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Synthesis of Spiro[indazole-3,3′-indolin]-2′-ones via [3 + 2] Dipolar Cycloaddition of Arynes with 3-Diazoindolin-2-ones and Indazolo[2,3-*c*]quinazolin-6(5*H*)-ones by Subsequent Thermal Isomerization

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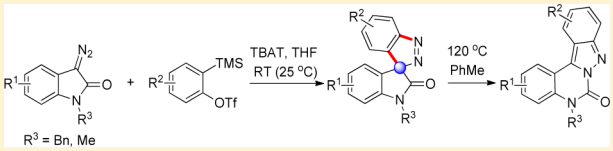
Supporting Information

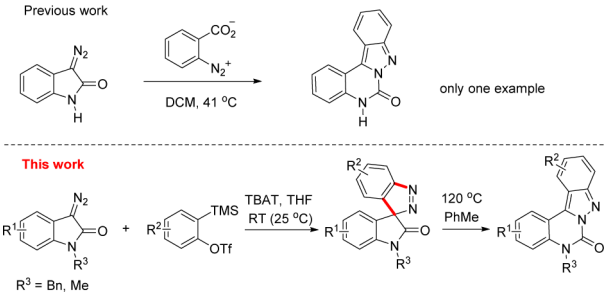
ABSTRACT: An efficient protocol for facile construction of spiro[indazole-3,3′-indolin]-2′-ones was developed via [3 + 2] dipolar cycloaddition of arynes with 3-diazoindolin-2-ones under mild conditions in excellent yields. Subsequent thermal isomerization of the spiro[indazole-3,3′-indolin]-2′-ones readily afforded indazolo[2,3-*c*]quinazolin-6(5*H*)-ones.



Spirooxindole as a privileged structural motif is widely found in both natural products and synthetic bioactive molecules. Owing to the considerable medicinal potential of the spirooxindole structural motif, many elegant and efficient synthetic strategies have been developed.[1] Literature methods have focused mainly on the preparation of oxindole spirofused with a structural unit such as cycloalkane, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, and oxazoline, among others. However, to the best of our knowledge, attempts to construct oxindole spirofused with indazole (i.e., spiro-[indazole-3,3′-indolin]-2′-one) have never succeeded. The key challenge lies in the fact that this class of 3,3-disubstituted 3*H*-indazoles, bearing a carbonyl group adjacent to the spirocyclic quaternary carbon, is usually susceptible to rearrangement via acyl migration.[4,5,9] On the other hand, the indazole moiety is also a pharmaceutically useful subunit, which is widely found in biologically active compounds with diverse pharmacological properties.[2] Spiro[indazole-3,3′-indolin]-2′-ones combine two biologically interesting scaffolds, which makes these hybrid molecules fascinating to medicinal chemists in the development of novel drug leads.[3] Thus, facile access to versatile spiro-[indazole-3,3′-indolin]-2′-ones from readily available starting materials is highly desirable.

Intermolecular [3 + 2] dipolar cycloaddition of arynes with cyclic diazo compounds is an attractive route for the construction of spiroindazoles; however, it has only been sporadically documented,[4,6] which might be ascribed to the difficulty in preparation and manipulation of the potentially explosive diazo compounds and the harsh reaction conditions for generation of arynes from anthranilic acid, halobenzenes, or other aryne precursors.[7] Early in 1973, Shechter had investigated the reaction of 3-diazooxindole with benzyne generated from diazotized anthranilic acid. The cyclized and isomerized product was obtained as the sole product, and this was the only example in his report (Scheme 1).[4] With the

Scheme 1. Approaches to Spiro[indazole-3,3′-indolin]-2′-ones and Indazolo[2,3-*c*]quinazolin-6(5*H*)-ones



emergence of new aryne precursors, e.g., *o*-(trimethylsilyl)aryl triflate[8] and the safe surrogates of diazo compounds, e.g., *N*-tosylhydrazone and hydrazonyl chloride, intermolecular [3 + 2] dipolar cycloaddition of arynes with diazo compounds became popular and prosperous.[9,10] Nevertheless, for nonaromatized 3,3-disubstituted 3*H*-indazoles, especially 3,3-disubstituted spirocyclic indazoles, there have been rare examples of success.[4−6,9]

Considering the limitations of the previous reports and our ongoing interest in diazo compounds for the synthesis of heterocycles;[11] herein, we wish to describe a [3 + 2] dipolar

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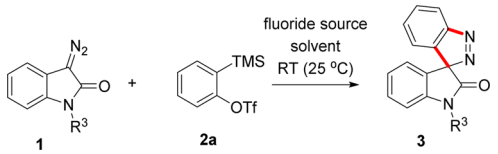
cycloaddition annulation of arynes with 3-diazoindolin-2-ones to afford spiro[indazole-3,3′-indolin]-2′-ones, which readily generate indazolo[2,3-*c*]quinazolin-6(5*H*)-ones upon thermal isomerization.

Our study commenced with a model reaction between 3-diazoindolin-2-one **1** and *o*-(trimethylsilyl)phenyl triflate (**2a**) in CH_3CN at room temperature. We first tested the effect of various *N*-protecting-groups of the oxindole on the annulation (Table 1). The dipolar cycloaddition reaction proceeded

Table 1. Optimization of the Reaction Conditions[a]



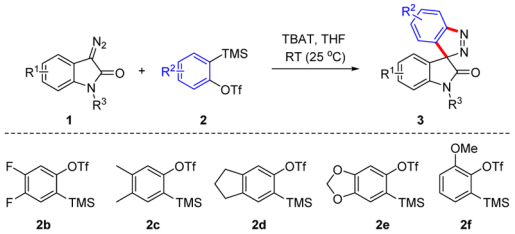
entry	R^3	1:2a	fluoride source (equiv)	solvent	yield[b] (%)
1	H	1:1.5	CsF (1.5)	CH_3CN	*d*
2	Ac	1:1.5	CsF (1.5)	CH_3CN	*d*
3	Ts	1:1.5	CsF (1.5)	CH_3CN	*d*
4	Bn	1:1.5	CsF (1.5)	CH_3CN	91
5	Bn	1:2.0	CsF (2.0)	CH_3CN	72
6[c]	Bn	1:2.0	KF (2.0)	CH_3CN	77
7	Bn	1:1.5	CsF (2.0)	CH_3CN	92
8	Bn	1:1.5	CsF (3.0)	CH_3CN	84
9	Bn	1:1.5	TBAT (1.5)	THF	94
10	Bn	1:1.5	TBAT (2.0)	THF	99
11	Bn	1:1.2	TBAT (2.0)	THF	99
12	Bn	1:1.5	TBAT (1.5)	PhMe	81

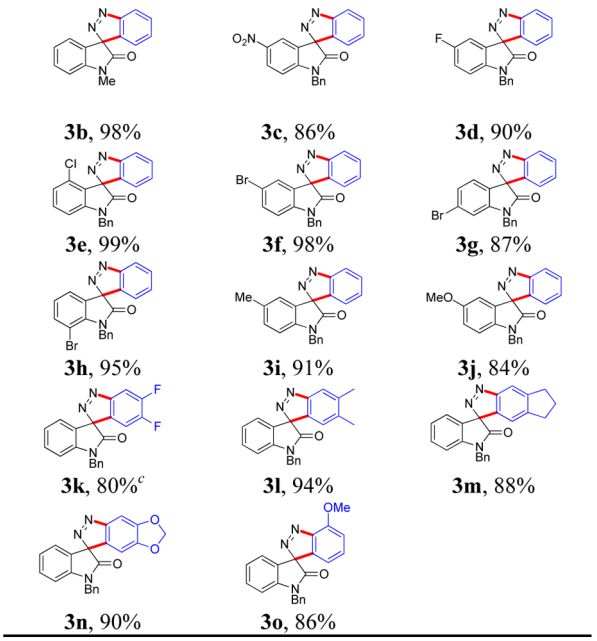
[a]Reaction conditions: **1** (0.3 mmol), **2a**, fluoride source, solvent (3 mL), air. [b]Isolated yield. [c]18-Crown-6 (2.0 equiv) was added as the additive. [d]No desired product was isolated. TBAT = tetrabutylammonium triphenyldifluorosilicate.

sluggishly, and the reaction systems were complex when R^3 was H, Ac or Ts, according to the TLC results (entries 1−3). To our delight, when R^3 came to Bn, the reaction system became clear, and the desired 1′-benzylspiro[indazole-3,3′-indolin]-2′-one (**3a**) could be isolated in 91% yield along with a trace amount of **1a** recovered (entry 4). The structure of **3a** was unambiguously determined by X-ray analysis (see SI).[14] It should be pointed out that such a unique spiro framework was isolated for the first time, to the best of our knowledge, although there had been analogous cyclic diazo substrates like 3-diazoindolin-2-one[4] and 2-diazo-1*H*-indene-1,3(2*H*)-dione documented in the literature.[5,9] This promising result encouraged us to further screen other relevant reaction conditions. Simultaneously increasing the ratio of **2a** and fluoride sources, CsF or KF/18-C-6, indeed accelerated the reaction but decreased the yield of **3a** slightly (entries 5 and 6). By only increasing the loading of CsF from 1.5 to 2.0 equiv to promote the reaction, the yield was improved slightly to 92% (entry 7); however, CsF in large excess was found to be detrimental to this transformation (entry 8). It was worth noting that when TBAT was used as the fluoride source and THF as the solvent instead, the reaction proceeded faster, and a higher yield of 94% was achieved (entry 9). Further increasing the amounts of TBAT led to almost quantitative yield of 99% (entry 10). In contrast, decreasing the amounts of **2a** had no effect on the efficiency of the transformation (entry 11). Finally, employing PhMe as the solvent, the desired product was obtained in a comparable yield (entry 12).

With the optimal conditions in hand (Table 1, entry 11), we set out to explore the scope and limitations of this novel [3 + 2] dipolar cycloaddition reaction. As shown in Table 2, the scope

Table 2. Scope of the [3 + 2] Dipolar Cycloaddition Reaction[a,b]





[a]Reaction conditions: **1** (0.5 mmol), **2** (1.2 equiv), TBAT (2.0 equiv), THF (5 mL), 25 °C. [b]Isolated yield. [c]The molar ratio of **1a**:**2b** was adjusted to 1:1.5.

of 3-diazoindolin-2-one **1** was first examined. When *N*-Me oxindole was employed, its performance was found to be comparable to that of *N*-Bn oxindole, indicating that an electron-donating group on the nitrogen of oxindole was critical for the success of this transformation. A series of *N*-Bn oxindole derivatives were then reacted with **2a**, furnishing the desired products (**3c**−**3j**) in excellent yields. Strong electron-withdrawing nitro and fluoro substrates showed good tolerance, affording **3c** and **3d** in 86 and 90% yields, respectively. A bromo group at the 5-, 6-, or 7-position of the oxindole was well-tolerated, and the desired spirooxindoles (**3f**−**3h**) were obtained in 87−98% yields. Notably, as for 4-bromo oxindole, which was not listed in Table 2, no desired product was observed, even at prolonged reaction times and higher temperatures, and the starting materials remained intact. We speculated that it was probably due to the bulkiness of the bromo group preventing the reaction partners from coming together. Interestingly, when an analogous 4-chloro oxindole was employed, it indeed proceeded smoothly and afforded the desired spirooxindole **3e** in 99% yield. Other substrates bearing electron-donating groups such as 5-methyl oxindole and 5-

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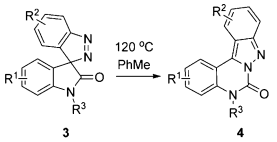
methoxyl oxindole also generated the expected products **3i** and **3j** in satisfactory yields. These results suggested that the position, except for substitution at C4, and the electronic nature of the substituents on the benzene moiety of the oxindoles had no pronounced effect on the yield.

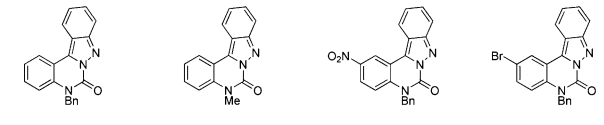
Next, we turned our attention to aryne precursors, and a variety of *o*-(trimethylsilyl)aryl triflates (**2b**−**2f**) were prepared and tested. The electron-poor substrate **2b** with a difluoro moiety was transformed smoothly into desired product **3k** in 80% yield by increasing the molar ratio of **1a**:**2b** to 1:1.5, which was different from that of Larcok's report.[9] In their reaction system, only a complex mixture was obtained when the aryne precursor **2b** was employed. Three symmetrical electron-rich substrates (**2c**−**2e**) were also fit for this transformation, and the corresponding spirooxindoles (**3l**−**3n**) were isolated in comparable yields. Monosubstituted substrate **2f** reacted to afford **3o** as a single regioisomer, which is in accordance with previous reports.[9,10] Thus, there is no limitation on the scope of arynes based on these results.

The spirooxindoles featuring an azo moiety tend to undergo rearrangement or isomerization reactions. In light of Shechter's results[4,5] and our observation that a considerable amount of isomerized product **4** was formed when CsF/THF was employed, we envisioned that **3** could be transformed into **4** or other heterocycles such as a dimer under thermal conditions. As expected, when **3a** was directly heated in the optimal solvent PhMe at 120 °C for 12 h, indazolo[2,3-*c*]quinazolin-6(5*H*)-one **4a** was obtained in 95% yield (Table 3). The exact structure of

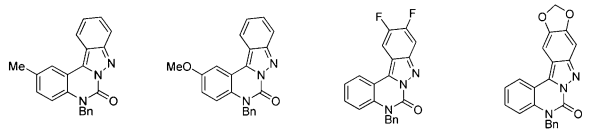
Table 3. Scope of the Isomerization Reaction[a]



3 4



4a, 95% **4b**, 98% **4c**, 85% **4f**, 99%



4i, 96% **4j**, 94% **4k**, 94% **4n**, 95%

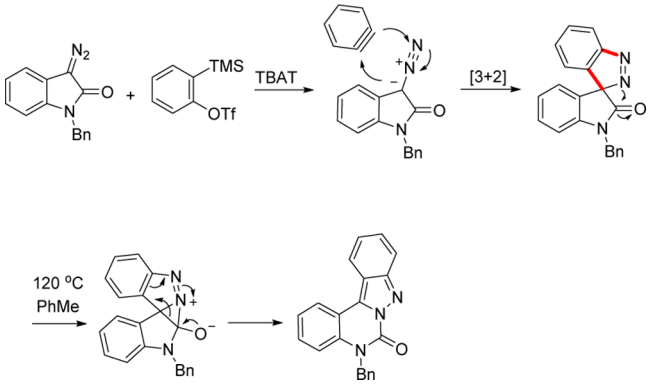
[a]Reaction conditions: **3** (0.2 mmol), PhMe (2 mL), 120 °C. Isolated yield.

4a was unambiguously characterized by X-ray analysis (see SI).[14] Indazolo[2,3-*c*]quinazolin-6(5*H*)-ones might be potentially useful drug candidates for its substructure pyrazolo[1,5-*c*]quinazolin-5(6*H*)-ones, and related derivatives have exhibited a broad range of bioactivities and been used as kinase CK2 inhibitors, non-nucleoside HIV-1 reverse transcriptase inhibitors, AMPA and kainate receptor antagonists, among others.[12] The present approach provided novel access to rapid construction of such a unique framework. Likewise, a library of indazolo[2,3-*c*]quinazolin-6(5*H*)-ones with complex structural diversities could be prepared from substrates **3b**−**3o**, and the representative products (**4b**−**4n**) are listed in Table 3. As shown in Table 3, the isomerization reaction of substrates with either electron-withdrawing group (**3c**, **3f**, and **3k**) or electron-donating group (**3i**, **3j**, and **3n**) at different positions and different protecting-groups (**3a**-**3b**) all proceeded well, affording the corresponding products (**4a**−**4n**) in 85−99% yields.

To further enhance the efficiency of the two-step strategy to indazolo[2,3-*c*]quinazolin-6(5*H*)-ones, we tried to combine the [3 + 2] dipolar cycloaddition and thermal rearrangement in one pot. However, as it was observed that the [3 + 2] dipolar cycloaddition in PhMe and the isomerization reaction in THF proceeded sluggishly, we still chose to conduct cyclization and isomerization in different solvents in two pots.

According to previous reports,[9,13] we put forward a putative mechanism for this process (Scheme 2) in which a [3 + 2]

Scheme 2. Proposed Mechanism



dipolar cycloaddition of benzyne and 3-diazoindolin-2-one proceeded to deliver spiro[indazole-3,3′-indolin]-2′-one, which underwent acyl migration and aromatization to form thermodynamically stable indazolo[2,3-*c*]quinazolin-6(5*H*)-one. Note that this mechanism is quite different from the reported diradical one, which proceeded via extrusion of nitrogen.[6]

In summary, a facile transition-metal-free method to construct spiro[indazole-3,3′-indolin]-2′-ones based on a [3 + 2] dipolar cycloaddition reaction of arynes with 3-diazoindolin-2-ones was developed in excellent yields (up to 99%). It is worth noting that this is the first report of the successful isolation of the relatively unstable spiro[indazole-3,3′-indolin]-2′-ones. Moreover, the synthetic practicality and effectiveness of this method were further highlighted by transformation of these azo spirooxindoles to pharmaceutically important indazolo[2,3-*c*]quinazolin-6(5*H*)-ones via thermal isomerization. Other transformations of these unique azo spirooxindoles are ongoing in our lab, which will be reported in due course.

EXPERIMENTAL SECTION

General Information. All isolated compounds were characterized on Varian 300, Bruker 400, JEOL 400, and Varian 600 MHz spectrometers in $CDCl_3$ or $(CD_3)_2CO$. Chemical shifts were reported as δ values relative to internal chloroform (δ 7.26 for ^{1}H NMR and 77.26 for ^{13}C NMR) and acetone (δ 2.05 for ^{1}H NMR and 29.84 for ^{13}C NMR). High-resolution mass spectra (HRMS) were obtained on a 4G mass spectrometer by using electrospray ionization (ESI) analyzed by quadrupole time-of-flight (QTof). All melting points were measured with the samples after column chromatography and uncorrected. Column chromatography was performed on silica gel. Anhydrous THF and PhMe were distilled over sodium benzophenone

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ketyl under Ar. All other solvents and reagents were used as obtained from commercial sources without further purification.

General Procedure for the Preparation of 3-Diazoxindolin-2-ones. *N*-Benzyl-3-diazoindolin-2-ones and *N*-methyl-3-diazoindolin-2-one were prepared according to the literature.[15] *N*-Acetyl-3-diazoindolin-2-one was prepared according to the literature.[16] *N*-Tosyl-3-diazoindolin-2-one was prepared according to the literature.[17] Compounds **1a**−**1j** are all known.

General Procedure for the Preparation of Spiro[indazole-3,3′-indolin]-2′-ones. To a solution of *N*-benzyl-3-diazooxindolin-2-one **1a** (125 mg, 0.500 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2a** (180 mg, 0.600 mmol) in THF (5 mL) was added TBAT (540 mg, 1.00 mmol), and the mixture was then stirred at room temperature for 15 h. After removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (PE:EA = 25:1) to give 1′-benzylspiro[indazole-3,3′-indolin]-2′-one **3a** (161 mg, 99%) as a yellow solid.

Other spiro[indazole-3,3′-indolin]-2′-ones were prepared following a similar method. Reaction conditions: **1** (0.5 mmol), **2** (1.2 equiv), TBAT (2.0 equiv), THF (5 mL), 25 °C, 10−24 h.

General Procedure for the Preparation of Indazolo[2,3-*c*]quinazolin-6(5*H*)-ones. The solution of 1′-benzylspiro[indazole-3,3′-indolin]-2′-one **3a** (65 mg, 0.20 mmol) in toluene (2 mL) was heated at 120 °C for 12 h. After removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (DCM: $(CH_3)_2CO$ = 100:1) to give 5-benzylindazolo[2,3-*c*]-quinazolin-6(5*H*)-one **4a** (62 mg, 95%) as a white solid.

Other indazolo[2,3-*c*]quinazolin-6(5*H*)-ones were prepared following a similar method. Reaction conditions: **3** (0.2 mmol), PhMe (2 mL), 120 °C, 12−24 h.

1′-Benzylspiro[indazole-3,3′-indolin]-2′-one. Compound **3a** (161 mg, *Y* = 99%, R_f = 0.42 (PE:EA = 5:1)) was isolated as a yellow solid; mp 127−128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 1H), 7.66 (td, *J* = 7.6, 0.9 Hz, 1H), 7.54 (td, *J* = 7.5, 0.9 Hz, 1H), 7.48−7.28 (m, 7H), 7.02−6.94 (m, 2H), 6.58 (dt, *J* = 7.5, 0.6 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 160.5, 143.7, 137.6, 134.8, 131.4, 130.8, 130.6, 129.3, 129.2, 128.3, 127.4, 124.8, 123.5, 122.8, 122.5, 111.4, 99.2, 45.2; ESI-HRMS *m*/*z* calcd for $C_{21}H_{16}N_3O$ $[M + H]^+$ 326.1288, found 326.1287.

1′-Methylspiro[indazole-3,3′-indolin]-2′-one. Compound **3b** (123 mg, *Y* = 98%, R_f = 0.28 (PE:EA = 2:1)) was isolated as a yellow solid; mp 177−178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 1H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51−7.41 (m, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.06−6.98 (m, 2H), 6.54 (d, *J* = 7.5 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 160.3, 146.1, 138.1, 131.0, 131.0, 130.2, 124.3, 123.6, 122.8, 122.1, 121.7, 109.4, 99.6, 27.5; ESI-HRMS *m*/*z* calcd for $C_{15}H_{12}N_3O$ $[M + H]^+$ 250.0975, found 250.0974.

1′-Benzyl-5′-nitrospiro[indazole-3,3′-indolin]-2′-one. Compound **3c** (160 mg, *Y* = 86%, R_f = 0.20 (PE:EA = 2:1)) was isolated as a yellow solid; mp 106−107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27−8.20 (m, 2H), 7.69−7.64 (t, *J* = 7.6 Hz, 1H), 7.57−7.52 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.38−7.30 (m, 6H), 7.02 (d, *J* = 8.7 Hz, 1H), 5.12 (d, *J* = 15.8 Hz, 1H), 5.05 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 160.6, 150.5, 144.0, 136.6, 134.0, 131.6, 130.9, 129.3, 128.5, 127.6, 127.3, 122.7, 122.6, 120.1, 110.1, 98.4. 45.2, (1C missing); ESI-HRMS *m*/*z* calcd for $C_{21}H_{15}N_4O_3$ $[M + H]^+$ 371.1139, found 371.1140.

1′-Benzyl-5′-fluorospiro[indazole-3,3′-indolin]-2′-one. Compound **3d** (155 mg, *Y* = 90%, R_f = 0.41 (PE:EA = 5:1)) was isolated as a gray solid; mp 123−124 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.30 (d, *J* = 7.6 Hz, 1H), 7.74 (td, *J* = 7.6, 1.2 Hz, 1H), 7.63 (td, *J* = 7.6, 1.2 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.42−7.39 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.19−7.16 (m, 2H), 6.61−6.58 (m, 1H), 5.17 (d, *J* = 15.8 Hz, 1H), 5.08 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 167.6, 161.2, 160.1 (d, *J* = 239.3 Hz), 142.2, 138.7, 136.5, 132.0, 131.2, 129.7, 128.6, 128.1, 124.3 (d, *J* = 8.9 Hz), 123.6, 122.5, 117.7 (d, *J* = 23.3 Hz), 112.9 (d, *J* = 25.4 Hz), 112.1 (d, *J* = 8.2 Hz), 110.2, 45.0; ESI-HRMS *m*/*z* calcd for $C_{21}H_{15}FN_3O$ $[M + H]^+$ 344.1194, found 344.1193.

1′-Benzyl-4′-chlorospiro[indazole-3,3′-indolin]-2′-one. Compound **3e** (178 mg, *Y* = 99%, R_f = 0.38 (PE:EA = 5:1)) was isolated as a yellow solid; mp 155−156 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.31 (d, *J* = 8.0 Hz, 1H), 7.73 (td, *J* = 7.6, 0.8 Hz, 1H), 7.61 (td, *J* = 7.2, 0.8 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.48−7.37 (m, 5H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.15 (d, *J* = 15.8 Hz, 1H), 5.08 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 Hz, $(CD_3)_2CO$) δ 167.0, 161.6, 147.6, 137.9, 136.4, 133.1, 131.8, 131.3, 131.1, 129.8, 128.7, 128.0, 124.6, 123.2, 122.6, 120.3, 109.9, 99.4, 45.2; ESI-HRMS *m*/*z* calcd for $C_{21}H_{15}ClN_3O$ $[M + H]^+$ 360.0898, found 360.0897.

1′-Benzyl-5′-bromospiro[indazole-3,3′-indolin]-2′-one. Compound **3f** (199 mg, *Y* = 98%, R_f = 0.48 (PE:EA = 5:1)) was isolated as a yellow solid; mp 178−179 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.31 (d, *J* = 8.0 Hz, 1H), 7.76 (td, *J* = 7.6, 1.2 Hz, 1H), 7.65 (td, *J* = 7.2, 0.8 Hz, 1H), 7.60−7.57 (m, 2H), 7.48−7.39 (m, 4H), 7.35−7.31 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 5.18 (d, *J* = 15.8 Hz, 1H). 5.09 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 167.5, 161.3, 145.4, 138.6, 136.4, 134.3, 132.1, 131.3, 129.8, 128.7, 128.1, 127.9, 124.9, 123.7, 122.6, 116.1, 113.0, 99.9, 45.1; ESI-HRMS *m*/*z* calcd for $C_{21}H_{15}BrN_3O$ $[M + H]^+$ 404.0393, found 404.0393.

1′-Benzyl-6′-bromospiro[indazole-3,3′-indolin]-2′-one. Compound **3g** (176 mg, *Y* = 87%, R_f = 0.31 (PE:EA = 5:1)) was isolated as a gray solid; mp 75−76 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.64−7.55 (m, 2H), 7.51−7.30 (m, 6H), 7.20 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 5.20 (d, *J* = 15.9 Hz, 1H), 5.11 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 167.8, 161.1, 147.5, 138.6, 136.2, 132.0, 131.2, 129.7, 128.6, 128.0, 127.0, 126.4, 124.7, 123.6, 122.5, 121.8, 114.3, 99.8, 44.9; ESI-HRMS *m*/*z* calcd for $C_{21}H_{15}BrN_3O$ $[M + H]^+$ 404.0393, found 404.0392.

1′-Benzyl-7′-bromospiro[indazole-3,3′-indolin]-2′-one. Compound **3h** (193 mg, *Y* = 95%, R_f = 0.46 (PE:EA = 5:1)) was isolated as a yellow solid; mp 66−67 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.30 (d, *J* = 7.5 Hz, 1H), 7.76−7.71 (m, 1H), 7.65−7.62 (m, 2H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.40−7.36 (m, 4H), 7.31−7.29 (m, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.2 Hz, 1H), 5.54 (s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 168.6, 161.2, 143.4, 138.7, 137.8, 137.2, 132.1, 131.2, 129.5, 128.0, 126.9, 125.7, 125.6, 124.3, 123.7, 122.5, 103.5, 99.8, 46.2; ESI-HRMS *m*/*z* calcd for $C_{21}H_{15}BrN_3O$ $[M + H]^+$ 404.0393, found 404.0392.

1′-Benzyl-5′-methylspiro[indazole-3,3′-indolin]-2′-one. Compound **3i** (154 mg, *Y* = 91%, R_f = 0.30 (PE:EA = 5:1)) was isolated as a white solid; mp 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43−7.29 (m, 6H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 5.08 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 160.2, 142.7, 138.4, 135.3, 133.4, 131.0, 130.1, 129.0, 128.0, 127.4, 125.0, 122.6, 122.0, 121.7, 110.1, 99.8, 44.9, 20.9, (1C missing); ESI-HRMS *m*/*z* calcd for $C_{22}H_{18}N_3O$ $[M + H]^+$ 340.1444, found 340.1445.

1′-Benzyl-5′-methoxyspiro[indazole-3,3′-indolin]-2′-one. Compound **3j** (149 mg, *Y* = 84%, R_f = 0.20 (PE:EA = 5:1)) was isolated as a red solid; mp 157−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.31−7.20 (m, 6H), 6.72 (br s, 2H), 6.04 (s, 1H), 4.92 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 160.2, 156.6, 138.4, 138.2, 135.2, 131.2, 130.3, 129.1, 128.1, 127.4, 122.8, 122.7, 122.2, 115.6, 111.1, 111.0, 99.8, 55.9, 45.0; ESI-HRMS *m*/*z* calcd for $C_{22}H_{18}N_3O_2$ $[M + H]^+$ 356.1394, found 356.1394.

1′-Benzyl-5,6-difluorospiro[indazole-3,3′-indolin]-2′-one. Compound **3k** (145 mg, *Y* = 80%, R_f = 0.38 (PE:acetone = 10:1)) was isolated as a white solid; mp 147−148 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.35 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.65 (dd, *J* = 8.8, 6.8 Hz, 1H), 7.50−7.48 (m, 2H), 7.44−7.38 (m, 3H), 7.34−7.30 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.04 (td, *J* = 7.2, 0.8 Hz, 1H), 6.74 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.19 (d, *J* = 15.8 Hz, 1H), 5.05 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 167.0, 156.7 (dd, *J* = 7.4, 2.0 Hz), 154.1 (dd, *J* = 97.7, 14.7 Hz), 151.6 (dd, *J* = 94.0, 14.8 Hz), 146.2,

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136.6, 135.8 (dd, J = 8.3, 2.8 Hz), 131.9, 129.7, 128.6, 128.1, 125.1, 124.4, 121.7, 112.9 (d, J = 21.6 Hz), 111.5 (d, J = 19.8 Hz), 111.4, 101.2 (d, J = 1.4 Hz), 45.1; ESI-HRMS m/z calcd for $C_{21}H_{14}F_2N_3O$ $[M + H]^+$ 362.1099, found 362.1098.

1′-Benzyl-5,6-dimethylspiro[indazole-3,3′-indolin]-2′-one. Compound **3l** (167 mg, Y = 94%, R_f = 0.25 (PE:EA = 5:1)) was isolated as a yellow solid; mp 163−164 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.05 (s, 1H), 7.50−7.47 (m, 2H), 7.43−7.32 (m, 4H), 7.25 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 5.16 (d, J = 15.8 Hz, 1H), 5.08 (d, J = 15.8 Hz, 1H), 2.45 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 168.3, 160.3, 146.1, 141.6, 140.0, 137.2, 136.9, 131.4, 129.7, 128.6, 128.1, 124.8, 124.2, 124.1, 123.2, 122.8, 111.1, 99.8, 44.9, 20.2, 20.2; ESI-HRMS m/z calcd for $C_{23}H_{20}N_3O$ $[M + H]^+$ 354.1601, found 354.1601.

1′-Benzyl-6,7-dihydro-5H-spiro[cyclopenta[f]indazole-3,3′-indolin]-2′-one. Compound **3m** (161 mg, Y = 88%, R_f = 0.22 (PE:EA = 5:1)) was isolated as a white solid; mp 182−183 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.06 (s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.42−7.30 (m, 4H), 7.26 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.15 (d, J = 16.0 Hz, 1H), 5.09 (d, J = 16.0 Hz, 1H), 3.07 (t, J = 7.4 Hz, 2H), 2.97−2.93 (m, 2H), 2.21−2.14 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 168.4, 161.0, 149.5, 147.9, 146.2, 138.4, 136.9, 131.4, 129.7, 128.6, 128.2, 124.8, 124.2, 123.4, 119.2, 118.0, 111.2, 99.3, 44.9, 33.2, 33.1, 26.7; ESI-HRMS m/z calcd for $C_{24}H_{20}N_3O$ $[M + H]^+$ 366.1601, found 366.1600.

1-Benzylspiro[indoline-3,3′-[1,3]dioxolo[4,5-f]indazol]-2-one. Compound **3n** (167 mg, Y = 90%, R_f = 0.34 (PE:EA = 5:1)) was isolated as a yellow solid; mp 200−201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.37−7.27 (m, 6H), 6.96 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.72 (s, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.09 (d, J = 8.8 Hz, 2H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 155.4, 151.5, 149.9, 145.1, 135.2, 133.9, 130.8, 129.2, 128.1, 127.4, 124.4, 123.7, 121.8, 110.4, 103.1, 102.8, 102.4, 98.7, 45.0; ESI-HRMS m/z calcd for $C_{22}H_{16}N_3O_3$ $[M + H]^+$ 370.1186, found 370.1185.

1′-Benzyl-7-methoxyspiro[indazole-3,3′-indolin]-2′-one. Compound **3o** (153 mg, Y = 86%, R_f = 0.35 (PE:EA = 5:1)) was isolated as a yellow solid; mp 160−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 7H), 7.08 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.90−6.86 (m, 2H), 6.56 (d, J = 7.2 Hz, 1H), 5.03 (s, 2H), 4.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 153.0, 148.9, 145.1, 141.0, 135.2, 133.1, 130.8, 129.2, 128.1, 127.4, 124.5, 123.7, 122.1, 114.5, 114.4, 110.4, 99.2, 57.7, 44.9; ESI-HRMS m/z calcd for $C_{22}H_{18}N_3O_2$ $[M + H]^+$ 356.1394, found 356.1394.

5-Benzylindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4a** (62 mg, Y = 95%, R_f = 0.23 (PE:EA = 1:1)) was isolated as a white solid; mp 203−204 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 7.2 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.34−7.18 (m, 9H), 5.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 146.9, 136.4, 134.4, 132.0, 129.9, 129.6, 129.2, 128.0, 126.9, 124.4, 124.3, 123.9, 121.5, 119.6, 117.5, 116.1, 115.3, 48.4; ESI-HRMS m/z calcd for $C_{21}H_{16}N_3O$ $[M + H]^+$ 326.1288, found 326.1287.

5-Methylindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4b** (49 mg, Y = 98%, R_f = 0.21 (PE:EA = 1:1)) was isolated as a white solid; mp 208−209 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.51−7.42 (m, 2H), 7.35−7.20 (m, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 146.2, 134.7, 131.5, 129.6, 129.2, 124.0, 123.4, 121.3, 119.5, 117.2, 114.8, 114.8, 31.9 (1C missing); ESI-HRMS m/z calcd for $C_{15}H_{12}N_3O$ $[M + H]^+$ 250.0975, found 250.0975.

5-Benzyl-2-nitroindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4c** (63 mg, Y = 85%, R_f = 0.20 (PE:EA = 1:1)) was isolated as a yellow solid; mp >260 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, J = 2.4 Hz, 1H), 8.32−8.29 (m, 2H), 8.05 (d, J = 9.2 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 7.47 (dd, J = 8.4, 7.2 Hz, 1H), 7.38−7.32 (m, 5H), 5.80 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.4, 146.5, 143.8, 138.4, 134.4, 130.3, 129.6, 128.6, 126.8, 126.0, 124.3, 121.0, 120.2, 119.4, 118.1, 116.9, 115.6, 49.1, (1C missing); ESI-HRMS m/z calcd for $C_{21}H_{15}N_4O_3$ $[M + H]^+$ 371.1139, found 371.1140.

5-Benzyl-2-bromoindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4f** (80 mg, Y = 99%, R_f = 0.22 (PE:EA = 1:1)) was isolated as a yellow solid; mp >250 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.58−7.51 (m, 2H), 7.40−7.24 (m, 7H), 5.72 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.2, 146.7, 135.1, 133.3, 132.5, 130.6, 129.8, 129.4, 128.2, 126.8, 126.2, 125.1, 121.2, 120.0, 117.8, 117.8, 117.5, 117.0, 48.6; ESI-HRMS m/z calcd for $C_{21}H_{15}BrN_3O$ $[M + H]^+$ 404.0393, found 404.0394.

5-Benzyl-2-methylindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4i** (65 mg, Y = 96%, R_f = 0.16 (PE:EA = 1:1)) was isolated as a white solid; mp >250 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.28−7.19 (m, 8H), 5.65 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 146.5, 135.3, 133.9, 131.7, 131.6, 130.7, 129.2, 128.9, 127.7, 126.6, 123.8, 123.3, 121.4, 119.1, 117.1, 115.6, 114.7, 47.9, 20.9; ESI-HRMS m/z calcd for $C_{22}H_{18}N_3O$ $[M + H]^+$ 340.1444, found 340.1443.

5-Benzyl-2-methoxyindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4j** (67 mg, Y = 94%, R_f = 0.33 (PE:EA = 1:1)) was isolated as a white solid; mp 249−250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.46 (br s, 1H), 7.26−7.22 (m, 6H), 7.15 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.59 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 150.7, 146.4, 135.5, 131.5, 129.3, 129.1, 128.1, 127.9, 126.8, 124.2, 121.1, 119.5, 117.3, 117.1, 116.6, 115.7, 106.9, 55.8, 48.3; ESI-HRMS m/z calcd for $C_{22}H_{18}N_3O_2$ $[M + H]^+$ 356.1394, found 356.1395.

5-Benzyl-10,11-difluoroindazolo[2,3-c]quinazolin-6(5H)-one. Compound **4k** (68 mg, Y = 94%, R_f = 0.17 (PE:EA = 1:1)) was isolated as a white solid; mp >260 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.2 Hz, 1H), 7.95 (t, J = 8.4 Hz, 1H), 7.68 (t, J = 8.6 Hz, 1H), 7.53−7.41 (m, 3H), 7.33−7.26 (m, 5H), 5.74 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6 (dd, J = 253.6, 18.2 Hz), 150.1 (dd, J = 248.9, 18.3 Hz), 147.8 (d, J = 11.6 Hz), 146.6, 135.2, 134.6, 132.0 (d, J = 8.6 Hz), 130.4, 129.3, 128.2, 126.9, 124.6, 123.6, 116.4, 114.8, 112.7 (d, J = 8.7 Hz), 106.6 (d, J = 21.0 Hz), 105.1 (d, J = 19.8 Hz), 48.6; ESI-HRMS m/z calcd for $C_{21}H_{14}F_2N_3O$ $[M + H]^+$ 362.1099, found 362.1097.

5-Benzyl-[1,3]dioxolo[4′,5′:5,6]indazolo[2,3-c]quinazolin-6(5H)-one. Compound **4n** (70 mg, Y = 95%, R_f = 0.24 (PE:EA = 1:1)) was isolated as a white solid; mp >250 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 6.9 Hz, 1H), 7.41−7.26 (m, 9H), 7.19 (s, 1H), 6.08 (s, 2H), 5.68 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 149.7, 147.9, 146.9, 135.7, 134.4, 131.1, 129.4, 129.2, 127.9, 126.9, 124.1, 123.4, 116.0, 115.4, 113.3, 102.0, 95.7, 95.2, 48.2; ESI-HRMS m/z calcd for $C_{22}H_{16}N_3O_3$ $[M + H]^+$ 370.1186, found 370.1187.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00990.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Crystallographic information for **3a** (CIF)

Crystallographic information for **4a** (CIF)

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Notes

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