the mobile phase; m.p. 82–84 °C. ^{1}H NMR: δ = 8.16 (d, J = 8.1 Hz, 1 H), 8.06 (d, J = 8.2 Hz, 2 H), 7.97 (d, J = 8.2 Hz, 2 H), 7.99 –7.93 (m, 1 H), 7.79–7.70 (m, 1 H), 7.53 (t, J = 7.2 Hz, 1 H), 7.22 (d, J = 1.6 Hz, 1 H), 6.26–6.04 (m, 1 H), 6.84 (d, J = 17.7 Hz, 1 H), 6.09–6.03 (m, 2 H), 5.25 (d, J = 5.8 Hz, 1 H, NCH), 3.10 (s, 3 H, NCH_3), 2.62 (s, 3 H) ppm. ^{13}C NMR: δ = 197.7, 160.3, 154.6, 151.6, 149.5, 143.4, 142.3, 137.3, 130.6, 129.4, 128.8, 128.5, 126.4, 124.3, 121.7, 120.9, 115.1, 115.0, 111.3, 109.1, 72.3 (CH-N), 46.7 (Me-N), 26.7 ppm. IR (KBr): $\tilde{\nu}$ = 1680, 1630 cm^{-1}. MS (EI): m/z (%) = 365 (100) [M – OCH_3]$^+$, 364 (50), 322 (90). $C_{25}H_{20}N_2O_3$ (396.44): calcd. C 75.74, H 5.08, N 7.07; found C 75.51, H 5.09, N 7.09.

4d: Yield 59%; 108 mg were obtained from 120 mg of **1b** and 142 mg of **2a**. Hexane/ethyl acetate, 85:15, v/v, as the mobile phase; m.p. 78–80 °C. ^{1}H NMR: δ = 8.14 (d, J = 8.5 Hz, 1 H), 7.99 (d, J = 7.2 Hz, 1 H), 7.72–7.68 (m, 1 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.02–6.85 (m, 6 H), 5.55 (s, 1 H, NCH), 3.80 (s, 3 H), 3.10 (s, 3 H, NCH_3), 2.24 (s, 3 H) ppm. ^{13}C NMR: δ = 160.3, 160.1, 155.8, 149.5, 137.9, 136.1, 131.8, 130.7, 130.3, 129.9, 129.3, 127.3, 125.6, 121.7, 115.6, 114.8, 113.8, 75.0 (CH-N), 55.3, 47.3 (Me-N), 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 1600, 1490 cm^{-1}. MS (EI): m/z (%) = 382 (100) [M]$^+$, 291 (31). $C_{25}H_{22}N_2O_2$ (382.45): calcd. C 78.51, H 5.80, N 7.32; found C 78.22, H 5.77, N 7.32.

4e: Yield 84%; 165 mg were obtained from 130 mg of **1c** and 151 mg of **2a**. Hexane/ethyl acetate, 85:15, v/v, as the mobile phase; m.p. 115–118 °C. ^{1}H NMR: δ = 8.14 (d, J = 8.5 Hz, 1 H), 8.00 (d, J = 8.0, Hz, 1 H), 7.73 (t, J = 7.2 Hz, 1 H), 7.59–7.47 (m, 3 H), 7.29 (d, J = 8.4 Hz, 2 H), 6.98 (d, J = 8.0 Hz, 2 H), 6.89 (d, J = 8.0 Hz, 2 H), 5.50 (s, 1 H, NCH), 3.09 (s, 3 H, NCH_3), 2.23 (s, 3 H) ppm. ^{13}C NMR: δ = 160.3, 154.8, 149.4, 138.1, 137.4, 135.0, 130.5, 129.8, 129.4, 129.3, 128.5, 127.4, 126.1, 121.8, 116.0, 114.8, 75.0 (CH-N), 47.2 (Me-N), 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 1620, 1590, 1540 cm^{-1}. MS (EI): m/z (%) = 388 (35), 386 (100) [M]$^+$, 297 (26), 295 (82). $C_{24}H_{19}ClN_2O$ (386.87): calcd. C 74.51, H 4.95, N 7.24; found C 74.73, H 4.94, N 7.22.

4f: Yield 43%; 75 mg were obtained from 123 mg of **1c** and 120 mg of **2d**. Hexane/ethyl acetate, 85:15, v/v, as the mobile phase; m.p. 93–94 °C. ^{1}H NMR: δ = 8.15 (d, J = 8.5 Hz, 1 H), 7.98 (d, J = 8.2 Hz, 1 H), 7.76 (t, J = 8.5 Hz, 1 H), 7.64 (d, J = 8.4 Hz, 2 H), 7.53 (t, J = 7.03 Hz, 1 H), 7.36 (d, J = 8.5 Hz, 2 H), 7.31–7.30 (m, 1 H), 6.20–6.17 (m, 1 H), 5.88 (d, J = 3.0 Hz, 1 H), 5.68 (br. s, 1 H, NCH), 3.08 (s, 3 H, NCH_3) ppm. ^{13}C NMR: δ = 161.0, 154.4, 151.4, 149.6, 143.1, 142.3, 137.4, 135.2, 130.7, 130.0, 129.5, 129.4, 128.7, 126.2, 121.8, 110.6, 109.3, 68.3 (CH-N), 46.6 (Me-N), 29.7 ppm. IR (KBr): $\tilde{\nu}$ = 1620, 1590, 1490 cm^{-1}. MS (EI): m/z (%) = 298 (27), 297 (48), 296 (72) [M + H – C_4H_3O]$^+$, 295 (100). $C_{21}H_{15}ClN_2O_2$ (362.81): calcd. C 69.52, H 4.17, N 7.72; found C 69.33, H 4.17, N 7.74.

4g: Yield 86%; 161 mg were obtained from 120 mg of **1c** and 151 mg of **2b**. Hexane/ethyl acetate, 80:20, v/v, as the mobile phase; m.p. 145–147 °C. ^{1}H NMR: δ = 8.14 (d, J = 8.5 Hz, 1 H), 7.96 (d, J = 8.17 Hz, 1 H), 7.79 (d, J = 8.5 Hz, 2 H), 7.75–7.68 (m, 1 H), 7.51 (t, J = 7.2 Hz, 1 H), 7.42 (d, J = 8.5 Hz, 2 H), 7.20–7.13 (m, 5 H), 6.32 (d, J = 15.8 Hz, 1 H), 6.07 (dd, J_1 = 15.8, J_2 = 6.7 Hz, 1 H), 5.22 (d, J = 6.7 Hz, 1 H, NCH), 3.10 (s, 3 H, NCH_3) ppm. ^{13}C NMR: δ = 160.2, 154.7, 149.4, 137.5, 135.9, 135.3, 132.9, 130.5, 129.9, 129.3, 128.7, 128.5, 128.0, 126.5, 126.1, 121.6, 115.0, 114.9, 73.0 (CH-N), 46.6 (Me-N) ppm. IR (KBr): $\tilde{\nu}$ = 1620, 1590, 1490 cm^{-1}. MS (EI): m/z (%) = 398 (37) [M]$^+$, 397 (29), 396 (82), 370 (15), 207 (100). $C_{25}H_{19}ClN_2O$ (398.88): calcd. C 75.28, H 4.80, N 7.02; found C 75.51, H 4.79, N 7.03.

4h: Yield 58%; 106 mg were obtained from 120 mg of **1c** and 142 mg of **2c**. Hexane/ethyl acetate, 80:20, v/v, as the mobile phase; m.p. 105–106 °C. ^{1}H NMR (300 MHz): δ = 8.15 (d, J = 8.6 Hz, 1 H), 7.98 (d, J = 8.3 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 2 H), 7.79–7.72 (m, 1 H), 7.52, (t, J = 7.5 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 2 H), 7.27 (d, J = 1.7 Hz, 1 H), 6.32–6.29 (m, 1 H), 6.19 (d, J = 15.8 Hz, 1 H), 6.14 (d, J = 3.3 Hz, 1 H), 6.08 (dd, J_1 = 15.8, J_2 = 6.0 Hz, 1 H), 5.22 (d, J = 6.0 Hz, 1 H, NCH); 3.11 (s, 3 H, NCH_3) ppm. ^{13}C NMR: δ = 160.6, 155.0, 152.0, 149.9, 142.7, 137.9, 135.7, 131.0, 130.2, 129.7, 129.2, 126.5, 124.7, 122.0, 121.2, 115.4, 115.1, 111.7, 109.5, 72.6 (CH-N), 47.1 (Me-N) ppm. IR (KBr): $\tilde{\nu}$ = 1630, 1590 cm^{-1}. MS (EI): m/z (%) = 389 (9) [M]$^+$, 388 (34), 387 (41), 386 (100), 295 (80). $C_{23}H_{17}ClN_2O_2$ (388.85): calcd. C 71.04, H 4.41, N 7.20; found C 71.10, H 4.40, N 7.22.

4i: Yield 87%; 177 mg were obtained from 140 mg of **1d** and 149 mg of **2a**. Hexane/ethyl acetate, 90:10, v/v, as the mobile phase; m.p. 74–76 °C. ^{1}H NMR: δ = 8.15 (d, J = 8.5 Hz, 1 H); 8.03 (d, J = 8.2 Hz, 1 H), 7.80–7.70 (m, 3 H), 7.59–7.50 (m, 2 H), 7.46 (t, J = 8.0 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 2 H), 6.89 (d, J = 8.0 Hz, 2 H), 5.51 (s, 1 H, NCH), 3.12 (s, 3 H, NCH_3), 2.22 (s, 3 H) ppm. ^{13}C NMR: δ = 160.6, 154.6, 149.6, 139.8, 138.5, 136.3, 131.9 (q, $J_{C\text{-}F}$ = 1 Hz), 130.9, 130.7 (q, $J_{C\text{-}F}$ = 32 Hz, C-CF_3), 129.6, 129.5, 129.0, 127.8, 126.6, 125.7 (q, $J_{C\text{-}F}$ = 4 Hz), 125.5 (q, $J_{C\text{-}F}$ = 4 Hz), 124.2 (q, $J_{C\text{-}F}$ = 272 Hz, CF_3), 122.1, 116.8, 115.1, 75.6 (CH-N), 55.6, 47.3 (Me-N), 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 1620, 1590, 1500 cm^{-1}. MS (EI): m/z (%) = 420 (100) [M]$^+$, 406 (9), 330 (75). $C_{25}H_{19}F_3N_2O$ (420.42): calcd. C 71.42, H 4.56, N 6.66; found C 71.21, H 4.64, N 6.64.

4j: Yield 50%; 94 mg were obtained as an oil from 130 mg of **1e** and 132 mg of **2a**. Hexane/ethyl acetate, 85:15, v/v, as the mobile phase. ^{1}H NMR: δ = 8.17 (d, J = 8.5 Hz, 1 H), 8.02, (two overlapping doublets, J = 8.3 Hz, 3 H); 7.80–7.68 (m, 1 H), 7.03 (d, J = 8.3 Hz, 2 H), 7.55 (t, J = 7.4 Hz, 1 H), 6.97 (d, J = 8.1 Hz, 2 H), 6.88 (d, J = 8.1 Hz, 2 H), 5.55 (s, 1 H, NCH), 4.38 (q, J = 7.1 Hz, 2 H), 3.12 (s, 3 H, NCH_3), 2.22 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 166.3, 160.3, 155.0, 149.4, 143.2, 138.1, 133.0, 130.6, 129.8, 129.5, 129.4, 129.2, 128.4, 127.3, 126.3, 121.8, 116.4, 114.9, 75.0 (CH-N), 61.1, 47.2 (Me-N), 21.1, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 1720, 1630, 1590, 1500 cm^{-1}. MS (EI): m/z (%) = 424 (25) [M]$^+$, 410 (13), 205 (100). $C_{27}H_{24}N_2O_3$ (424.49): calcd. C 76.39, H 5.70, N 6.60; found C 76.10, H 5.68, N 6.62.

4k: Yield 61%; 117 mg were obtained from 125 mg of **1f** and 151 mg of **2a**. Hexane/ethyl acetate, 80:20, v/v, as the mobile phase; m.p. 83–85 °C. ^{1}H NMR: δ = 8.15 (d, J = 8.5 Hz, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 7.81–7.71 (m, 1 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.59 (d, J = 8.2 Hz, overlapped with a multiplet, 3 H), 6.99 (d, J = 8.0 Hz, 2 H), 6.88 (d, J = 8.0 Hz, 2 H), 5.52 (s, 1 H, NCH); 3.13 (s, 3 H, NCH_3), 2.24 (s, 3 H) ppm. ^{13}C NMR: δ = 160.6, 153.8, 149.4, 143.2, 138.4, 136.0, 132.0, 130.8, 129.4, 129.2, 127.6, 126.7,

121.9, 118.6, 116.5, 114.9, 112.4, 75.3 (CH-N), 47.0 (Me-N), 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 2200, 1630, 1590, 1500 cm^{-1}. MS (EI): *m/z* (%) = 377 (100) $[M]^+$, 362 (10), 286 (94). $C_{25}H_{19}N_3O$ (377.44): calcd. C 79.55, H 5.07, N 11.13; found C 79.59, H 5.08, N 11.11.

4l: Yield 68%; 134 mg were obtained from 135 mg of **1g** and 140 mg of **2a**. Hexane/ethyl acetate, 92:8, v/v, as the mobile phase; m.p. 55–56 °C. ^1H NMR: δ = 7.44–7.40 (m, 1 H); 7.32–7.15 (m, 3 H), 6.94–6.78 (m, 4 H), 6.74 (d, J = 8.1 Hz, 2 H), 5.36 (s, 1 H, NCH), 3.76 (s, 3 H), 3.14 (s, 3 H, NCH_3), 2.18 (s, 3 H) ppm. ^{13}C NMR: δ = 158.3, 156.5, 154.5 (dd, $J_{C\text{-}F}$ = 2, $J_{C\text{-}F}$ = 1 Hz, C quat.), 137.8, 137.4 (dd, $J_{C\text{-}F}$ = 12, $J_{C\text{-}F}$ = 2 Hz, C quat.), 136.2, 131.3, 130.6, 129.0, 128.1, 127.2, 121.6 (t, $J_{C\text{-}F}$ = 0.02 Hz, C quat.), 121.3, 116.4 (dd, $J_{C\text{-}F}$ = 11, $J_{C\text{-}F}$ = 4 Hz, C quat.), 110.8, 105.8 (dd, $J_{C\text{-}F}$ = 23, $J_{C\text{-}F}$ = 29 Hz, C-H), 101.5 (dd, $J_{C\text{-}F}$ = 23, $J_{C\text{-}F}$ = 5 Hz, C-H), 75.7 (CH-N), 55.6, 47.2 (Me-N), 21.2 ppm. IR (neat): $\tilde{\nu}$ = 1600, 1590, 1550 cm^{-1}. MS (EI): *m/z* (%) = 418 (100) $[M]^+$. $C_{25}H_{20}F_2N_2O_2$ (418.44): calcd. C 71.76, H 4.82, N 6.69; found C 72.03, H 4.80, N 6.72.

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