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Synthesis of Spirocyclic Pyrazolones by Oxidative C−N Bond Formation

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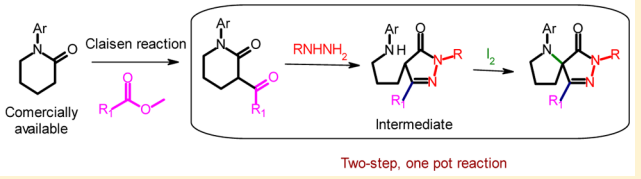
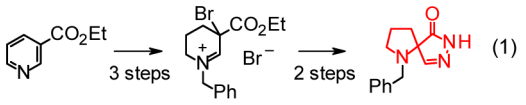
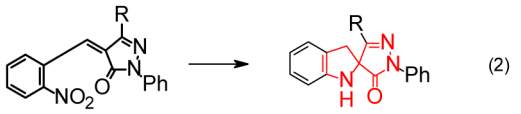
Supporting Information

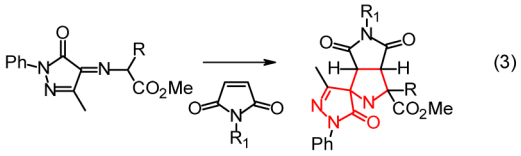
ABSTRACT: The two-step synthesis of spirocyclic pyrazolone derivatives from simple and commercially available reagents is described. The unusual reaction of 1,3-dicarbonyls with hydrazines and an iodine-mediated oxidative carbon−nitrogen bond formation, joined in a two-step, one-pot reaction, allows the straightforward synthesis of these spirocycles.

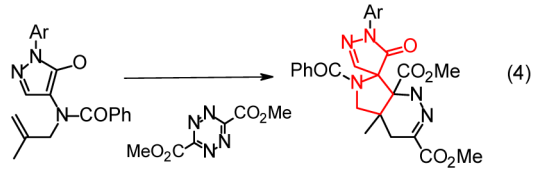


Pyrazolones exhibit a great variety of biological activities such as analgesic, antibacterial, antifungal, antiinflammatory, antidiabetic, and anxiolytic activity.[1] They also have found applications as dyes and pigments.[1] As part of our research into biologically active compounds, we became interested in spirocyclic pyrazolones. To our knowledge, there is only one report of the preparation of spirocycles of pyrrolidine and pyrazolone rings. A low-yielding synthesis of an *N*-benzylpyrrolidine pyrazolone spirocycle from unstable and hygroscopic 1-benzyl-5-(ethyoxycarbonyl)-2,3,4,5-tetrahydropyridinium bromide was described by Ponticelli and co-workers (eq 1).[2]





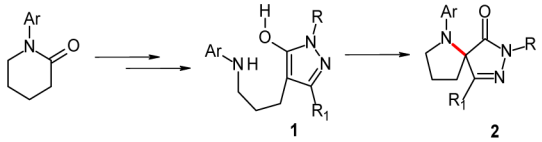




Other related 5,5-spirocycles were obtained by the reduction of 4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one by sodium borohydride in the presence of Pd/C (eq 2),[3] 1,3-cycloaddition of maleimide with azomethine ylide (eq 3),[4] or [4 + 2] cycloaddition with tetrazine followed by intramolecular cyclization (eq 4).[5] All of these strategies were low yielding and/or required many steps.

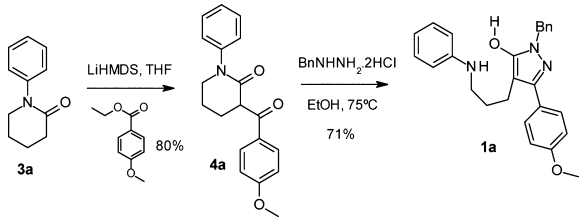
Herein, we report the preparation of spirocyclic pyrazolones **2** from *N*-arylpiperidin-2-ones via hydroxypyrazoles **1** by oxidative C−N bond formation (Scheme 1).

Scheme 1. Synthetic Approach



We started our work with the development of a method for the preparation of **1a** as a model for the exploration of the desired oxidative C−N bond formation. This compound was easily made in two steps, starting with the Claisen reaction of 1-phenylpiperidin-2-one (**3a**) and ethyl 4-methoxybenzoate[6] to obtain dicarbonyl **4a** in good yield.[7] There are a few isolated examples in the literature for the transformation of similar 1,3-dicarbonyls into ring-opened derivatives such as **1**.[8] Gratifyingly, the reaction of **4a** with benzylhydrazine provided **1a** in 71% yield on a 2 g scale (Scheme 2).[9]

Scheme 2. Preparation of the Ring-Opened Derivative 1a



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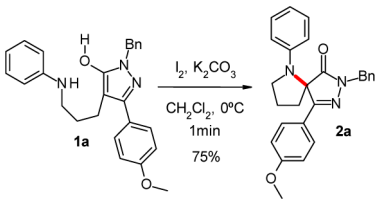
With an efficient method in hand to obtain derivative **1a**, we turned to the oxidative C−N bond formation. We hypothesized that treatment of **1a** with reactants such as NBS or I_2 could afford the bromo- or iodopyrazolone,[10] which would undergo displacement by the aniline nitrogen[11] or could form the N-halogenated[12] intermediate followed by displacement by the carbon of the pyrazolone. Thus, when we treated **1a** with NBS and K_2CO_3 in dichloromethane at 0 °C or rt, we observed a mixture of **2a**, starting material, and mono- and dibrominated derivatives by LC−MS. When NBS was replaced by I_2, full conversion to spirocycle **2a**[13] was observed in 1 min (Scheme 3). Screening of the reaction conditions with iodine

Scheme 3. Oxidative C−N Bond Formation



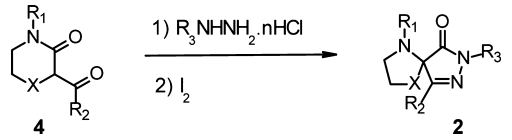
(Supporting Information, Table S1) showed that C−N bond formation worked in good yield regardless of the solvent and temperature used. Surprisingly, the reaction took place with a similar yield in the absence of base.

Taking into account that the formation of both **1a** and **2a** can be carried out in ethanol, we then attempted a two-step, one-pot reaction. Thus, after the reaction of the 1,3-dicarbonyl **4a** with benzylhydrazine was complete, addition of I_2 afforded **2a** in a 80% yield, a significant improvement over the 58% yield obtained in the two-step process. The lower overall yield of the stepwise procedure could be explained by the instability of **1a** during isolation.[14]

Table 1 shows the scope of the reaction. R_1 can be an electron-rich aromatic ring with electron donating groups at the *para* (**2b**, **2c**) or *meta* position (**2d**). An *o*-Me group (**2e**) did not provide the desired product.[15] R_1 can be also a phenyl ring with electron-withdrawing groups such as chlorine, trifluoromethyl, or cyano (**2f**−**h**). Reaction with *p*-CN substitution proceeded in low yield (24%) even after heating at 75 °C overnight under otherwise standard conditions. Pleasingly, the addition of AgOTf, which renders I_2 more electrophilic, improved the yield to 62%. R_2 tolerates phenyl rings with electron-donating and electron-withdrawing groups (**2a**−**k**) in any position. The reaction is also compatible with heterocycles (**2l**,**m**) and aliphatic chains such as ethyl (**2n**). We envisioned the use of cycles other than piperidone.[16] Morpholin-3-one gave spirocycle **2o** in good yield. Finally, we found other hydrazines can be used in the reaction. Thus, the use of phenylhydrazine gave **2p** in 93% yield, and hydrazine gave **2q** in 79% yield.

To gain insight into the mechanism of the oxidative coupling, TEMPO was added before I_2. No effect was observed on the outcome of the reaction, suggesting that no radical mechanism is operative. Three possible mechanisms could be envisioned (Scheme 4): (a) formation of intermediate **I** followed by displacement with the aniline nitrogen, (b) formation of intermediate **II** and attack of the carbon of the pyrazolone,[12a,b] and (c) iodination to form **II** with subsequent intramolecular iodination to afford **I** and displacement by the aniline.[12c]

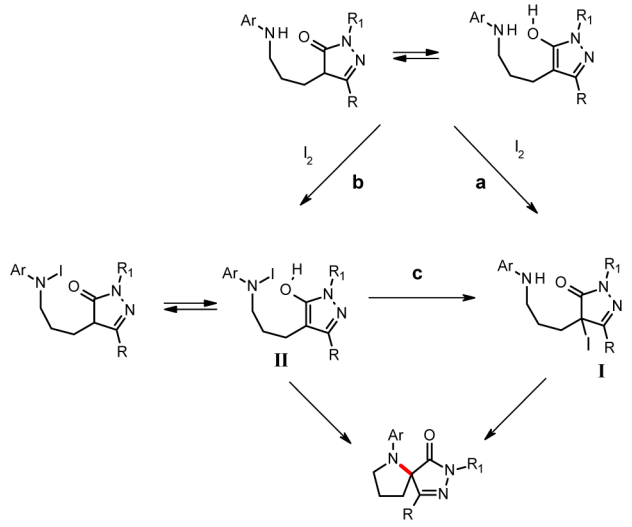
Table 1. Substrate Scope[a]



compd	R_1	R_2	R_3	X	yield (%)
2a	Ph	*p*-MeOPh	Bn	C	80
2b	*p*-MeOPh	*p*-MeOPh	Bn	C	76
2c	*p*-MePh	*p*-MeOPh	Bn	C	68
2d	*m*-MePh	*p*-MeOPh	Bn	C	72
2e	*o*-MePh	*p*-MeOPh	Bn	C	0
2f	*p*-ClPh	*p*-MeOPh	Bn	C	66
2g	*p*-CF_3Ph	*p*-MeOPh	Bn	C	57
2h[b]	*p*-CNPh	*p*-MeOPh	Bn	C	62
2i[c]	Ph	*o*-MePh	Bn	C	47
2j	Ph	*m*-BrPh	Bn	C	73
2k	Ph	*p*-CNPh	Bn	C	88
2l	Ph	4-pyridyl	Bn	C	78
2m	Ph	2-thienyl	Bn	C	77
2n	Ph	Et	Bn	C	78
2o	Ph	*p*-MeOPh	Bn	O	82
2p[d]	*p*-ClPh	*p*-MeOPh	Ph	C	93
2q[e]	Ph	*p*-MeOPh	H	C	79

[a]Reaction conditions: **4** (1 equiv) and benzylhydrazine·2HCl (1.1 equiv) in EtOH (0.25 M) were heated at 75 °C overnight, I_2 (1.05 equiv) was added at 0 °C, and the mixture was stirred for 30 min. [b]I_2 (2 equiv) and AgOTf (2 equiv) were added, and the mixture was stirred for 1 h. [c]Benzylhydrazine·2HCl (1.5 equiv), 90 °C, then I_2 (1.7 equiv). [d]Phenylhydrazine·HCl was used. [e]Hydrazine·H_2O (1.7 equiv) then I_2 (3 equiv).

Scheme 4. Possible Reaction Mechanisms



We believe that the mechanisms **b** and **c** are more plausible on the basis of recent publications by Baran and co-workers[12a,b] and Zhang and co-workers[12c] and some experimental observations: (1) the oxidative coupling is rapid in all attempted solvents (<1 min), while halogenation of pyrazolones is usually described to be slower;[10] (2) when a reaction to obtain **2h** was run in the absence of AgOTf, **I** was neither observed by LC−MS nor isolated, although starting material remained. Formation of **I** should not be affected by a distal CN group, but the subsequent ring closure might reasonably be

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expected to be much slower. Thus, if pathway a were operative, **I** should be observed in the case of incomplete reaction to form **2h**. In contrast, the presence of a CN group would be expected to decrease the nucleophilicity of the aniline nitrogen toward iodination (pathway b) but not negatively impact ring closure. We surmise that AgOTf is necessary to increase the electrophilicity of I_2 in the formation of intermediate **II**.

In summary, we have described the straightforward synthesis of 5,5-spirocyclic pyrazolones in two reactions from simple and commercially available starting materials by a metal-free C−N oxidative coupling. The synthesis is quite versatile, allowing introduction of different substituents at three positions of the spirocycle.

EXPERIMENTAL SECTION

General Considerations. All experiments were conducted under an inert atmosphere. ^{1}H NMR spectra were recorded on 300 MHz instruments. ^{13}C NMR spectra were recorded at 75 MHz. LC−MS data were obtained on a single quad mass spectrometer using ESI. High-resolution mass spectrometry (HRMS) data were obtained on a TOF mass spectrometer using ESI. Flash chromatography was performed using SiO_2 cartridges. All commercial reagents were used as supplied. THF was dried over activated 4 Å molecular sieves.

4-(3-Anilinopropyl)-2-benzyl-5-(4-methoxyphenyl)pyrazol-3-ol (1a). Ethanol (25 mL) and pyridine (1 mL, 12.6 mmol) were added to a resealable tube containing 3-(4-methoxybenzoyl)-1-phenylpiperidin-2-one (**4a**) (2 g, 6.3 mmol) and benzylhydrazine dihydrochloride (1.9 g, 9.5 mmol) under nitrogen atmosphere. The tube was capped, and the mixture was stirred at 80 °C for 24 h. The mixture was cooled to rt and diluted with ethyl acetate. The organic layer was washed with $NaHCO_3$ (sat) and brine, dried over anhydrous sodium sulfate, and filtered, and the solvent was removed. The residue was chromatographed in a silica gel cartridge (50 g) eluting with dichloromethane/ethyl acetate 10%, 20%, and 30% to obtain 1.85 g (71%) of the title compound as a white solid (mixture of tautomers). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.69 (s, 0.23H), 10.23 (bs, 0.77H), 7.48 (d, J = 8.8 Hz, 1.7H), 7.42 (d, J = 8.3 Hz, 0.4H), 7.33−7.17 (m, 6H), 7.04 (t, J = 7.8 Hz, 2.3H), 7.01−6.96 (m, 0.5H), 6.86 (d, J = 8.8 Hz, 1.7H), 6.51−6.47 (m, 3.5H), 5.65 (bs, 0.2H), 5.51 (bs, 0.7H), 5.12 (s, 1.7H), 4.90 (s, 0.5H), 4.86 (s, 0.1H), 3.77 (s, 0.5H), 3.74 (s, 3H), 3.00−2.93 (m, 2.2H), 2.59−2.55 (m, 1.5H), 1.76−1.64 (m, 2.2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 158.2, 149.8, 148.8, 146.6, 138.1, 128.8, 128.4, 127.8, 127.5, 127.1, 115.3, 113.7, 111.8, 97.9, 55.0, 49.5, 42.5, 29.4, 20.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{28}N_3O_2$ 414.2176, found 414.2196.

Experimental Procedure for the Synthesis of Dicarbonyls 4. A solution of LiHMDS in THF (1M, 2.2 equiv) was added via syringe to a solution of **3** (1 equiv) in anhydrous THF (2.5 mL/mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 45 min, and then the ester (1.05 equiv) was added. The ice bath was removed, and the mixture was stirred for 4 h. Water was poured into the mixture. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water and brine, dried over anhydrous sodium sulfate, and filtered, and the solvent was removed. Compounds were obtained as a mixture of tautomers.

*3-(4-Methoxybenzoyl)-1-phenylpiperidin-2-one (**4a**).* Following the general procedure from **3a** (500 mg, 2.85 mmol) and ethyl 4-methoxybenzoate (3 mmol), 708 mg (80%) of the title compound was obtained as a yellowish solid after washing with hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (d, J = 8.5 Hz, 2H), 7.40−7.21 (m, 5H), 6.93 (d, J = 8.5 Hz, 2H), 4.56 (t, J = 6.0 Hz, 1H), 3.85 (s, 3H), 3.80−3.66 (m, 2H), 2.38−2.30 (m, 1H), 2.25−2.12 (m, 2H), 2.01−1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.6, 167.2, 163.7, 143.1, 131.6, 129.4, 129.1, 126.8, 126.2, 113.8, 55.5, 51.4, 50.1, 25.3, 21.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{20}NO_3$ 310.1437, found 310.1424.

*3-(4-Methoxybenzoyl)-1-(4-methoxyphenyl)piperidin-2-one (**4b**).* Following the general procedure from **3b** (250 mg, 1.22 mmol) and ethyl 4-methoxybenzoate (1.28 mmol), 321 mg (77%) of the title compound was obtained as a white solid after washing with hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.91 (m, 4H), 4.54 (t, J = 6.0 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.71−3.65 (m, 2H), 2.37−2.25 (m, 1H), 2.19−2.15 (m, 2H), 1.99−1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.7, 167.4, 163.7, 158.2, 136.0, 131.6, 129.4, 127.4, 114.4, 113.8, 55.54, 55.50, 51.8, 50.1, 25.3, 21.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{22}NO_4$ 340.1543, found 340.1536.

*3-(4-methoxybenzoyl)-1-p-tolylpiperidin-2-one (**4c**).* Following the general procedure from **3c** (250 mg, 1.32 mmol) and ethyl 4-methoxybenzoate (1.39 mmol), 268 mg (59%) of the title compound was obtained as a white solid after washing with hexane and MTBE: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (d, J = 8.8 Hz, 0.3H), 7.50 (d, J = 8.8 Hz, 2H), 7.25−7.17 (m, 4H), 6.93 (d, J = 8.8 Hz, 2.3H), 4.55 (t, J = 6.0 Hz, 0.15H), 3.86 (s, 0.45H), 3.84 (s, 3H), 3.72−3.67 (m, 2H), 2.69−2.64 (m, 2H), 2.36 (s, 3H), 2.33 (s, 0.45H), 2.37−2.33 (m, 4H), 2.23−2.12 (m, 0.3H), 1.98−1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.7, 171.2, 169.0, 167.3, 163.7, 160.4, 140.5, 136.9, 136.7, 131.7, 129.94, 129.92, 129.8, 129.4, 128.4, 126.2, 126.1, 113.8, 113.4, 96.4, 55.6, 55.4, 51.8, 51.6, 50.2, 26.1, 25.3, 23.6, 21.4, 21.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{22}NO_3$ 324.1594, found 324.1589.

*3-(4-Methoxybenzoyl)-1-m-tolylpiperidin-2-one (**4d**).* Following the general procedure from **3d** (700 mg, 3.7 mmol) and ethyl 4-methoxybenzoate (3.88 mmol), 761 mg (64%) of the title compound was obtained as a white solid after washing with hexane and MTBE: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (d, J = 8.8 Hz, 2H), 7.26 (t, J = 7.7 Hz, 1H), 7.12−7.04 (m, 3H), 6.94 (d, J = 8.8 Hz, 2H), 4.55 (t, J = 6.1 Hz, 1H), 3.85 (s, 3H), 3.79−3.67 (m, 2H), 2.39−2.30 (m, 1H), 2.34 (s, 3H), 2.23−2.12 (m, 2H), 2.05−1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.6, 167.1, 163.6, 143.0, 138.9, 131.5, 129.3, 128.9, 127.6, 126.9, 123.1, 113.7, 55.5, 51.5, 50.1, 25.2, 21.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{22}NO_3$ 324.1594, found 324.1584.

*3-(4-Methoxybenzoyl)-1-o-tolylpiperidin-2-one (**4e**).* Following the general procedure from **3e** (260 mg, 1.37 mmol) and ethyl 4-methoxybenzoate (1.44 mmol), 270 mg (61%) of the title compound was obtained as a white solid after washing with hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (d, J = 9.1 Hz, 2H), 7.26−7.11 (m, 4H), 6.94 (d, J = 8.8 Hz, 2H), 4.61−4.55 (m, 1H), 3.86 (s, 3H), 3.76−3.44 (m, 2H), 2.43−2.18 (m, 6H), 2.03−1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.7, 196.5, 166.6, 166.4, 163.65, 163.59, 141.8, 135.8, 134.6, 131.4, 131.0, 130.8, 129.3, 129.1, 127.72, 127.69, 127.4, 127.1, 126.9, 126.6, 113.71, 113.67, 55.4, 51.1, 50.9, 49.9, 49.8, 25.3, 21.3, 20.8, 17.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO_3$ 346.1413, found 346.1400.

*1-(4-Chlorophenyl)-3-(4-methoxybenzoyl)piperidin-2-one (**4f**).* Following the general procedure from **3f** (1.2 g, 5.74 mmol) and ethyl 4-methoxybenzoate (6.02 mmol), 1.8 g (91%) of the title compound was obtained as a white solid after washing with hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.04−7.99 (m, 1H), 7.52−7.48 (m, 1H), 7.40−7.32 (m, 2H), 7.29−7.23 (m, 2H), 6.97−6.90 (m, 2H), 4.55 (t, J = 6.3 Hz, 0.5H), 3.86 (s, 1.5H), 3.84 (s, 1.5H), 3.74−3.68 (m, 2H), 2.69−2.64 (m, 1.2H), 2.38−2.14 (m, 1.5H), 2.00−1.90 (m, 1.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.5, 170.9, 169.3, 167.3, 163.7, 160.4, 141.5, 141.3, 132.2, 132.0, 131.4, 129.7, 129.1, 129.0, 127.9, 127.6, 127.4, 113.7, 113.3, 96.1, 55.4, 55.2, 51.4, 51.2, 50.0, 25.9, 25.2, 23.3, 21.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{18}ClNNaO_3$ 366.0867, found 366.0856.

*3-(4-Methoxybenzoyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one (**4g**).* Following the general procedure from **3g** (1 g, 4.11 mmol) and ethyl 4-methoxybenzoate (4.32 mmol), 842 mg (55%) of the title compound was obtained as a white solid after chromatography on silica gel eluting with hexane/ethyl acetate 10%, 20%, and 40%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 4.58 (t, J = 6.2 Hz, 1H), 3.86 (s, 3H), 3.78−3.74 (m, 2H), 2.38−2.18 (m, 3H), 2.05−1.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 196.4, 167.5, 163.9, 146.1 (q, J = 1.4 Hz), 131.5, 129.1, 128.6 (q, J =

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33.3 Hz), 126.3, 126.1 (q, J = 3.7 Hz), 124.0 (q, J = 271.3 Hz), 113.9, 55.6, 51.0, 50.2, 25.3, 21.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{19}F_3NO_3$ 378.1311, found 378.1324.

*4-[3-(4-Methoxybenzoyl)-2-oxo-1-piperidyl]benzonitrile (**4h**).* Following the general procedure from **3h** (250 mg, 1.25 mmol) and ethyl 4-methoxybenzoate (1.31 mmol), 320 mg (71%) of the title compound was obtained as a white solid after washing with hexane: ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.01 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.73 (t, J = 7.3 Hz, 1H), 3.86 (s, 3H), 3.81−3.76 (m, 2H), 2.20−1.85 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 196.7, 167.6, 163.4, 147.1, 132.8, 131.2, 128.8, 126.3, 118.6, 113.9, 108.2, 55.6, 50.0, 49.8, 25.0, 20.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{18}N_2NaO_3$ 357.1209, found 357.1207.

*3-(2-Methylbenzoyl)-1-phenylpiperidin-2-one (**4i**).* Following the general procedure from **3a** (250 mg, 1.43 mmol) and methyl 2-methylbenzoate (1.50 mmol), 340 mg (81%) of the title compound was obtained as a white solid after chromatography on silica gel eluting with hexane/ethyl acetate 10%, 20%, and 50%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47−7.39 (m, 2H), 7.35−7.22 (m, 7H), 3.73−3.69 (m, 2H), 2.38 (s, 3H), 2.30−2.26 (m, 2H), 1.97−1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.7, 170.3, 142.7, 135.7, 135.3, 130.4, 129.3, 129.0, 128.0, 127.1, 126.4, 125.6, 97.8, 51.8, 25.0, 23.3, 19.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{20}NO_2$ 294.1488, found 294.1478.

*3-(3-Bromobenzoyl)-1-phenylpiperidin-2-one (**4j**).* Following the general procedure from **3a** (250 mg, 1.43 mmol) and methyl 3-bromobenzoate (1.5 mmol), 330 mg (65%) of the title compound was obtained as a white solid after chromatography on silica gel eluting with hexane/ethyl acetate 30%, 50%, and 100%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.17 (m, 0.5H), 7.98 (d, J = 8.0 Hz, 0.5H), 7.69−7.66 (m, 0.5H), 7.55−7.51 (m, 0.5H), 7.48−7.35 (m, 7H), 4.53 (t, J = 6.7 Hz, 0.5H), 3.78−3.71 (m, 2H), 2.64−2.60 (m, 1.5H), 2.44−2.32 (m, 0.5H), 2.26−2.13 (m, 1H), 2.06−1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 197.0, 170.8, 167.5, 166.6, 142.8, 142.7, 138.4, 137.7, 136.1, 132.4, 132.2, 131.3, 130.2, 129.7, 129.36, 129.28, 127.9, 127.2, 127.1, 126.9, 126.4, 126.2, 122.9, 122.2, 97.6, 51.7, 51.5, 50.5, 25.8, 25.0, 23.4, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{17}BrNO_2$ 358.0437, found 358.0448.

*4-(2-Oxo-1-phenylpiperidine-3-carbonyl)benzonitrile (**4k**).* Following the general procedure from **3a** (750 mg, 4.28 mmol) and methyl 4-cyanobenzoate (4.5 mmol), 1.1 g (84%) of the title compound was obtained as a white solid after chromatography on silica gel eluting with dichloromethane: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.16−8.13 (m, 0.5H), 7.77−7.63 (m, 3.5H), 7.45−7.25 (m, 5H), 4.59−4.53 (m, 0.25H), 3.79−3.72 (m, 2H), 2.63−2.59 (m, 1.4H), 2.49−2.40 (m, 0.25H), 2.28−2.21 (m, 0.4H), 2.06−1.96 (m, 1.7H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 198.6, 170.5, 167.1, 166.1, 143.3, 142.9, 140.2, 140.1, 133.2, 132.7, 129.9, 129.5, 129.4, 129.3, 127.3, 126.9, 126.6, 118.9, 115.6, 112.5, 99.1, 51.7, 51.2, 50.6, 25.2, 24.6, 23.1, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$ 305.1284, found 305.1277.

*1-Phenyl-3-(pyridine-2-carbonyl)piperidin-2-one (**4l**).* Following the general procedure from **3a** (250 mg, 1.43 mmol) and methyl isonicotinate (1.5 mmol), 275 mg (68%) of the title compound was obtained as a pale brown solid after washing with MTBE: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.81−8.78 (m, 0.15H), 8.71−8.68 (m, 2H), 7.83−7.81 (m, 0.15H), 7.47−7.34 (m, 7H), 4.53 (dd, J = 6.3, 7.7 Hz, 0.08H), 3.75−3.72 (m, 2.15H), 2.65−2.61 (m, 2H), 2.45−2.33 (m, 0.08H), 2.25−2.15 (m, 0.15H), 2.01−1.93 (m, 2.15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 197.7, 170.4, 166.1, 165.8, 150.7, 149.8, 143.2, 142.6, 142.4, 142.3, 129.2, 129.1, 127.2, 127.0, 126.1, 126.0, 122.5, 121.9, 98.4, 51.5, 51.4, 50.5, 25.4, 24.4, 23.1, 21.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{16}N_2NaO_2$ 303.1104, found 303.1098.

*1-Phenyl-3-(thiophene-2-carbonyl)piperidin-2-one (**4m**).* Following the general procedure from **3a** (250 mg, 1.43 mmol) and ethyl thiophene-2-carboxilate ester (1.5 mmol), 342 mg (83%) of the title compound was obtained as a pale brown solid after chromatography on silica gel eluting with hexane/ethyl acetate 20%, 40%, and 60%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.87 (dd, J = 1.1, 3.8 Hz, 1H), 7.66 (dd, J = 1.1, 4.9 Hz, 1H), 7.48−7.30 (m, 6H), 7.15−7.10 (m, 1H), 4.41 (t, J = 6.4 Hz, 1H), 3.80−3.69 (m, 2H), 2.87 (t, J = 6.6 Hz, 0.5H), 2.47−2.34 (m, 1H), 2.30−2.15 (m, 2H), 2.10−1.93 (m, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 190.6, 166.4, 143.8, 143.0, 134.6, 133.9, 129.6, 129.24, 129.18, 128.7, 128.3, 127.2, 127.0, 126.2, 96.2, 51.9, 51.5, 51.1, 25.8, 25.3, 23.2, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{16}NO_2S$ 286.0896, found 286.0902.

*1-Phenyl-3-propanoylpiperidin-2-one (**4n**).* Following the general procedure from **3a** (400 mg, 2.28 mmol) and ethyl propionate (2.4 mmol), 322 mg (61%) of the title compound was obtained as a pale brown waxy solid after chromatography on silica gel eluting with hexane/ethyl acetate 10%, 20%, and 40%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42−7.37 (m, 2H), 7.28−7.22 (m, 3H), 3.70−3.63 (m, 2H), 2.98−2.85 (m, 0.5H), 2.73−2.61 (m, 0.5H), 2.55−2.51 (m, 1H), 2.35−2.26 (m, 1.5H), 2.16−1.85 (m, 2.5H), 1.17 (t, J = 7.5 Hz, 1.3H), 1.08 (t, J = 7.3 Hz, 1.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 208.3, 175.3, 170.8, 167.0, 142.9, 129.2, 129.1, 127.0, 126.7, 126.2, 126.1, 94.7, 54.9, 51.5, 51.3, 36.5, 25.5, 23.8, 23.7, 23.2, 21.5, 10.6, 7.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$ 232.1332, found 232.1320.

*2-(4-Methoxybenzoyl)-4-phenylmorpholin-3-one (**4o**).* Following the general procedure from **3i** (850 mg, 4.8 mmol) and ethyl 4-methoxybenzoate (5.04 mmol), 680 mg (91% purity, 42%) of the title compound was obtained as a yellowish solid after chromatography on silica gel eluting with hexane/ethyl acetate 10%, 20%, 30%, and 50%. m/z 312 $[M + H]^+$. Due to the presence of tautomers and impurities, ^{1}H NMR and ^{13}C NMR are not described, but spectra can be found in Supporting Information.

Experimental Procedure for the Synthesis of Spirocycles 2. A resealable tube was charged with **4** (1 equiv) and the corresponding hydrazine derivative (1.1 equiv). The tube was purged with a nitrogen stream, and then ethanol (4 mL/mmol) and pyridine (if required) (2 equiv) were added via syringe. The tube was capped and the mixture was stirred at 75 °C overnight (typically 16 h) until starting material was consumed. The tube was cooled in an ice bath, and iodine was added (1.05 equiv). When the intermediate had been consumed by LC−MS (in some cases it was necessary to add 0.1 more equiv of iodine), the mixture was diluted with ethyl acetate and saturated $NaHCO_3$. The aqueous layer was discarded, the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and filtered, and the solvent was removed. Compounds were purified by chromatography on silica gel. Deviations from these standard conditions are indicated in each example.

*8-Benzyl-6-(4-methoxyphenyl)-4-phenyl-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2a**).* Following the general procedure from **4a** (106 mg, 0.34 mmol), 112 mg (80%) of the title compound was obtained as a white solid after chromatography in silica gel eluting with hexane/dichloromethane 20%, 40%, 60%, and 100%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.62−7.58 (m, 2H), 7.47−7.43 (m, 2H), 7.39−7.32 (m, 3H), 6.98−6.92 (m, 2H), 6.82−6.78 (m, 2H), 6.62 (t, J = 7.5 Hz, 1H), 6.21−6.17 (m, 2H), 5.12 (d, J = 14.8 Hz, 1H), 4.86 (d, J = 14.8 Hz, 1H), 3.88−3.74 (m, 2H), 3.76 (s, 3H), 2.53−2.47 (m, 1H), 2.33−2.28 (m, 2H), 2.16−2.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.8, 161.2, 159.0, 145.1, 136.5, 129.4, 128.8, 128.7, 128.0, 127.9, 122.8, 117.9, 114.2, 112.6, 71.6, 55.3, 50.1, 48.9, 38.1, 22.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{25}N_3O_2$ 412.2019, found 412.2042.

*8-Benzyl-4,6-bis(4-methoxyphenyl)-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2b**).* Following the general procedure from **4b** (300 mg, 0.88 mmol), 297 mg (76%) of the title compound was obtained as a pale yellow solid after chromatography in silica gel eluting with hexane/ethyl acetate 20%, 30%, and 40%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68−7.64 (m, 2H), 7.44−7.33 (m, 5H), 6.83−6.79 (m, 2H), 6.55−6.50 (m, 2H), 6.18−6.15 (m, 2H), 5.10 (d, J = 14.8 Hz, 1H), 4.83 (d, J = 14.8 Hz, 1H), 3.87−3.70 (m, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 2.53−2.44 (m, 1H), 2.39−2.26 (m, 2H), 2.24−2.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.1, 161.2, 159.2, 152.1, 139.6, 136.5, 128.8, 128.7, 128.0, 127.8, 122.9, 115.0, 114.1, 113.8,

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71.9, 55.6, 55.3, 50.4, 48.8, 38.0, 22.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{27}N_3O_3$ 442.2125, found 442.2131.

*8-Benzyl-6-(4-methoxyphenyl)-4-p-tolyl-4,7,8-triazaspiro[4.4]-non-6-en-9-one (**2c**).* Following the general procedure from **4c** (260 mg, 0.80 mmol), 232 mg (68%) of the title compound was obtained as a pale yellow solid after chromatography in silica gel eluting with hexane/ethyl acetate 10% and 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66−7.61 (m, 2H), 7.47−7.43 (m, 2H), 7.40−7.32 (m, 3H), 6.83−6.76 (m, 4H), 6.16−6.12 (m, 2H), 5.11 (d, J = 14.8 Hz, 1H), 4.87 (d, J = 14.8 Hz, 1H), 3.86−3.74 (m, 2H), 3.76 (s, 3H), 2.54−2.45 (m, 1H), 2.35−2.26 (m, 2H), 2.15−205 (s, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.9, 161.2, 159.1, 143.0, 136.6, 129.9, 128.8, 128.7, 128.0, 127.8, 126.9, 122.9, 114.2, 112.7, 71.7, 55.3, 50.2, 48.8, 38.1, 22.6, 20.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{27}N_3O_2$ 426.2176, found 426.2192.

*8-Benzyl-6-(4-methoxyphenyl)-4-m-tolyl-4,7,8-triazaspiro[4.4]-non-6-en-9-one (**2d**).* Following the general procedure from **4d** (400 mg, 1.24 mmol), 376 mg (72%) of the title compound as a pale yellow solid was obtained after chromatography in silica gel eluting with hexane/ethyl acetate 10% and 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.63−7.59 (m, 2H), 7.48−7.44 (m, 2H), 7.38−7.31 (m, 3H), 6.84−6.78 (m, 3H), 6.45 (d, J = 7.4 Hz, 1H), 6.12 (s, 1H), 5.96 (dd, J = 2.6, 8.1 Hz, 1H), 5.11 (d, J = 14.8 Hz, 1H), 4.85 (d, J = 14.8 Hz, 1H), 3.89−3.71(m, 2H), 3.76 (s, 3H), 2.54−2.42 (m, 1H), 2.32−2.25 (m, 2H), 2.15−2.04 (m, 1H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.6, 161.2, 159.1, 145.2, 139.1, 136.6, 129.2, 128.8, 128.7, 128.0, 127.8, 122.9, 119.0, 114.2, 113.4, 109.8, 71.6, 55.3, 50.1, 48.8, 38.3, 22.5, 21.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{27}N_3O_2$ 426.2176, found 426.2189.

*8-Benzyl-4-(4-chlorophenyl)-6-(4-methoxyphenyl)-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2f**).* Following the general procedure from **4f** (235 mg, 0.68 mmol), 206 mg (66%) of the title compound was obtained as a pale yellow solid after chromatography in silica gel eluting with hexane/ethyl acetate 10%, 20%, and 30%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60−7.55 (m, 2H), 7.46−7.33 (m, 5H), 6.88−6.80 (m, 4H), 6.10−6.06 (m, 2H), 5.12 (d, J = 14.8 Hz, 1H), 4.83 (d, J = 14.8 Hz, 1H), 3.87−73(m, 2H), 3.77 (s, 3H), 2.55−2.44 (m, 1H), 2.36−2.28 (m, 2H), 2.17−2.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.3, 161.3, 158.5, 143.7, 136.3, 129.2, 128.8, 128.7, 128.1, 127.8, 122.8, 122.5, 114.3, 113.8, 71.6, 55.3, 50.3, 49.0, 38.1, 22.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{24}ClN_3O_2$ 446.1630, found 446.1644.

*8-Benzyl-6-(4-methoxyphenyl)-4-[4-(trifluoromethyl)phenyl]-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2g**).* Following the general procedure from **4g** (490 mg, 1.3 mmol), 272 mg (57%) of the title compound was obtained as a white solid after chromatography in silica gel eluting with hexane/ethyl acetate 10% and 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.59−7.55 (m, 2H), 7.48−7.35 (m, 5H), 7.15 (d, J = 8.8 Hz, 2H), 6.84−6.80 (m, 2H), 6.18−6,15 (m, 2H), 5.14 (d, J = 14.8 Hz, 1H), 4.86 (d, J = 14.8 Hz, 1H), 3.92−3.76 (m, 2H), 3.77 (s, 3H), 2.59−2.44 (m, 1H), 2.37−2.32 (m, 2H), 2.19−2.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.0, 161.5, 158.2, 147.5, 136.3, 128.9, 128.8, 128.1, 127.8, 126.7 (c, J = 3.7 Hz), 122.4, 119.3 (c, J = 32.2 Hz), 114.3, 112.1, 71.5, 55.4, 50.3, 49.1, 38.0, 22.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{24}F_3N_3O_2$ 480.1893, found 480.1916.

*4-[8-Benzyl-6-(4-methoxyphenyl)-9-oxo-4,7,8-triazaspiro[4.4]-non-6-en-4-l]benzonitrile (**2h**).* Following the general procedure from **4h** (400 mg, 1.2 mmol), 313 mg (62%) of the title compound was obtained as a white solid after stirring for 1 h with iodine (2.4 mmol) and silver trifluoroacetate (2.4 mmol) and after chromatography in silica gel eluting with hexane/ethyl acetate 20%, 30%, and 40%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53−7.50 (m, 2H), 7.48−7.35 (m, 5H), 7.17−7.13 (m, 2H), 6.84−6.79 (m 2H), 6.12−6.08 (m, 2H), 5.14 (d, J = 14.5 Hz, 1H), 4.83 (d, J = 14.5 Hz, 1H), 3.90−3.81 (m, 2H), 3.78 (s, 3H), 2.58−2.52 (m, 1H), 2.37−2.33 (m, 2H), 2.21−2.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.4, 161.5, 157.7, 148.0, 136.1, 133.7, 128.9, 128.8, 128.3, 127.7, 122.1, 120.1, 114.4, 112.7, 100.0, 71.4, 55.4, 50.4, 49.2, 38.0, 22.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{24}N_4O_2$ 437.1972, found 437.1984.

*8-Benzyl-6-o-tolyl-4-phenyl-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2i**).* Following the general procedure from **4i** (310 mg, 1.06 mmol), benzylhydrazine 2HCl (1.6 mmol), and pyridine (3.18 mmol) after stirring at 90 °C overnight, 196 mg (47%) of the title compound was obtained as a white solid after stirring for 30 min with iodine (1.8 mmol) and after chromatography in silica gel eluting with hexane/ethyl acetate 10%, 20%, and 30%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48−7.43 (m, 2H), 7.40−7.33 (m, 3H), 7.26−7.18 (m, 2H), 7.09−6.98 (m, 4H), 6.68 (t, J = 7.3 Hz, 1H), 6.22 (d, J = 8.0 Hz, 2H), 5.13 (d, J = 14.5 Hz, 1H), 4.89 (d, J = 14.5 Hz, 1H), 3.82−3.73 (m, 1H), 3.62−3.55 (m, 1H), 2.47 (s, 3H), 2.39−2.20 (m, 2H), 2.17−2.09 (m, 1H), 1.86−1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.6, 159.7, 145.2, 137.7, 136.3, 131.3, 129.6, 129.5, 129.4, 128.9, 128.7, 128.6, 127.9, 126.0, 117.9, 112.7, 72.8, 50.0, 49.0, 37.6, 22.8, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{25}N_3O$ 396.2070, found 396.2075.

*8-Benzyl-6-(3-bromophenyl)-4-phenyl-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2j**).* Following the general procedure from **4j** (310 mg, 0.87 mmol), 279 mg (73%) of the title compound was obtained as a white solid after chromatography in silica gel eluting with hexane/ethyl acetate 10%, 20%, and 30%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.88 (t, J = 1.7 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.48−7.33 (m, 6H), 7.14 (t, J = 8.0 Hz, 1H), 6.95 (t, J = 7.8 Hz, 2H), 6.64 (t, J = 7.41 Hz, 1H), 6.16 (d, J = 8,0 Hz, 2H, 5.15 (d, J = 14.7 Hz, 1H), 4.87 (d, J = 14.7 Hz, 1H), 3.88−3.74 (m, 2H), 2.57−2.47 (m, 1H), 2.35−2.27 (m, 2H), 2.18−2.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.7, 157.6, 144.9, 136.2, 133.1, 131.9, 130.3, 129.4, 129.3, 128.82, 128.79, 128.0, 124.7, 122.9, 118.2, 112.6, 71.4, 50.1, 49.1, 37.8, 22.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{22}BrN_3O$ 460.1019, found 460.1013.

*4-(8-Benzyl-9-oxo-4-phenyl-4,7,8-triazaspiro[4.4]non-6-en-6-yl)-benzonitrile (**2k**).* Following the general procedure from **4k** (600 mg, 1.97 mmol), 706 mg (88%) of the title compound as a yellow solid was obtained after chromatography in silica gel eluting with hexane/ethyl acetate 30%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.47−7.36 (m, 5H), 6.95 (t, J = 8.0 Hz, 2H), 6.65 (t, J = 7.3 Hz, 1H), 6.14 (d, J = 8.0 Hz, 2H), 5.16 (d, J = 14.8 Hz, 1H), 4.89 (d, J = 14.8 Hz, 1H), 3.88−3.77 (m, 2H), 2.61−2.50 (m, 1H), 2.38−2.28 (m, 2H), 2.19−2.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.7, 157.0, 144.8, 136.0, 133.9, 132.5, 129.5, 128.8, 128.2, 126.6, 118.44, 118.41, 113.4, 112.6, 71.3, 50.2, 49.2, 37.7, 22.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{22}N_4O$ 407.1866, found 407.1876.

*8-Benzyl-4-phenyl-6-(4-pyridyl)-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2l**).* Following the general procedure from **4l** (230 mg, 0.82 mmol), 244 mg (78%) of the title compound was obtained as a yellow solid after chromatography in silica gel eluting with dichloromethane/ethyl acetate 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.56 (d, J = 6.0 Hz, 2H), 7.51−7.33 (m, 7H), 6.97−6.91 (m, 2H), 6.64 (t, J = 7.4 Hz, 1H), 6.15−6.11 (m, 2H), 5.17 (d, J = 14.8 Hz, 1H), 4.89 (d, J = 14.8 Hz, 1H), 3.86−3.78 (m, 2H), 2.61−2.52 (m, 1H), 2.37−2.27 (m, 2H), 2.21−2.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.8, 156.2, 149.1, 144.7, 138.0, 135.9, 129.6, 128.9, 128.8, 128.2, 120.3, 118.5, 112.5, 71.1, 50.2, 49.3, 37.5, 22.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{22}N_4O$ 383.1866, found 383.1876.

*8-Benzyl-4-phenyl-6-(2-thienyl)-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2m**).* Following the general procedure from **4m** (316 mg, 1.11 mmol), 332 mg (77%) of the title compound was obtained as a white solid after chromatography in silica gel eluting with hexane/ethyl acetate 20%, 30%, and 40%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47 (dd, J = 7.7, 1.6 Hz, 2H), 7.41−7.25 (m, 5H), 6.97−6.92 (m, 3H), 6.62 (t, J = 7.4 Hz, 1H), 6.15 (d, J = 7.7 Hz, 2H), 5.12 (d, J = 14.8 Hz, 1H), 4.86 (d, J = 14.8 Hz, 1H), 3.82 (dd, J = 7.5, 5.4 Hz, 2H), 2.54−2.42 (m, 1H), 2.40−2.35 (m, 2H), 2.24−2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.4, 156.0, 145.07, 136.4, 132.1, 129.4, 128.9, 128.8, 128.4, 128.0, 127.8, 127.6, 118.0, 112.7, 71.7, 50.4, 49.1, 38.7, 22.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{21}N_3OS$ 388.1478, found 388.1483.

*8-Benzyl-6-ethyl-4-phenyl-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2n**).* Following the general procedure from **4n** (275 mg, 1.19 mmol),

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309 mg (78%) of the title compound was obtained as a colorless waxy solid after chromatography in silica gel eluting with hexane/ethyl acetate 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.44−7.38 (m, 5H), 6.98−6.92 (m, 2H), 6.66−6.61 (m, 1H), 6.08−6.05 (m, 2H), 5.02 (d, J = 14.8 Hz, 1H), 4.78 (d, J = 14.8 Hz, 1H), 3.74−3.60 (m, 2H), 2.44−2.35 (m, 6H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 175.7, 166.6, 145.2, 136.5, 129.3, 128.8, 128.7, 127.8, 117.7, 112.3, 72.0, 50.1, 48.7, 37.4, 23.3, 21.0, 9.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{23}N_3O$ 334.1914, found 334.1925.

*3-Benzyl-1-(4-methoxyphenyl)-6-phenyl-9-oxa-2,3,6-triazaspiro-[4.4]non-1-en-4-one (**2o**).* Following the general procedure from **4o** (390 mg, 91% purity, 1.14 mmol), 387 mg (82%) of the title compound was obtained as a pale brown solid after chromatography in silica gel eluting with hexane/ethyl acetate 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.76−7.72 (m, 2H), 7.37−7.32 (m, 5H), 7.05−6.98 (m, 2H), 6.86−6.81 (m, 2H), 6.74 (t, J = 7.4 Hz, 1H), 6.44−6.39 (m, 2H), 5.07 (d, J = 15.1 Hz, 1H), 4.79−4.69 (m, 2H), 4.49−4.43 (m, 1H), 4.04 (td, J = 7.7, 4.9 Hz, 1H), 3.97−3.89 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.6, 161.5, 154.3, 142.6, 136.0, 129.5, 128.7, 128.5, 128.2, 127.9, 122.2, 119.7, 114.2, 113.9, 91.5, 65.9, 55.3, 48.7, 47.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{23}N_3O_3$ 414.1812, found 414.1824.

*4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-8-phenyl-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2p**).* Following the general procedure from **4f** (100 mg, 0.29 mmol) and $PhNHNH_2HCl$ (0.32 mmol), 116 mg (93%) of the title compound was obtained as a pale yellow solid after chromatography in silica gel eluting with hexane/ethyl acetate 20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.08−8.04 (m, 2H), 7.76−7.72 (m, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.27−7.22 (m, 1H), 7.07−7.03 (m, 2H), 6.91−6.86 (m, 2H), 6.35−6.32 (m, 2H), 3.92−3.78 (m, 2H), 3.81 (s, 3H), 2.60−2.51 (m, 1H), 2.48−2.40 (m, 2H), 2.23−2.14 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.2, 161.7, 159.1, 143.8, 138.3, 129.5, 129.1, 128.1, 125.4, 123.1, 122.2, 118.8, 114.4, 113.7, 72.9, 55.4, 50.5, 38.7, 22.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{22}ClN_3O_2$ 432.1473, found 432.1485.

*6-(4-Methoxyphenyl)-4-phenyl-4,7,8-triazaspiro[4.4]non-6-en-9-one (**2q**).* Following the general procedure from **4a** (440 mg, 1.42 mmol) and hydrazine monohydrate (2.42 mmol) (no pyridine was added), 363 mg (79%) of the title compound was obtained as a pale brown solid after stirring for 30 min with iodine (4.26 mmol) and after chromatography in silica gel eluting with hexane/ethyl acetate 25% and 50%: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.62 (S, 1H), 7.65−7.60 (m, 2H), 7.18−7.11 (m, 2H), 6.86−6.81 (m, 2H), 6.70 (t, J = 7.3 Hz, 1H), 6.44−6.40 (m, 2H), 3.90−3.80 (m, 2H), 3.78 (s, 3H), 2.52−2.40 (m, 1H), 2.37−2.30 (m, 2H), 2 8−2.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 178.5, 161.3, 160.3, 145.2, 129.6, 127.9, 122.8, 118.1, 114.3, 112.5, 70.7, 55.3, 50.1, 38.2, 22.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{19}N_3O_2$ 322.1550, found 322.1553.

■ ASSOCIATED CONTENT

Supporting Information

Table of reaction screening, figures of ^{1}H and ^{13}C NMR spectra of all new compounds, and structure of **2a** with key HMBC and COSY correlations. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00796.

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Notes

The authors declare no competing financial interest.

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(13) Full assignment was achieved using a combination of 1D and 2D NMR experiments.

(14) Solid **1a** was found to partially decompose in a matter of days at room temperature when open to the air.

(15) LC−MS showed 11% of the ring-opened derivative, 36% dicarbonyl (starting material), and 34% of a compound with m/z = 409, consistent with 1-benzyl-3-(4-methoxyphenyl)-7-(*o*-tolyl)-5,6-dihydro-4*H*-pyrazolo[3,4-*b*]pyridine. A reasonable explanation is that the *o*-methyl group breaks the conjugation of the aromatic ring with the nitrogen making the aniline group a poorer leaving group.

(16) A dicarbonyl derived from pyrrolidin-2-one reacted with benzylhydrazine to give the ring-opened derivative with complete conversion by LC−MS, but only 8% of spirocycle was observed by LC−MS after addition of iodine, even when reaction was heated at 80 °C overnight. A dicarbonyl derived from azepan-2-one reacted with benzylhydrazine to give primarily 1-benzyl-3-(4-methoxyphenyl)-8-phenyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]azepine as judged by LC−MS (m/z = 409), ^{1}H NMR, and ^{13}C NMR; 8% of the desired ring-opened derivative was observed by LC−MS.

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