Synthesis of 2,2-Disubstituted Azaindolines by Intramolecular Cyclization in Acidic Media

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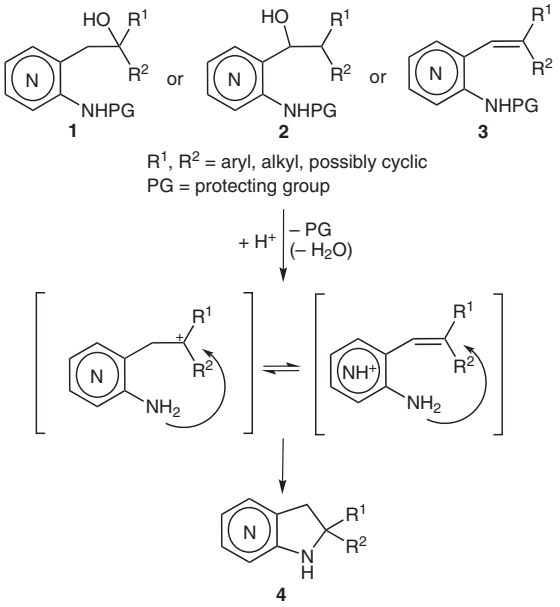
Abstract: The synthesis of a diverse array of 2,2-disubstituted azaindolines is reported. The bicyclic core is built by a simple acidic treatment of conveniently substituted aminopyridines.

Key words: azaindolines, cyclization, nucleophilic addition, spiro compounds, pyridines

2,2-Disubstituted azaindoline is an attractive scaffold as no general method for synthesizing this heterocyclic building block is described. The strategies furnishing the scarce examples include intramolecular [1,5]-dipolar cyclization,[1] addition of a malonate on an imine intermediate,[2] intramolecular Chichibabin reaction,[3] or palladium-catalyzed C–H activation of a *tert*-butyl-aminopyridine.[4]

Herein we report the synthesis of a variety of 2,2-disubstituted azaindolines from the cyclization of hydroxyalkyl- or alkenyl-aminopyridines in acidic conditions.

Our strategy relies on the nucleophilic attack of an amino group attached to a pyridine onto either a carbocationic or an alkenyl intermediate (Scheme 1). These species could be generated by acidic treatment of a tertiary alcohol (type **1**), a secondary alcohol (type **2**), or an alkene (type **3**).

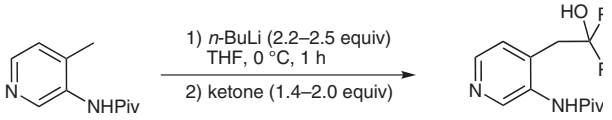


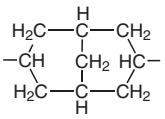
Scheme 1

A similar approach was developed successfully to obtain structurally close 2-substituted 7-azaindoles from 2-amino-3-(2-hydroxyethyl)pyridine derivatives although furnishing the azaindoline intermediate with low yield.[5,6] Cyclization of the substrates was obtained by transforming the hydroxyl moiety into a good leaving group such as a trifluoroacetate or a mesylate, followed by acidic treatment. Similarly, 2-substituted 5-azaindolines were synthesized through intramolecular cyclization of 4-*tert*-butoxycarbonylamino-3-(2-mesyloxypropyl)pyridine upon basic treatment.[7]

In addition, 2,2-disubstituted indolines have been isolated from 2-(2,2-disubstituted 2-aminoethyl)anilines[8] or from 2-(2,2-disubstituted hydroxyethyl)anilines derivatives after acidic treatment.[9]

Table 1 Synthesis of 4-(2-Hydroxyethyl)-3-pivaloylaminopyridines of Type **1**



Entry	Ketone	R^1	R^2	Product	Yield (%)
1	acetone	Me	Me	**1a**	35
2	acetophenone	Ph	Me	**1b**	62
3	*tert*-butylphenylketone	Ph	*t*-Bu	**1c**	88
4	cyclobutanone	$-(CH_2)_3-$		**1d**	78
5	cyclopentanone	$-(CH_2)_4-$		**1e**	40
6	cyclohexanone	$-(CH_2)_5-$		**1f**	73
7	tetrahydropyranone	$-(CH_2)_2O(CH_2)_2-$		**1g**	59
8	*N*-benzyl-4-piperidinone	$-(CH_2)_2N(Bn)(CH_2)_2-$		**1h**	69
9	cycloheptanone	$-(CH_2)_6-$		**1i**	82
10	2-adamantanone			**1j**	75

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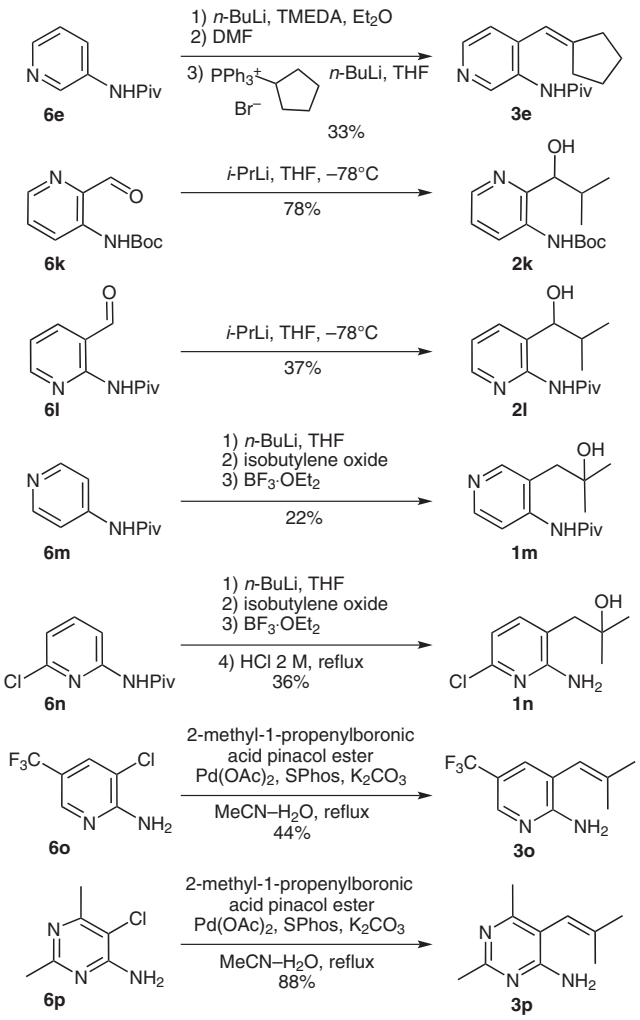
In order to study the feasibility of our approach, a first set of 4-(2-hydroxyethyl)-3-pivaloylaminopyridines **1** was prepared starting from 3-pivaloylamino-4-methyl-pyridine (**5**). Treatment of **5** with more than two equivalents of *n*-BuLi followed by the addition of ketones furnished 4-(2-hydroxyethyl)-3-pivaloylaminopyridines **1** with moderate to good yields (Table 1).

Other synthetic approaches were also envisaged for pyridines **1**–**3**. Cyclopentylidenemethyl-pyridine **3e** was isolated from a Wittig reaction on the 4-formylated analogue of **6e** (Scheme 2).[10] Compounds **2k** and **2l** were prepared by addition of *i*-PrLi to formyl-aminopyridines **6k** and **6l**, whereas **1m** and **1n** were obtained by trapping with isobutylene the product, resulting from the regioselective *ortho* lithiation of aminopyridine **6m**[11] and **6n**.[10] Aminoisopropylidenepyridine **3o** and aminoisopropylidenepyrimidine **3p** were synthesized by Suzuki coupling[12] between 2-methyl-1-propenylboronic acid pinacol ester and unprotected **6o** and **6p**, respectively (Scheme 2).

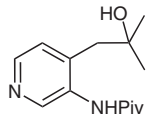
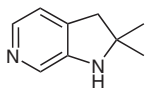
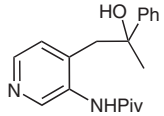
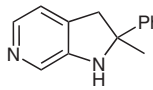
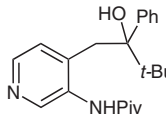
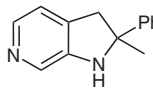
At first, cyclization of substrates possessing alkyl and/or aryl R^1 and R^2 substituents was envisaged. Treating pyridines **1a** and **1b** bearing dimethyl or methyl/phenyl substituents in refluxing 2 M HCl led to the cyclized 2,2-disubstituted 6-azaindolines with good yields (Table 2, entries 1 and 2).[13] Replacing the methyl R^2 substituent in **1b** with a *tert*-butyl resulted in low yield of the cyclized product **4c**, even after prolonged heating (Table 2, entry 3). Co-products of this reaction were determined to be resulting from hydrolysis of the pivalamide moiety along with isomeric alkenes coming from dehydration.



SPhos : 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

Scheme 2

Table 2 Cyclization of Substrates Possessing Alkyl and/or Aryl as R^1 and R^2 Substituents

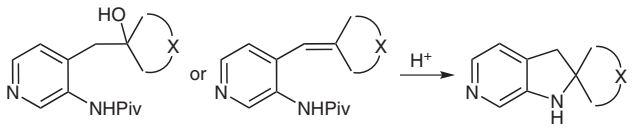
Entry	Substrate	Product	Conditions	Yield (%)
1	 **1a**	 **4a**	2 M HCl, reflux, 96 h	71
2	 **1b**	 **4b**	2 M HCl, reflux, 18 h	81
3	 **1c**	 **4c**	2 M HCl, reflux, 144 h	7

We next turned our attention to the synthesis of 6-azaindolines with cyclic R^1-R^2 substituent. When treated in refluxing 2 M HCl, 4-(2-hydroxyethyl)-3-pivaloylaminopyridines **1e**, **1f**, **1i**, and **1j** were converted into their corresponding 2,2-disubstituted 6-azaindolines with good to excellent yields (Table 3, entries 2, 4, 7, and 8). It is worth noting that when R^1-R^2 formed a strained spirocyclobutyl ring, cyclized product **4d** was obtained with a low yield whereas very bulky groups such as spiroadamantyl in **1j** were not an obstacle in forming the cyclized product **4j** in good yield (Table 3, entries 1 and 8).

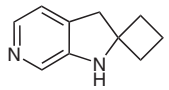
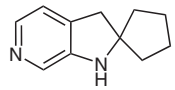
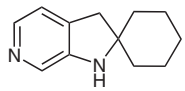
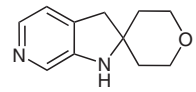
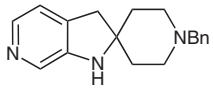
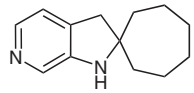
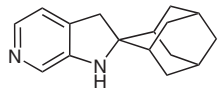
Introducing heteroatoms, such as oxygen or nitrogen, into the cyclic R^1-R^2 chain resulted in disrupting the formation of the cyclized products. For instance, oxygen-containing **1g** required 6 M HCl to reach full conversion furnishing 6-azaindoline **4g** in 53% yield (Table 3, entry 5). When this oxygen atom was replaced by a benzylamine in **1h**, cyclized product **4h** could not be isolated (Table 3, entry 6). In this particular case, only the products resulting from hydrolysis of the pivalamide moiety along with isomeric alkenes coming from dehydration could be isolated. Other acidic conditions such as PTSA in refluxing toluene, sulfuric acid, methanesulfonic acid, concentrated or diluted hydrochloric acid could not produce the cyclized azaindoline.

Confirming our initially proposed strategy, acidic treatment of 4-cyclopentylidenemethyl-pyridine **3e** produced

Table 3 Cyclization of Substrate Possessing Cyclic Alkyl R^1–R^2 Substituents



1d–j 3e 4d–j

Entry	Substr.	Product	Conditions	Yield (%)
1	**1d**	 **4d**	6 M HCl, reflux, 48 h	6
2	**1e**	 **4e**	2 M HCl, reflux, 18 h	84
3	**3e**		2 M HCl, reflux, 6 h	90
4	**1f**	 **4f**	2 M HCl, reflux, 12 h	98
5	**1g**	 **4g**	6 M HCl, reflux, 120 h	53
6	**1h**	 **4h**	6 M HCl, reflux, 48 h	–[a]
7	**1i**	 **4i**	2 M HCl, reflux, 18 h	95
8	**1j**	 **4j**	2 M HCl, reflux, 18 h	65

[a] Not observed.

6-azaindoline **4e** in good yield (Table 3, entry 3). This result shows that starting material containing an alkenyl functionality as the electrophile can be an excellent alternative to their corresponding tertiary alcohol analogues.

With this efficient methodology toward 6-azaindolines in hand, we turned our attention to 4-, 7-, and 5-isomeric azaindolines. Starting from the corresponding pyridines **2k**, **2l**, and **1m**, 4-, 7-, and 5-azaindolines **4k–m** could be obtained with good yields (Table 4, entries 1–3). While many 6-azaindolines of type **4** were obtained from pyridines bearing either a tertiary alcohol or an alkene moiety, synthesis of 4-azaindolines **4k** and 7-azaindolines **4l** was achieved from the corresponding secondary alcohol **2k** and **2l** (Table 4, entries 1 and 2). The lower lability of the secondary alcohol in an acidic media was circumvented by using a higher concentration of HCl (6 M).

The presence of substituents on the pyridine ring can hamper the formation of cyclized azaindolines as **4n** was isolated with 33% yield when **1n** was treated with refluxing 6 M HCl for 90 hours (Table 4, entry 4). This issue was overcome for **1n** and **3o** by using concentrated sulfuric acid, a more acidic medium, affording **4n** and **4o** in high yields (Table 4, entry 5 and 6).

While sulfuric acid was inefficient in furnishing **4p** from pyrimidine **3p**, heating at 200 °C under microwave irradiation a solution of **3p** in methanesulfonic acid gave diazaindoline **4p** with good yield (Table 4, entry 8). Isolation of **4o** and **4p** confirmed that alkenyl containing starting materials are suitable substrates for this cyclization.

In conclusion, acidic treatment can be an easy way to produce 2,2-disubstituted azaindolines from hydroxyalkyl- or alkenyl-aminopyridines. While formation of the cyclized products is highly dependent on the acidic conditions, all 4-, 5-, 6-, and 7-(2,2-disubstituted)-azaindolines isomers could be synthesized starting from a broad range of substrates, showing the wide applicability of this original methodology.[13]

Table 4 Synthesis of 4-, 5-, and 7-Isomeric 2,2-Dimethylazaindolines

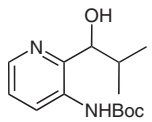
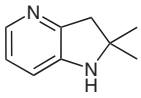
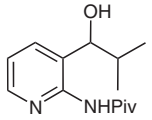
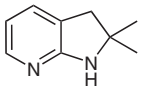
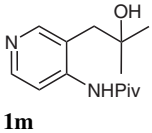
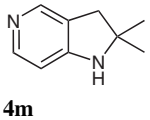
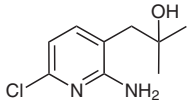
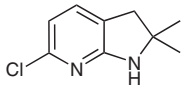
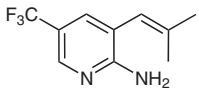
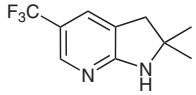
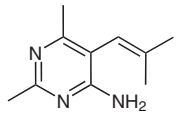
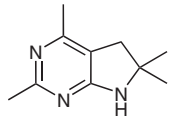
Entry	Substrate	Product	Conditions	Yield (%)
1	 **2k**	 **4k**	6 M HCl, reflux, 72 h	63
2	 **2l**	 **4l**	6 M HCl, reflux, 48 h	80
3	 **1m**	 **4m**	6 M HCl, reflux, 120 h	72

Table 4 Synthesis of 4-, 5-, and 7-Isomeric 2,2-Dimethylazaindolines (continued)

Entry	Substrate	Product	Conditions	Yield (%)
4	 **1n**	 **4n**	6 M HCl, reflux, 90 h	33
5			H_2SO_4 96%; r.t., 2 h	96
6	 **3o**	 **4o**	H_2SO_4 96%; r.t., 4 h	95
7	 **3p**	 **4p**	H_2SO_4 96%; r.t., 4 h	–[a]
8			MsOH, MW, 200 °C, 5 min	68

[a] Not observed.

References and Notes

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(13) **Representative Procedures for the Synthesis of 4-(2-Hydroxyethyl)-3-pivaloylaminopyridines of Type 1**
Compound 1a
To a solution of pyridine **5** (960 mg, 4.9 mmol, 1.0 equiv) in anhyd THF (10 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 4.3 mL, 10.8 mmol, 2.2 equiv), and the solution was stirred at 0 °C for 1 h. After addition at –78 °C of acetone (547 μL, 7.4 mmol, 1.5 equiv), the mixture was stirred for 1 h at –78 °C then overnight at r.t. The reaction medium was quenched by addition of H_2O (10 mL), the aqueous phase was extracted with EtOAc, and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (cyclohexane–EtOAc, 20:80) afforded **1a** as a yellow solid (430 mg, 35%); mp 159–161 °C. IR (neat): 3380, 3278, 2972, 2933, 2870, 1652, 1564, 1521, 1469, 1411, 1379, 1365, 1179, 1113, 914, 779, 722 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 8.82 (s, 1 H), 8.22 (d, *J* = 4.9 Hz, 1 H), 7.22 (d, *J* = 4.9 Hz, 1 H), 5.64 (s, 1 H), 2.71 (s, 2 H), 1.25 (s, 9 H), 1.19 (s, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.3, 145.5, 144.4, 139.3, 134.6, 126.9, 71.5, 44.5, 29.5, 27.5. ESI-MS: *m/z* = 251 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{14}H_{23}N_2O_2$ $[M + H^+]$: 251.1752; found: 251.1760.

Compound 1b
Off-white powder; mp 179–181 °C. IR (neat): 3350, 3060, 2970, 1675, 1566, 1520, 1478, 1416, 1310, 1207, 1064, 751, 698 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.91 (s, 1 H), 8.80 (s, 1 H), 8.10 (d, *J* = 4.9 Hz, 1 H), 7.48 (dd, *J* = 7.5, 1.4 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.23 (dd, *J* = 7.5, 1.4 Hz, 1 H), 6.99 (d, *J* = 4.9 Hz, 1 H), 6.36 (s, 1 H), 2.94 (d, *J* = 13.3 Hz, 2 H), 1.49 (s, 3 H), 1.29 (s, 9 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.3, 148.3, 145.4, 144.3, 138.6, 134.6, 128.0, 126.9, 126.6, 124.9, 75.5, 45.8, 28.5, 27.5. ESI-MS: *m/z* = 313 $[M + H]^+$. Anal Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.76; H, 8.02; N, 9.05.

Compound 1j
White powder; mp 246–248 °C. IR (neat): 3269, 2916, 2862, 1671, 1515, 1417, 1326, 1168, 1055, 928, 699, 667 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.77 (s, 1 H), 8.79 (s, 1 H), 8.20 (d, *J* = 4.9 Hz, 1 H), 7.27 (d, *J* = 4.9 Hz, 1 H), 5.23 (s, 1 H), 2.93 (s, 2 H), 2.16 (d, *J* = 12.6 Hz, 2 H), 2.07 (d, *J* = 12.6 Hz, 2 H), 1.85 (s, 1 H), 1.72 (s, 2 H), 1.69 (s, 1 H), 1.65 (s, 2 H), 1.60 (s, 2 H), 1.45 (d, *J* = 12.6 Hz, 2 H), 1.25 (s, 9 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.4, 145.6, 144.3, 139.1, 135.0, 126.3, 76.6, 38.1, 36.6, 34.2, 32.3, 27.5, 27.0, 26.8. ESI-MS: *m/z* = 343 $[M + H]^+$. Anal Calcd for $C_{21}H_{30}N_2O_2$: C, 73.65; H, 8.83; N, 8.18. Found: C, 73.40; H, 9.00; N, 7.99.

Representative Procedures for the Synthesis of 2,2-Disubstituted Azaindoline of Type 4
Compound 4a
A solution of **1a** (215 mg, 0.86 mmol) in 2 M HCl (8.6 mL) was heated at reflux for 96 h. After cooling to r.t., aq NaOH was added until pH 10. The crude was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (*n*-heptane–EtOAc) afforded **4a** as a brown solid (90 mg, 71%); mp 49–51 °C. IR (neat): 3199, 2958, 1604, 1496, 1445, 1363, 1258, 1227, 1176, 1038, 817, 725 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 7.75 (d, *J* = 4.6 Hz, 1 H), 7.73 (s, 1 H), 7.01 (d, *J* = 4.6 Hz, 1 H), 5.69 (br s, 1 H), 2.74 (d, *J* = 0.9 Hz, 2 H), 1.22 (s, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 147.7, 138.2, 136.2, 129.3, 120.0, 60.8, 43.0, 28.6. ESI-MS: *m/z* = 149 $[M + H]^+$. Anal Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N,

18.90. Found: C, 72.62; H, 8.19; N, 18.89.

Compound 4b

A solution of **1b** (200 mg, 0.64 mmol) in 2 M HCl (6.4 mL) was heated at reflux for 18 h. After cooling to r.t., aq NaOH was added until pH 10. The crude was extracted with Et_2O, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford **4b** as a white powder (109 mg, 81%); mp >118 °C (dec.). IR (neat): 3164, 2963, 1603, 1491, 1441, 1276, 1170, 1080, 1037, 824, 763, 696 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 7.86 (s, 1H), 7.80 (d, *J* = 4.5 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.22 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.04 (d, *J* = 4.5 Hz, 1H), 6.43 (s, 1H), 3.22 (d, *J* = 16.6 Hz, 1H), 3.05 (d, *J* = 16.6 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 148.5, 147.8, 138.6, 136.0, 129.4, 128.3, 126.4, 125.3, 120.2, 66.5, 44.7, 29.4. ESI-MS: *m/z* = 211 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{14}H_{15}N_2$ $[M + H^+]$: 211.1238; found: 211.1235.

Compound 4j

A solution of **1j** (1.0 g, 2.92 mmol) in 2 M HCl (25 mL) was heated at reflux for 18 h. After cooling to r.t., aq NaOH was added until pH = 10. The crude was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (CH_2Cl_2–MeOH) afforded **4j** as an off-white powder (456 mg, 65%); mp 234–236 °C. IR (neat): 3252, 2885, 2856, 1603, 1498, 1460, 1449, 1254, 1099, 1036, 816, 721 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 7.77 (s, 1 H), 7.71 (d, *J* = 4.4 Hz, 1 H), 6.98 (d, *J* = 4.4 Hz, 1 H), 6.27 (s, 1 H), 2.93 (s, 2 H) 2.08 (d, *J* = 12.6 Hz, 2 H), 1.88–1.80 (4 H), 1.71–1.58 (8 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 147.4, 137.8, 135.8, 128.9, 119.8, 68.2, 37.7, 37.0, 34.1, 32.9, 26.5, 26.4. ESI-MS: *m/z* = 241 $[M + H]^+$. Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.56; H, 8.62; N, 11.73.