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Catalyst-Free Synthesis of Spiropyrazolines from Chalcones and Cyclic Ketone *N*-Tosylhydrazones

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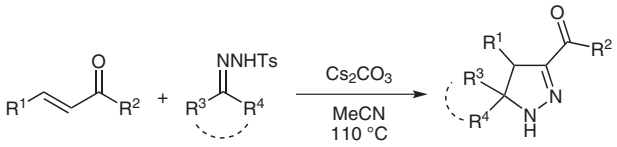

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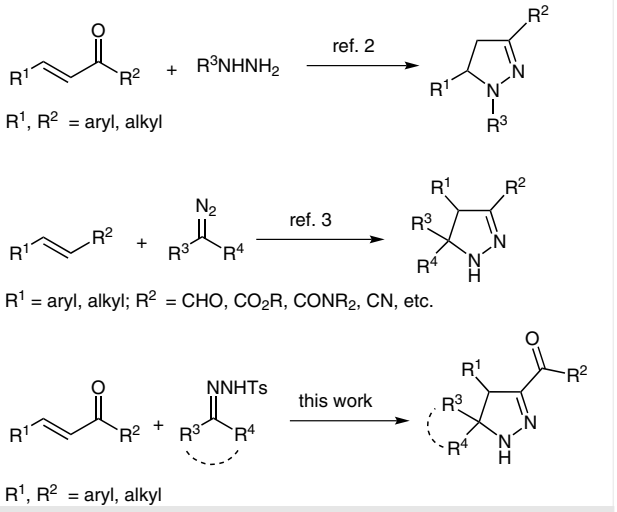
Abstract Treatment of cyclic ketone *N*-tosylhydrazones with chalcones in the presence of cesium carbonate at 110 °C affords spiropyrazolines with high selectivity and excellent yields. This protocol possesses many advantages such as readily available and stable starting materials, high selectivity, operational simplicity, and catalyst-free conditions.

Key words spiropyrazolines, *N*-tosylhydrazones, chalcones, selective, catalyst-free

Pyrazolines have been a subject of consistent interest due to the presence of their structural motifs in a large number of functional materials[1] and pharmaceuticals.[2] The biological activities attributed to pyrazolines include antioxidant,[2a] anti-inflammatory,[2b] analgesic,[2b] antiinfective,[2c] antinociceptive,[2d] antihyperglycemic,[2e] antifungal,[2f] antiamoebic,[2g] antileishmanial,[2h] antimicrobial,[2h] antitubercular,[2h] anticonvulsant,[2i] antidepressant,[2j] anti-HIV,[2k] and anticancer.[2l] Besides, pyrazolines are also important starting materials for the syntheses of azaprolines and diamines.[3a] The significance and prevalence of this class of compounds has served to stimulate continual interest in synthetic community. Most of bioactive pyrazolines were synthesized by annulation of α,β-unsaturated ketones (chalcones in most cases) with hydrazines (Scheme 1).[2] However, different pyrazolines are required in an increasing number of applications, which makes the development of new pyrazoline platforms a high priority.

Syntheses of pyrazolines via cycloaddition of enones with diazo compounds or nitrile imines have also been reported,[3] in which the enone substrates were centered on acrylamides,[3a–h] acrylates,[3i–l] acroleins[3m,n] and acrylonitriles.[3k] In contrast, cycloadditions of acrylketones with diazo compounds to afford pyrazolines are rare.[3o] It is noteworthy that diazo compounds can react with unsaturated ketones via tandem carbonyl ylide formation and cycloaddition to afford oxapolycycles.[4] Also noteworthy is that treatment of cyclic α,β-unsaturated ketones with diazoacetates in the presence of Lewis acids did not afford pyrazolines, in which an elegant catalytic carbon insertion into the β-vinyl C–H bond of the cyclic α,β-unsaturated ketones took place.[5] On the other hand, most of diazo compounds are inherently dangerous and not readily available, which has limited the scope and generality of their applications.[6] Unsurprisingly, their use on large scale has been avoided due to their toxicity and unpredictable explosive behavior.[6] The in situ generation of diazo compounds from *N*-tosylhydrazones is a useful way to circumvent this problem. As *N*-tosylhydrazones are readily prepared from carbonyl com-



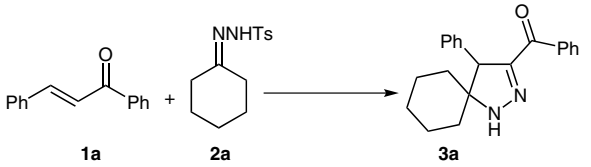
Scheme 1 Synthesis of pyrazolines

pounds, this strategy offers new synthetic opportunities for the unconventional modification of carbonyl compounds.[7] In this regard, Cabal and Barluenga developed a cyclopropanation of acrylates/acrylonitriles with *N*-tosylhydrazones.[8] In connection with our consistent interest in the selective synthesis of various functional heterocycles,[9] herein we would like to report a practical synthesis of spiropyrazolines from chalcones and cyclic ketone *N*-tosylhydrazones under catalyst-free conditions (Scheme 1). It is worth mentioning that catalyst-free reactions are gaining much attention for their low cost, safety and eco-friendliness, which agree well with the principles of green chemistry.

The reaction of chalcone (**1a**) with cyclohexanone tosylhydrazone (**2a**) was used as a probe for evaluating the reaction conditions, and the representative results are summarized in Table 1. Treatment of **1a** (0.5 equiv) and **2a** (1.0 equiv) in the presence of cesium carbonate (Cs_2CO_3, 1.0 equiv) in dioxane at 110 °C afforded pyrazoline **3a** in 84% yield within two h (Table 1, entry 1). The reaction was complex when the loading of **1a** was increased from half an equivalent to one equivalent. Base played an important role in this transformation. Only trace of pyrazoline **3a** was obtained when lithium hydroxide (LiOH) or sodium carbonate (Na_2CO_3) was used as the base under otherwise identical conditions (Table 1, entries 1–3). With potassium hydroxide (KOH) or potassium *tert*-butanolate (KO*t*-Bu) as the base, the reaction was complex (Table 1, entries 4 and 5). Potassium carbonate (K_2CO_3) was also an effective base for this reaction (Table 1, entry 6) and might be useful for a large-scale process. However, Cs_2CO_3 was chosen in our investigation because it led to the best isolated yield (Table 1, entries 1–6). With the use of ethanol (EtOH), *N*,*N*-dimethylformamide (DMF), dimethoxyethane (DME), toluene (PhMe), and benzonitrile (PhCN) in comparison to dioxane, relatively lower yields were observed (Table 1, entries 1, 7–11). Fortuitously, with the use of acetonitrile (MeCN), the reaction proceeded smoothly to afford pyrazoline **3a** with an excellent yield (Table 1, entry 12). Although the reaction could take place at 80 °C (Table 1, entry 13), 110 °C seemed to be the best reaction temperature from the view point of reaction efficiency (Table 1, entries 1, 13, and 14). Furthermore, when scaling up **1a** to 2.08 grams, the reaction still provided an excellent yield (Table 1, entry 15).

With the optimized reaction conditions in hand, the scope of the reaction was subsequently investigated (Table 2). With the cyclic ketone moiety of *N*-tosylhydrazones bearing methyl, ethyl, *tert*-butyl, and acetamido, cyclohexanone tosylhydrazones **2a**–**e** reacted smoothly with chalcone (**1a**) in the presence of Cs_2CO_3 at 110 °C to afford spiropyrazolines **3a**–**e** in moderate to excellent yields within 2–5 hours (Table 2, entries 1–5). Tetrahydropyran-4-one tosylhydrazone (**2f**) and 1-methylpiperidin-4-one tosylhydrazone (**2g**) reacted with chalcone (**1a**) uneventfully under the standard conditions to generate spiropyrazolines **3f**,**g** in 63% and 72% yields, respectively (Table 2, entries 6 and 7).

Table 1 Survey of Conditions for the Synthesis of Spiropyrazolines from Chalcone (**1a**) and Tosylhydrazone **2a**[a]



1a **2a** **3a**

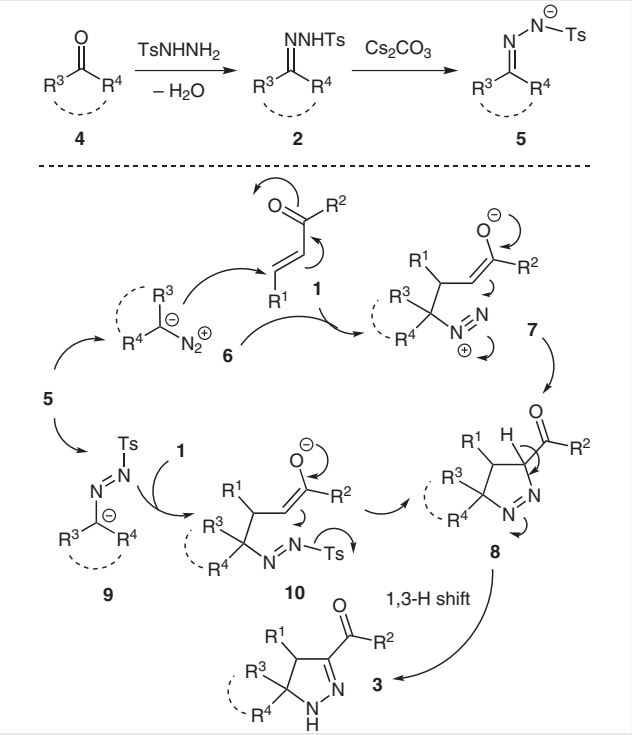
Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Cs_2CO_3	1,4-dioxane	110	2	84
2	LiOH	1,4-dioxane	110	2	trace
3	Na_2CO_3	1,4-dioxane	110	2	trace
4	KOH	1,4-dioxane	110	2	–[b]
5	KO*t*-Bu	1,4-dioxane	110	2	–[b]
6	K_2CO_3	1,4-dioxane	110	2	79
7	Cs_2CO_3	EtOH	110	2	–[b]
8	Cs_2CO_3	DMF	110	4	57
9	Cs_2CO_3	DME	110	4	50
10	Cs_2CO_3	PhMe	110	4	65
11	Cs_2CO_3	PhCN	110	4	53
12	Cs_2CO_3	MeCN	110	2	88
13	Cs_2CO_3	MeCN	80	7	10
14	Cs_2CO_3	MeCN	120	2	80
15[c]	Cs_2CO_3	MeCN	110	2	87

[a] General conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), base (0.2 mmol) in solvent (1.0 mL).
[b] Complex mixture.
[c] Reaction was carried out at 2.08 g scale of **1a** (10.0 mmol).

By treating 1-Boc-piperidin-4-one tosylhydrazone (**2h**) with chalcone (**1a**) under the standard conditions, spiropyrazoline **3h** was obtained in 99% yield (Table 2, entry 8). 1-Phenethylpiperidin-4-one tosylhydrazone (**2i**) and cyclopentanone tosylhydrazone (**2j**) reacted smoothly with chalcone (**1a**) under the standard conditions to give spiropyrazolines **3i**,**j** in good yields (Table 2, entries 9 and 10). With the aromatic ring of chalcones bearing methyl (an electron-donating group) and chloro (an electron-withdrawing group) groups, chalcones **1b**,**c** reacted equally well with *N*-tosylhydrazone **2i** under the standard conditions to generate spiropyrazolines **3k**,**l** in excellent yields (Table 2, entries 11 and 12). Besides chalcones, 3-decen-2-one (**1d**) and β-phenyl-α,β-unsaturated butanone (**1e**) have also been investigated, which reacted with **2i** under the standard conditions to afford spiropyrazolines **3m**,**n** in 80–82% yields (Table 2, entries 13 and 14). Acyclic ketone tosylhydrazone **2k**

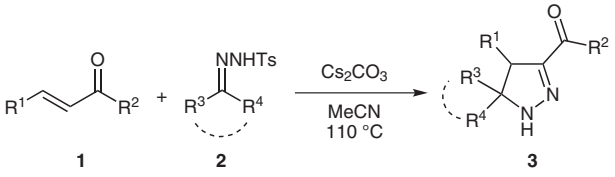
reacted smoothly with chalcone (**1a**) under the standard conditions to give pyrazoline **3o** in 81% yield (Table 2, entry 15, *trans*/*cis* = 4:1 based on its ^{1}H NMR chart), in which the 1,3-*trans* stereochemistry of the major isomer was deduced from the observed NOE correlation between H_a (δ = 4.47 ppm)/H_b (δ = 1.88 ppm). A series of functional groups including methyl, chloro, Boc, and acetamido were found to be well tolerated under these reaction conditions.

A plausible mechanism to rationalize this spiropyrazoline synthesis is illustrated in Scheme 2. Condensation of cyclic ketones **4** with tosylhydrazide generates cyclic ketone *N*-tosylhydrazones **2**, which undergo deprotonation to form *N*-tosylhydrazone salts **5**. Tautomerization of compounds **5** with the remove of *N*-Ts function forms diazo compounds **6**, which undergo 1,3-cycloadditions with α,β-unsaturated ketones **1** followed by a 1,3-hydrogen shift to afford spiropyrazolines **3**. On the other hand, tautomerization of compounds **5** without the remove of *N*-Ts function forms compounds **9**, which undergo Michael addition with α,β-unsaturated ketones **1** to generate the intermediates **10**. Finally, compounds **10** undergo a intramolecular substitution followed by a 1,3-hydrogen shift to afford spiropyrazolines **3**.



Scheme 2 Proposed mechanism

Table 2 Synthesis of Spiropyrazolines from Chalcones and Cyclic Ketone *N*-Tosylhydrazones[a]



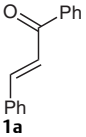
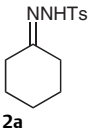
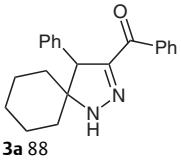
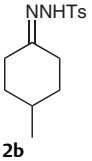
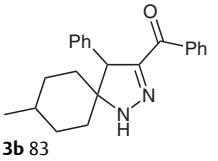
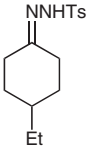
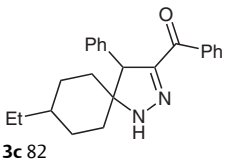
Entry	1	2	Time (h)	Yield of **3** (%)[10]
1	 **1a**	 **2a**	2	 **3a** 88
2	**1a**	 **2b**	4	 **3b** 83
3	**1a**	 **2c**	4	 **3c** 82

Table 2 (continued)

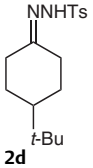
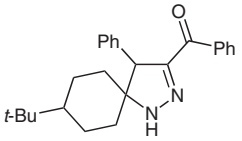
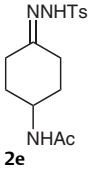
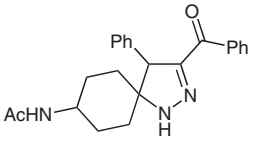
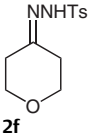
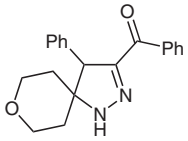
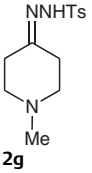
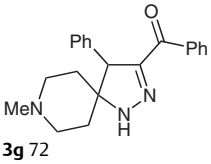
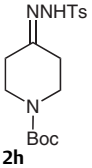
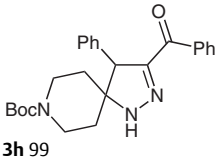
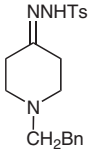
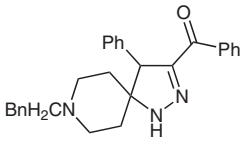
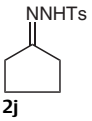
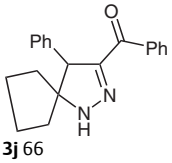
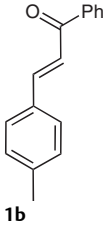
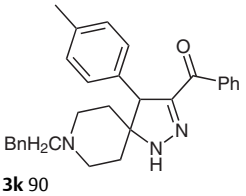
Entry	1	2	Time (h)	Yield of **3** (%)[10]
4	**1a**	 **2d**	4	 **3d** 62
5	**1a**	 **2e**	5	 **3e** 60
6	**1a**	 **2f**	5	 **3f** 63
7	**1a**	 **2g**	3	 **3g** 72
8	**1a**	 **2h**	8	 **3h** 99
9	**1a**	 **2i**	3	 **3i** 89
10	**1a**	 **2j**	4	 **3j** 66
11	 **1b**	**2i**	4	 **3k** 90

Table 2 (continued)

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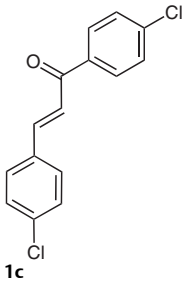
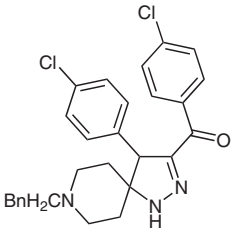
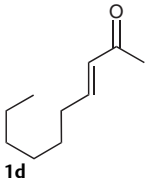
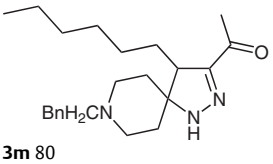
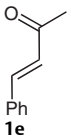
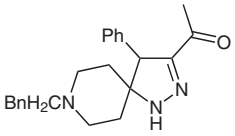
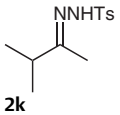
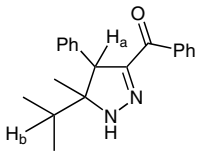
12	 **1c**	**2i**	3	 **3l** 93
13	 **1d**	**2i**	3	 **3m** 80
14	 **1e**	**2i**	3	 **3n** 82
15	**1a**	 **2k**	4	 **3o** 81

[a] General conditions: **1** (0.1 mmol), **2** (0.2 mmol), Cs_2CO_3 (0.2 mmol) in MeCN (1.0 mL).

In summary, we have developed a simple approach for the synthesis of spiropyrazolines from chalcones and cyclic ketone *N*-tosylhydrazones under catalyst-free conditions. In view of the readily available and stable starting materials, the high efficiency/selectivity, and the excellent functional-group tolerance, this protocol is expected to find considerable applications for the synthesis of functional pyrazolines, a structural motif for a large number of pharmaceuticals and functional materials.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379616.

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(10) **Synthetic Procedure for Spiropyrazolines 3**

A mixture of cyclohexanone (**4a**, 21 µL, 0.2 mmol) and *N*-tosylhydrazide (38.0 mg, 0.2 mmol) in MeOH (mL) was stirred at r.t. for 3 h, and then the solvent was removed in vacuo to give cyclohexanone tosylhydrazone (**2a**, 63.6 mg) in 100% yield. Subsequently, the mixture of the resulting cyclohexanone *N*-tosylhydrazone (**2a**, 63.6 mg, 0.2 mmol), Cs_2CO_3 (66.5 mg, 0.2 mmol) and chalcone (**1a**, 20.8 mg, 0.1 mmol) in MeCN (1.0 mL) was stirred at 110 °C (screw-capped vial) for 2 h under argon, cooled to r.t., and H_2O (10 mL) and EtOAc (10 mL) were added. The two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (100–200 mesh) to afford the desired spiropyrazoline **3a** (30.0 mg) in 88% yield.

Spiropyrazoline **3a**: pale yellow solid; mp 180–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.3 Hz, 2 H), 7.52–7.05 (m, 9 H), 4.24 (s, 1 H), 1.72–1.24 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 153.1, 137.5, 136.1, 132.1, 129.9, 128.6, 128.4, 127.9, 127.1, 67.1, 57.7, 37.3, 31.6, 25.2, 23.4, 22.4. FTIR (film): 3315, 2930, 2855, 1625, 1449, 1423, 1226, 870, 718, 699 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{21}H_{22}N_2NaO$ $[M + Na]^+$: 341.1624; found: 341.1619.

Spiropyrazoline **3b**: pale yellow solid; mp 174–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.4 Hz, 2 H), 7.54–7.07 (m, 8 H), 6.77 (s, br, 1 H), 4.16 (s, 1 H), 2.03–1.03 (m, 9 H), 0.90 (d, *J* = 5.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 152.9, 137.5, 136.2, 132.1, 129.9, 128.4, 128.3, 127.9, 127.1, 68.7, 59.2, 37.3, 31.8 (d), 31.4, 31.1, 22.0. FTIR (film): 33327, 2949, 2924, 2867, 1708, 1673, 1624, 1598, 1449, 1422, 1221, 857, 717, 699 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{22}H_{25}N_2$ $[M + H]^+$: 333.1961; found: 333.1960.

Spiropyrazoline **3c**: pale yellow solid; mp 169–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 6.3 Hz, 2 H), 7.56–7.13 (m, 8 H), 5.99 (s, br, 1 H), 4.21 (s, 1 H), 2.06–0.87 (m, 14 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 152.7, 137.4, 136.1, 132.0, 129.9, 128.5, 128.3, 127.9, 127.0, 69.0, 59.2, 38.0, 31.7, 29.3, 29.1, 28.6, 11.3. FTIR (film): 3306, 2956, 2924, 2856, 1610, 1574, 1531, 1447, 1425, 1219, 860, 717, 698 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{27}N_2O$ $[M + H]^+$: 347.2118; found: 347.2149.

Spiropyrazoline **3d**: pale yellow solid; mp 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.1 Hz, 2 H), 7.55–7.07 (m, 8 H), 5.65 (s, br, 1 H), 4.16 (s, 1 H), 2.10–0.90 (m, 9 H), 0.84 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 152.8, 137.4, 136.1, 132.0, 129.9, 128.3, 128.2, 127.9, 127.0, 68.7, 59.4, 46.9, 38.0, 32.5, 32.2, 27.3, 24.0, 23.4. FTIR (film): 3313, 2948, 2866, 1611, 1447, 1426, 1223, 1120, 860, 697 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{25}H_{31}N_2O$ $[M + H]^+$: 375.2431; found: 375.2437.

Spiropyrazoline **3e**: pale yellow solid; mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 6.6 Hz, 2 H), 7.54–7.05 (m, 8 H), 6.08 (s, br, 1 H), 4.16 (s, 1 H), 3.72 (s, br, 1 H), 2.06–1.13 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 169.8, 1152.2, 137.4, 135.8, 132.2, 129.8, 128.5, 128.2, 128.0, 127.3, 68.0, 58.6, 47.1, 35.7, 30.3, 29.0, 28.3, 23.1. FTIR (film): 3286, 2928, 2854, 1629, 1539, 1471, 1448, 1431, 1369, 1221, 1143, 1125, 860, 719, 700 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{26}N_3O_2$ $[M + H]^+$:

376.2020; found: 375.2015.

Spiropyrazoline **3f**: white solid; mp 185–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.3 Hz, 2 H), 7.56–7.16 (m, 8 H), 6.59 (s, br, 1 H), 4.37 (s, 1 H), 3.83 (dd, *J* = 28.5, 4.1 Hz, 2 H), 3.54 (s, 2 H), 1.88–1.42 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.3, 153.3, 137.2, 135.2, 132.4, 129.9, 128.7, 128.6, 128.0, 127.5, 66.9, 65.5, 64.0, 57.2, 37.6, 31.7. FTIR (film): 3300, 2957, 2924, 2852, 1626, 1575, 1535, 1448, 1429, 1384, 1225, 1105, 861, 718, 700 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{20}H_{21}N_2O_2$ $[M + H]^+$: 321.1598; found: 321.1596.

Spiropyrazoline **3g**: yellow solid; mp 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.3 Hz, 2 H), 7.53–7.11 (m, 8 H), 6.78 (s, br, 1 H), 4.28 (s, 1 H), 2.67–2.18 (m, 7 H), 1.87–1.44 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.3, 152.9, 137.3, 135.5, 132.2, 129.9 (d), 128.5, 127.9, 127.3, 66.9, 53.0, 51.8, 45.8, 36.7, 31.0, 29.6. FTIR (film): 3304, 2924, 2853, 1625, 1449, 1431, 1378, 1226, 1131, 860, 718, 699 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{21}H_{24}N_3O$ $[M + H]^+$: 334.1914; found: 334.1916.

Spiropyrazoline **3h**: yellow foam; mp 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.6 Hz, 2 H), 7.52–7.11 (m, 9 H), 4.31 (s, 1 H), 3.64–3.18 (m, 4 H), 1.74–1.33 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.2, 154.5, 152.6, 137.2, 135.3, 132.2, 129.8, 128.6, 128.4, 127.9, 127.4, 79.8, 67.7, 56.9, 41.0, 39.7, 36.3, 30.9, 28.3. FTIR (film): 3300, 1692, 1671, 1630, 1449, 1422, 1366, 1265, 1247, 1164, 860, 700 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{25}H_{30}N_3O_3$ $[M + H]^+$: 420.2282; found: 420.2283.

Spiropyrazoline **3i**: yellow foam; mp 61–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.6 Hz, 2 H), 7.57–7.14 (m, 13 H), 6.70 (s, br, 1 H), 4.32 (s, 1 H), 2.86–1.52 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.3, 153.1, 139.7, 137.3, 135.5, 132.3, 129.9, 128.8, 128.6, 128.4, 128.3, 128.0, 127.4, 126.2, 67.4, 60.1, 57.2, 51.0, 49.8, 36.6, 33.4, 30.9. FTIR (film): 3309, 2926, 1624, 1575, 1536, 1494, 1449, 1428, 1375, 1225, 1128, 860, 749, 718, 699 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{28}H_{30}N_3O$ $[M + H]^+$: 424.2383; found: 424.2389.

Spiropyrazoline **3j**: yellow solid; mp 141–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.8 Hz, 2 H), 7.52–7.12 (m, 8 H), 6.48 (s, br, 1 H), 4.24 (s, 1 H), 1.91–1.37 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.3, 152.9, 137.6, 137.5, 132.1, 129.9, 128.6, 128.0, 127.9, 127.1, 78.5, 57.2, 41.0, 31.7, 22.9, 22.7. FTIR (film): 3304, 2957, 2873, 1673, 1598, 1575, 1526, 1494, 1448, 1423, 1229, 1156, 717, 699 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{20}H_{21}N_2O$ $[M + H]^+$: 305.1648; found: 305.1648.

Spiropyrazoline **3n**: pale yellow solid; mp 157–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.04 (m, 10 H), 6.56 (s, br, 1 H), 4.07 (s, 1 H), 2.86–2.31 (m, 11 H), 1.88–1.44 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 153.4, 139.8, 135.3, 128.7, 128.6, 128.5, 128.4, 127.3, 126.1, 68.0, 60.2, 56.1, 50.9, 49.8, 36.5, 33.5, 31.0, 25.5. FTIR (film): 3300, 2926, 2812, 1655, 1541, 1496, 1455, 1432, 1376, 1345, 1191, 1128, 1079, 889, 749, 701 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{28}N_3O$ $[M + H]^+$: 362.2227; found: 362.2220.