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A Hofmann Rearrangement–Ring Expansion Cascade for the Synthesis of 1-Pyrrolines: Application to the Synthesis of 2,3-Dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium Salts

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Abstract: Treatment of cyclobutanecarboxamide with bis(trifluoroacetoxy)iodobenzene, PhI(O-$COCF_3)_2$, resulted in the formation of 1-pyrroline via Hofmann rearrangement of the former followed by in situ ring expansion reaction of the cyclobutylamine intermediate. Further elaboration of this methodology to the synthesis of 2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium salts has also been described.

Keywords: 1-pyrroline; 2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium salt; cascade reaction; cyclobutanecarboxamide; rearrangement; ring expansion

Introduction

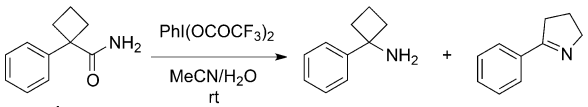
The ring expansion reaction of small and strained molecules has attracted the interest of organic chemists for decades.[1] However, unlike the ring expansion of three-membered rings which have been well studied and widely applied in natural products synthesis,[2] ring expansion reaction of four-membered rings remains relatively underutilized.[2d,e,3]

The best known ring expansion reaction of cyclobutane derivatives was the Wagner–Meerwein-type 1,2-shift reaction via the generation of a carbenium ion adjacent to the cyclobutane ring[4–6] or a transition-metal-catalyzed process[7,8] to provide cyclopentane analogues. Ring expansions with the generation of an adjacent nitrenium ion to give nitrogen-containing heterocyclic homologues were rare.[9] Herein, we report a Hofmann rearrangement–ring expansion cascade of cyclobutanecarboxamides to generate 1-pyrroline derivatives, which are key intermediates for the synthesis of a large variety of functionalized aza-heterocycles that exhibit significant biological and pharmacological activities.[10] It was envisioned that under the reaction conditions, nucleophilic attack of bis(trifluoroacetoxy)iodobenzene (BTI) with cyclobutylamine (Hofmann rearrangement product) generating a reactive intermediate would trigger ring expansion of the cyclobutane ring.

Results and Discussion

Initial studies were carried out with 1-phenylcyclobutanecarboxamide **1a**, which could be easily accessed through hydrolysis of 1-phenylcyclobutanecarbonitrile.[11] As shown in Table 1, treatment of **1a** with

Table 1. Results for treatment of 1-phenylcyclobutanecarboxamide with bis(trifluoroacetoxy)iodobenzene (BTI).



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

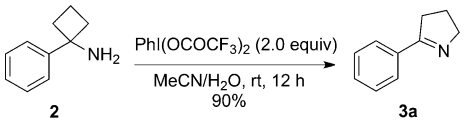
Entry	Equiv. of BTI	Yield of **2** (%)[a]	Yield of **3a** (%)[a]
1	1	59	7
2	1.5	25	50
3	2	6	81
4	2.5	–	91
5	3	–	91

[a] Isolated yield.

1 equivalent of BTI mainly resulted in the formation of the Hofmann rearrangement product **2** (59% isolated yield, entry 1). The ring expansion product 2-phenyl-1-pyrroline **3a** was isolated only as a minor product (7%). We then investigated the effects of the quantities of BTI to the reaction. As can be seen from Table 1, the yield of **3a** improved while that of **2** decreased with increasing amount of BTI (entries 1–4). In the presence of 2.5 equivalent of BTI, pyrroline **3a** was isolated in the highest 91% yield while no trace of amine **2** was evident on TLC plate (entry 4). However, no improvement was observed when 3 equivalent of BTI was applied (entry 5). The reaction conditions were then explored and it was found that other solvent systems such as DMF, DMF/H_2O or DCM were less satisfactory and the reaction was ideally carried out at ambient temperature.

Next, we investigated the synthesis of other pyrroline derivatives from the corresponding cyclobutanecarboxamides, and the results are collected in Table 2. In the presence of 2.5 equivalent of BTI, all 1-arylcyclobutanecarboxamides with either an *ortho*-, *meta*-, or *para*-substituted aromatic ring could react to give the 2-aryl-1-pyrrolines (entries 2–8). In general, substrates with a strong electron-withdrawing group gave lower product yield (entries 2–4 vs 5, entry 6 vs 7). Under the conditions, 3,3-dimethyl-1-phenylyclobutanecarboxamide **1i** (entry 9) and the dicyclobutanecarboxamide **1j** (entry 10) could also be converted into pyrroline **3i** and dipyrroline **3j**, respectively. The cascade reaction of pyridin-2-ylcyclobutanecarboxamide **1k** and pyridin-3-ylcyclobutanecarboxamide **1l** were then explored. While **1l** reacted cleanly to give **3l** in 83% isolated yield (entry 12), reaction of **1k** gave a mixture of products, from which the desired pyridinylpyrroline **3k** was isolated in 35% yield. Following known literature procedure,[12] **3l** could be converted into the natural product nicotine. Finally, the cascade reaction of 1-alkylcyclobutanecarboxamides **1m** and **1n** was also successful and gave the corresponding pyrrolines **3m** and **3n** in 84% and 63% isolated yield, respectively (entries 13, 14).

In a separate study, it was found that 1-phenylcyclobutylamine **2** could be converted into 2-phenyl-1-pyrroline **3a** in 90% isolated yield by treatment with excess BTI (Scheme 1). Based on the results obtained, a plausible mechanism was proposed in Scheme 2. Nucleophilic attack of cyclobutanecarboxamide **I** to BTI gave intermediate **II**, which on rearrangement



2 3a

Scheme 1. Formation of 2-phenyl-1-pyrroline **3a** via ring expansion of 1-phenylcyclobutylamine **2**.

Table 2. Synthesis of 1-pyrrolines from cyclobutanecarboxamides.[a]

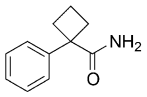
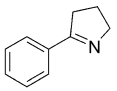
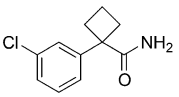
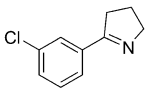
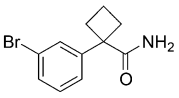
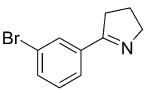
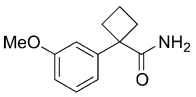
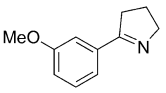
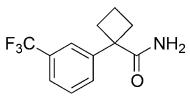
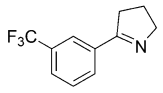
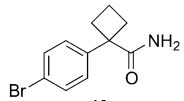
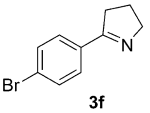
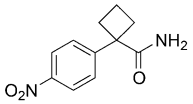
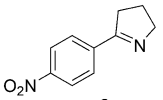
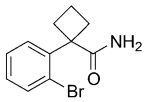
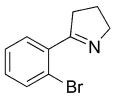
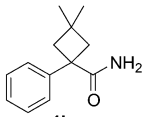
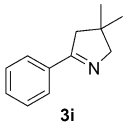
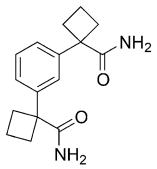
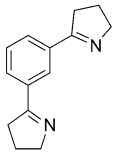
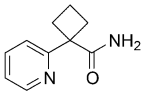
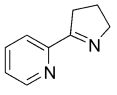
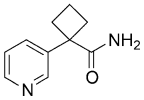
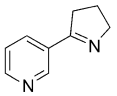
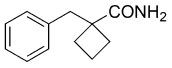
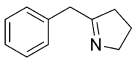
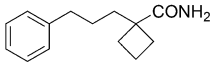
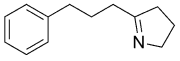
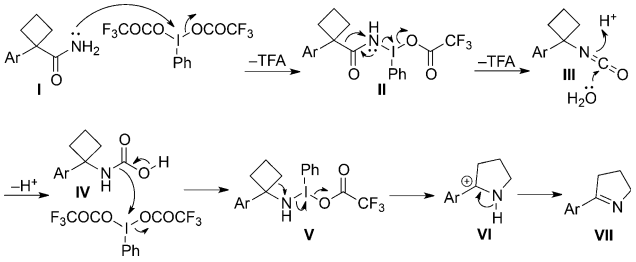
Entry	1-Arylcyclobutanecarboxamide	2-Aryl-1-pyrroline	Yield (%)[b]
1	 **1a**	 **3a**	91
2	 **1b**	 **3b**	91
3	 **1c**	 **3c**	90
4	 **1d**	 **3d**	95
5	 **1e**	 **3e**	85
6	 **1f**	 **3f**	90
7	 **1g**	 **3g**	82
8	 **1h**	 **3h**	64
9	 **1i**	 **3i**	88
10[c]	 **1j**	 **3j**	80
11	 **1k**	 **3k**	35
12	 **1l**	 **3l**	83

Table 2. (Continued)

Entry	1-Arylcyclobutanecarboxamide	2-Aryl-1-pyrroline	Yield (%)[b]
13	 **1m**	 **3m**	84
14	 **1n**	 **3n**	63

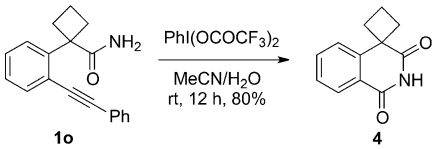
[a] Reaction conditions: BTI (2.5 equiv), MeCN, H_2O, rt.
[b] Isolate yield.
[c] 5 equivalents of BTI was used.



Scheme 2. Proposed mechanism.

yielded isocyanate **III**. Hydrolysis of **III** resulted in the formation of the unstable carbamic acid **IV**, which collapsed by losing a molecule of CO_2 and simultaneously attack BTI to give **V**. Ring expansion of **V** gave carbenium ion **VI**, and finally deprotonation provided 1-pyrroline **VII**. Poor result was obtained for the transformation of **1k** to **3k** probably because the corresponding carbenium ion intermediate (**VI**, Ar = pyridin-2-yl) was unstable.

Having established the methodology, we then investigated its utility in chemical synthesis. Hydropyrrolo[2,1-*a*]isoquinoline and analogues exist widely in nature.[13] We envisioned that these molecules might be accessed through a Hofmann rearrangement-ring expansion-cyclization cascade of alkynylphenylcyclobutanecarboxamides (e. g., **1o** in Scheme 3) in the presence of BTI. However, treatment of **1o** with BTI resulted in the formation of isoquinoline-1,3-dione **4**

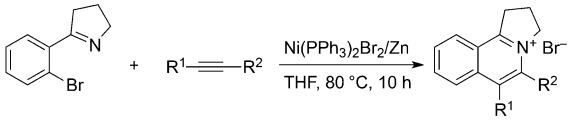


Scheme 3. Synthesis of isoquinoline-1,3-dione **4**.

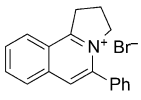
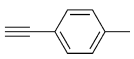
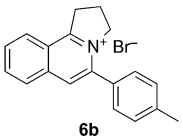
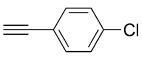
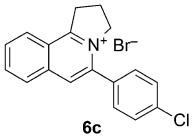
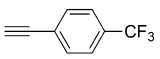
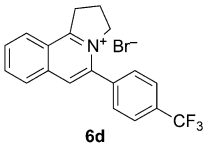
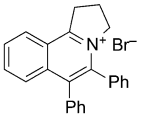
in 80% isolated yield. Complete cleavage of C–C triple bond with hypervalent iodanes to provide the corresponding carboxylic acids, esters, amides and ketoesters have been reported in the literature.[14] To the best of our knowledge, this example represents the first non-metallic approach for the cleavage cum functionalization of alkynes to obtain isoquinoline-1,3-diones. Obviously, alkyne cleavage (possibly with the aid of the amide functionality) with BTI proceeded much faster than the Hofmann rearrangement reaction.

Next, we tested the nickel-catalyzed cyclization of bromophenylpyrroline **3h** with alkynes.[15] To our delight, the reaction proceeded as expected with terminal alkynes **5a–d** (entries 1–4, Table 3) as well as diphenylacetylene **5e** (entry 5, Table 3) to give the corresponding 2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium salts **6a–e** in good to excellent isolated yield.

Table 3. Nickel-catalyzed cyclization of bromophenylpyrroline **3h** with alkynes for the synthesis of 2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium salts.



3h **5** **6**

Entry	Alkyne **5**	Product **6**	Yield (%)[a]
1	**5a**	 **6a**	75
2	 **5b**	 **6b**	77
3	 **5c**	 **6c**	72
4	 **5d**	 **6d**	90
5	**5e**	 **6e**	85

[a] Isolate yield.

Conclusions

In summary, we have developed an approach for the synthesis of 1-pyrrolines via a Hofmann rearrangement–ring expansion cascade of cyclobutanecarboxamides. This approach is well adapted for the nickel-catalyzed synthesis of 2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium salts.

Experimental Section

General

Melting points were determined on a XT4 A hot-stage apparatus and are uncorrected. IR spectra were obtained using an IFS25 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Agilent AV400 instrument. High-resolution mass spectra were recorded on a Micromass Q-TOF mass spectrometer.

General procedure for the synthesis of 3a–n

To a solution of 1-arylcyclobutanecarboxamide **1a–n** (1.0 mmol, 1.0 equiv) in acetonitrile (6 mL) and water (2 mL) was added bis(trifluoroacetoxy)iodobenzene (BTI, 2.5 mmol, 2.5 equiv). The resulting mixture was stirred at ambient temperature for 12 h before being slowly poured into saturated K_2CO_3 solution (10 mL). The resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were washed with brine, then dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 2-aryl-1-pyrroline **3a–n**.

2-Phenyl-1-pyrroline (3a).[16] Orange oil (132 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.81 (m, 2H), 7.44–7.37 (m, 3H), 4.05 (tt, J = 7.5, 2.0 Hz, 2H), 2.97–2.92 (m, 2H), 2.07–1.99 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 134.5, 130.3, 128.4, 127.6, 61.4, 34.9, 22.6 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{11}N$: 146.0964 $[M + H]^+$; found 146.0949.

2-(3′-Chlorophenyl)-1-pyrroline (3b).[17] Colorless solid (163 mg, 91%); mp 47–48 °C [ref. 17, mp 54 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 1.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.38–7.29 (m, 2H), 4.07–4.03 (m, 2H), 2.92–2.86 (m, 2H), 2.06–1.98 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 136.2, 134.5, 130.3, 129.7, 127.7, 125.7, 61.5, 35.0, 22.6 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}ClN$: 180.0575 $[M + H]^+$; found 180.0576.

2-(3′-Bromophenyl)-1-pyrroline (3c).[17] Yellow solid (202 mg, 90%); mp 42–43 °C [ref. 17, mp 49–50 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 4.04 (t, J = 7.3 Hz, 2H), 2.94–2.89 (m, 2H), 2.08–2.00 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 136.5, 133.1, 130.6, 129.9, 126.1, 122.6, 61.5, 34.9, 22.6 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}BrN$: 224.0069 $[M + H]^+$; found 224.0066.

2-(3′-Methoxyphenyl)-1-pyrroline (3d).[18] Orange oil (166 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 1H), 7.35–7.27 (m, 2H), 6.94 (ddd, J = 8.0, 2.6, 1.1 Hz, 1H), 4.03 (tt, J = 7.5, 2.0 Hz, 2H), 3.81 (s, 3H), 2.94–2.89 (m, 2H), 2.05–1.97 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 159.6, 135.8, 129.3, 120.4, 116.9, 111.7, 61.4, 55.3, 35.0, 22.6 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NO$: 176.1070 $[M + H]^+$; found 176.1062.

2-(3′-Trifluoromethylphenyl)-1-pyrroline (3e).[19] Orange oil (181 mg, 85%); ^{1}H NMR (400 MHz, DMSO): δ = 8.10 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 3.96 (tt, J = 7.3, 1.9 Hz, 2H), 2.96–2.92 (m, 2H), 1.99–1.90 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 135.3, 130.9 (q, J_{F-C} = 32.4 Hz), 130.7 (q, J_{F-C} = 1.2 Hz), 128.9, 126.7 (q, J_{F-C} = 3.7 Hz), 124.4 (q, J_{F-C} = 3.9 Hz), 123.9 (q, J_{F-C} = 271.0 Hz), 61.7, 34.9, 22.7 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}F_3N$: 214.0838 $[M + H]^+$; found 214.0808.

2-(4′-Bromophenyl)-1-pyrroline (3f).[16] Colorless solid (202 mg, 90%); mp 79–80 °C [ref. 16, mp 83–84 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 7.7 Hz, 2H), 7.51 (d, J = 7.7 Hz, 2H), 4.03 (m, 2H), 2.88 (m, 2H), 2.06–1.98 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 133.4, 131.6, 129.1, 124.7, 61.6, 34.8, 22.7 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}BrN$: 224.0069 $[M + H]^+$; found 224.0063.

2-(4′-Nitrophenyl)-1-pyrroline (3g).[20] Colorless solid (156 mg, 82%); mp 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26–8.23 (m, 2H), 8.00–7.97 (m, 2H), 4.10 (tt, J = 7.5, 2.2 Hz, 2H), 2.99–2.94 (m, 2H), 2.13–2.05 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 148.8, 140.2, 128.4, 123.6, 62.0, 35.1, 22.7 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}N_2O_2$: 191.0815 $[M + H]^+$; found 191.0815.

2-(2′-Bromophenyl)-1-pyrroline (3h).[21] Orange oil (143 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, J = 8.0, 1.0 Hz, 1H), 7.42 (dd, J = 7.6, 1.6 Hz, 1H), 7.30 (td, J = 7.5, 1.0 Hz, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H), 4.01 (tt, J = 7.5, 2.0 Hz, 2H), 2.96 (tt, J = 8.5, 2.0 Hz, 2H), 2.07–2.00 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 137.7, 133.2, 130.3, 130.0, 127.2, 121.0, 61.4, 38.5, 23.4 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}BrN$: 226.0049 $[M + H]^+$; found 226.0037.

2-Phenyl-4,4-dimethyl-1-pyrroline (3i).[22] Colorless oil (152 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.78 (m, 2H), 7.41–7.38 (m, 3H), 3.79 (s, 2H), 2.77 (s, 2H), 1.17 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 134.8, 130.3, 128.4, 127.4, 74.6, 49.9, 38.4, 28.1 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}N$: 174.1277 $[M + H]^+$; found 174.1259.

1,3-Bis(1′-pyrrolin-2′-yl)benzene (3j). The title compound was obtained by treatment of **1j** with 5 equivalent of BTI. Colorless solid (170 mg, 80%); mp 127–128 °C; IR (KBr): ν_{max} = 1620, 1575, 1443, 1321, 1264, 1198 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (t, J = 1.4 Hz,1H), 7.91 (dd, J = 7.7, 1.4 Hz, 2H), 7.43 (t, J = 7.7 Hz, 1H), 4.08–4.03 (m, 4H), 2.99–2.94 (m, 4H), 2.06–1.98 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 134.7, 129.4, 128.6, 126.9, 61.6, 35.0, 22.7 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N_2$: 213.1386 $[M + H]^+$; found 213.1374.

2-(2′-Pyridyl)-1-pyrroline (3k).[23] Colorless solid (51 mg, 35%); mp 41–42 °C [ref. 23, mp 44–46 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, J = 4.8 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.74–7.69 (m, 1H), 7.31–7.28 (m, 1H), 4.09 (tt, J = 7.3, 2.1 Hz, 2H), 3.11–3.06 (m, 2H), 2.06–1.98 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 153.3, 149.0, 136.3, 124.5, 121.8, 62.1, 34.9, 22.5 ppm; HRMS (ESI): *m/z* calcd for $C_9H_{10}N_2$: 147.0917 $[M + H]^+$; found 147.0913.

2-(3′-Pyridyl)-1-pyrroline (3l).[24] Colorless solid (121 mg, yield 83%); mp 34–35 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (m, 1H), 8.64 (m, 1H), 8.18 (m, 1H), 7.34 (m, 1H), 4.07 (m, 2H), 2.95 (m, 2H), 2.06 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 151.1, 149.0, 134.7, 130.2, 123.4, 61.6, 34.8, 22.5 ppm; HRMS (ESI): *m/z* calcd for $C_9H_{10}N_2$: 147.0917 $[M + H]^+$; found 147.0920.

5-Benzyl-1-pyrroline (3m).[25] Colorless oil (134 mg, yield 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2H), 7.24–7.20 (m, 3H), 3.85–3.80 (m, 2H), 3.67 (s, 2H), 2.41–2.37 (m, 2H), 1.86–1.78 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 137.1, 129.1, 128.7, 126.7, 61.0, 40.8, 36.6, 22.7 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{13}N$: 160.1121 $[M + H]^+$; found 160.1133.

5-(3-Phenylpropyl)-1-pyrroline (3n). Colorless oil (118 mg, yield 63%); IR (NaCl): ν_{max} = 2942, 2863, 1643, 1603, 1496, 1453 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2H), 7.19–7.15 (m, 3H), 3.82–3.77 (m, 2H), 2.66 (t, *J* = 2.7 Hz, 2H), 2.45–2.40 (m, 2H), 2.37–2.33 (m, 2H), 1.98–1.90 (m, 2H), 1.87–1.79 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 142.0, 128.6, 128.4, 125.9, 60.9, 37.3, 35.7, 33.3, 28.0, 22.6 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{17}N$: 188.1434 $[M + H]^+$; found 188.1434.

1′*H*-spiro[cyclobutane-1,4′-isoquinoline]-1′,3′(2′*H*)-dione (4)

To a solution of 1-[2′-(phenylethynyl)phenyl]cyclobutane-1-carboxamide (275 mg, 1.0 mmol, 1.0 equiv) in acetonitrile (10 mL) and water (4 mL) was added BTI (1075 mg, 2.5 mmol, 2.5 equiv). The resulting mixture was stirred at ambient temperature for 12 h before being slowly poured into 10% aqueous NaOH (10 mL). The resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were washed with brine, then dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with 25% ethyl acetate in petroleum ether as eluent to give 1′*H*-spiro[-cyclobutane-1,4′-isoquinoline]-1′,3′(2′*H*)-dione **4** (161 mg, 80%) as a colorless solid; mp 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 1H), 8.19 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.76–7.72 (m, 1H), 7.47–7.43 (m, 1H), 3.01–2.94 (m, 2H), 2.50–2.39 (m, 3H), 2.35–2.22 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 164.6, 145.1, 134.9, 128.4, 127.5, 125.7, 123.6, 47.1, 34.8, 15.7 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}NO_2$: 202.0863 $[M + H]^+$; found 202.0863.

General procedure for the synthesis of 6a–e

A seal tube (35 mL) containing $Ni(PPh_3)_2Br_2$ (0.05 mmol, 0.05 equiv), Zn (0.5 mmol, 0.5 equiv) and 2-(2′-bromophenyl)-1-pyrroline **3h** (1.0 mmol, 1.0 equiv) was evacuated and purged with nitrogen gas three times. Freshly distilled THF (5.0 mL) and alkyne **5a–e** (1.0 mmol, 1.0 equiv) were added to the system. The resulting mixture was stirred at 80 °C for 10 h. The mixture was diluted with dichloromethane (15 mL), filtered through a pad of celite and silica gel and washed with methanol (50 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel with dichloromethane/methanol as eluent to give 2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium salt **6a–e**.

5-Phenyl-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium bromide (6a).Colorless solid (245 mg, 75%); mp 236–237 °C; IR (KBr): ν_{max} = 2998, 1634, 1567, 1497, 1454, 1348 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.51 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.27 (s, 1H), 8.21 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 8.06 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.76–7.73 (m, 2H), 7.68–7.64 (m, 3H), 4.83 (t, *J* = 7.8 Hz, 2H), 4.15 (t, *J* = 7.8 Hz, 2H), 2.66–2.58 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 165.1, 145.1, 139.5, 137.6, 133.9, 132.2, 131.8, 130.6, 130.3, 129.6, 129.2, 126.3, 125.5, 60.8, 33.6, 21.8 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N$: 246.1277; found 246.1280.

5-(*p*-Tolyl)-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium bromide (6b). Colorless solid (262 mg, 77%); mp 250–251 °C; IR (KBr): ν_{max} = 2922, 1632, 1565, 1508, 1434, 1377, 1341 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.49 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.23 (s, 1H), 8.21–8.17 (m, 1H), 8.06–8.02 (m, 1H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 4.82 (t, *J* = 7.7 Hz, 2H), 4.12 (t, *J* = 7.9 Hz, 2H), 2.65–2.57 (m, 2H), 2.49 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 165.0, 145.3, 142.4, 139.6, 137.5, 132.0, 131.0, 130.9, 130.5, 129.5, 129.1, 126.2, 125.5, 125.4, 60.8, 33.6, 21.9, 21.5 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N$: 260.1434; found 260.1440.

5-(4-Chlorophenyl)-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium bromide (6c). Colorless solid (260 mg, 72%); mp 193–194 °C; IR (KBr): ν_{max} = 2924, 1638, 1572, 1496, 1464, 1376 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.50 (d, *J* = 8.4 Hz, 1H), 8.31–8.28 (m, 2H), 8.23–8.19 (m, 1H), 8.06–8.04 (m, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 4.81 (t, *J* = 7.7 Hz, 2H), 4.13 (t, *J* = 7.9 Hz, 2H), 2.62 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 165.4, 143.9, 139.5, 138.2, 137.7, 132.4, 132.3, 130.5, 129.6, 129.2, 126.6, 125.6, 60.8, 33.6, 21.8 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}ClN$: 280.0888; found 280.0890.

5-(4-(Trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium bromide (6d). Colorless solid (355 mg, 90%); mp 248–249 °C; IR (KBr): ν_{max} = 2925, 1634, 1570, 1466, 1437, 1323 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.53 (d, *J* = 8.4 Hz, 1H), 8.34–8.32 (m, 2H), 8.25–8.21 (m, 1H), 8.11–8.06 (m, 1H), 8.00–7.96 (m, 4H), 4.83 (t, *J* = 7.6 Hz, 2H), 4.16 (t, *J* = 7.9 Hz, 2H), 2.67–2.60 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 164.3, 142.0, 138.0, 136.4, 136.2, 132.2 (q, J_{F-C} = 32.7 Hz), 131.1, 130.4, 128.4, 127.9, 125.8 (q, J_{F-C} = 3.8 Hz), 125.4, 124.4, 123.9 (q, J_{F-C} = 271.8 Hz), 59.5, 32.3, 20.5 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{15}F_3N$: 314.1151; found 314.1152.

5,6-Diphenyl-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-4-ium bromide (6e). Colorless solid (342 mg, 85%); mp 214–215 °C; IR (KBr): ν_{max} = 2924, 1622, 1590, 1461, 1443, 1379 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.58–8.56 (m, 1H), 8.12–8.04 (m, 2H), 7.75–7.73 (m, 1H), 7.45–7.39 (m, 5H), 7.38–7.34 (m, 3H), 7.29–7.24 (m, 2H), 4.65–4.61 (m, 2H), 4.20 (t, *J* = 7.9 Hz, 2H), 2.65–2.61 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 163.8, 143.0, 139.3, 138.4, 137.5, 134.8, 133.1, 132.0, 131.7, 131.2, 131.1, 129.9, 129.8, 129.7, 129.5, 128.1, 125.7, 61.7, 33.8, 21.3 ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{20}N$: 322.1590; found 322.1593.

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