JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

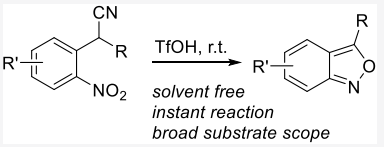
TfOH-Promoted Decyanative Cyclization toward the Synthesis of 2,1-Benzisoxazoles

Mengge Zhang, Yonggang Meng, Yangang Wu, and Chuanjun Song*

Cite This: J. Org. Chem. 2021, 86, 7326−7332 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A novel solvent-free, TfOH-promoted decyanative cyclization approach for the synthesis of 2,1-benzisoxazoles has been developed. The reactions are complete instantly at room temperature and result in the formation of the desired 2,1-benzisoxazoles in a 34−97% isolated yield.



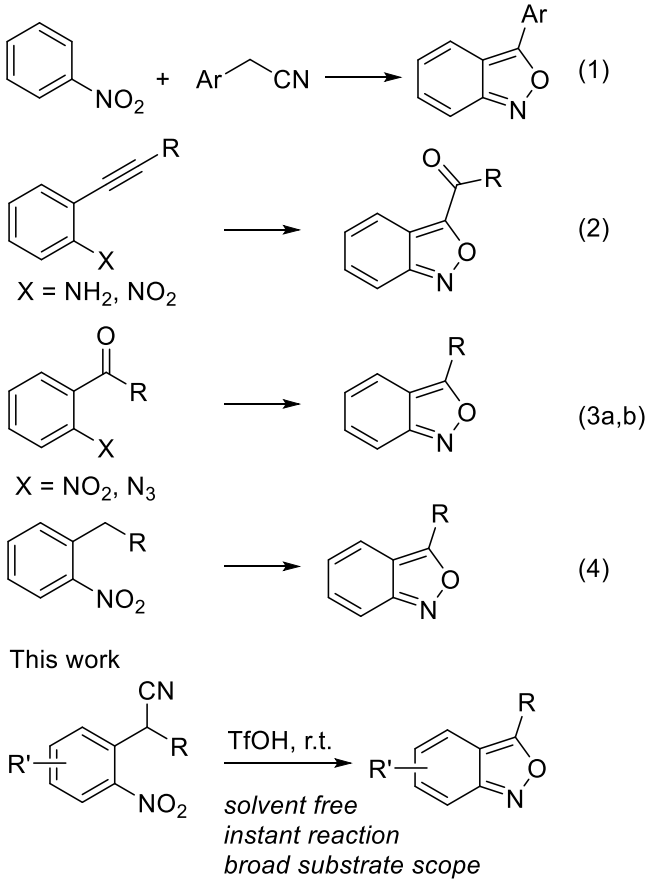
INTRODUCTION

2,1-Benzisoxazoles (anthranils) are useful building blocks for the synthesis of drug molecules,[1] 2-aminoarylketons,[2] and fused heterocyclic molecules such as benzazepines,[3] indoles,[4] quinolines,[5] and acridines.[6] Moreover, derivatives of benzisoxazoles have been found to show antimicrobial,[7] antitubulin,[8] antifungal,[9] and antitumor activities.[10] A number of methods for the synthesis of benzisoxazoles have been developed (Scheme 1). The condensation of nitrobenzenes and arylacetonitriles (1)[11] and the transition-metal-catalyzed heterocyclization of (2-amino/nitro)phenylacetylenes (2)[12] are limited to the synthesis of 3-aryl-2,1-benzisoxazoles and 3-acyl-2,1-benzisoxazoles, respectively. General methods for the synthesis of 2,1-benzisoxazoles involve the reductive heterocyclization of 2-nitroacylbenzenes (3a),[13] thermolysis or metal-catalyzed cyclization of 2-azidoacylbenzenes (3b),[14] and acid- or base-catalyzed dehydrative cyclization of 2-nitrobenzyl compounds (4).[15] Among these, the latter method seems to be the most versatile to access variously substituted 2,1-benzisoxazoles. However, the requirement of prolonged heating of the acid-catalyzed reaction[15a−c] limits the functional group tolerance. As part of our recent interest toward the synthesis of heterocyclic compounds via C−N and C−O bond formation under transition-metal-free conditions,[16] we herein report a TfOH-promoted, solvent-free, room temperature, instant decyanative cyclization approach for the synthesis of 2,1-benzisoxazoles.

RESULTS AND DISCUSSION

2-(2-Nitrophenyl)acetonitrile **1a** was used as a substrate for the optimization of reaction conditions. In sharp contrast with literature reports,[15a−c] the reaction was complete instantly in the presence of 8 equiv of TfOH at ambient temperature in dichloromethane (DCM), which resulted in the formation of 2,1-benzisoxazole-3-carboxylate **2a** in an 85% isolated yield (Table 1, entry 1). No reaction occurred in other solvents tested (entries 2−5). To our delight, **2a** could be isolated in a 91% yield in the absence of the solvent (entry 6). Next, other acids were inspected under solvent-free conditions (entries 7−

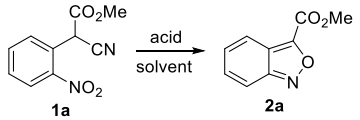
Scheme 1. Comparation of Previous and Present Methods for the Synthesis of 2,1-Benzisoxazoles



Received: January 13, 2021
Published: May 20, 2021

https://doi.org/10.1021/acs.joc.1c00091
J. Org. Chem. 2021, 86, 7326−7332

Table 1. Optimization of Reaction Conditions



1a 2a

entry	acid (equiv)	solvent	temp. (°C)	yield[a] (%)
1	TfOH (8.0)	DCM	r.t.	85
2	TfOH (8.0)	MeOH	r.t.	0[b]
3	TfOH (8.0)	THF	r.t.	0[b]
4	TfOH (8.0)	DMF	r.t.	0[b]
5	TfOH (8.0)	MeCN	r.t.	0[b]
6	**TfOH (8.0)**		**r.t.**	**91**
7	conc. HCl (8.0)		r.t.	0[b]
8	MsOH (8.0)		r.t.	0[b]
9	TFA (8.0)		r.t.	0[b]
10	conc. H_2SO_4 (8.0)		r.t.	trace
11	TfOH (7.0)		r.t.	85
12	TfOH (9.0)		r.t.	89
13	TfOH (8.0)		0	81

[a]Isolated yield. [b]No reaction, starting material recovered.

10). Only trace amount of the desired **2a** was obtained when conc. H_2SO_4 was used, while no reaction occurred with other acids. Variation of the equivalent of TfOH (entries 11 and 12) or lowering the reaction temperature (entry 13) did not improve the yield of **2a**.

With the optimal reaction conditions in hand, we then examined the TfOH-promoted decyanative cyclization of various 2-(2-nitrophenyl)acetonitriles for the synthesis of 2,1-benzisoxazoles. As shown in Table 2, a variety of 2-methoxycarbonyl-2-(2-nitrophenyl)acetonitriles reacted smoothly under the reaction conditions to provide 2,1-benzisoxazole-3-carboxylates **2a**–**g** in excellent isolated yields. Next, the reactions of the 2-aryl substituted substrates **1h**–**r** were examined. The desired products **2h**–**o**,**q** were obtained in moderate isolated yields. In general, substrates with an electron-withdrawing-group-substituted phenyl ring gave higher product yields than those with an electron-donating-group-substituted phenyl ring. The reaction of **1p** with a 2,6-dichlorophenyl ring resulted in the formation of **2p** in an excellent isolated yield. It is interesting to notice that the reaction of **1r** with 2-nitrophenyl as well as 2-methyl-6-nitrophenyl group gave **2r** in a 64% isolated yield. No trace of the alternative product (structure not shown) resulting from heterocyclization involving the 2-nitrophenyl moiety was observed. Under the reaction conditions, 3-alkyl-substituted products **2s**–**u** could also be obtained as expected. Finally, the reaction of 2-nitrophenylacetonitrile **1v** (R = H) yielded 2,1-benzisoxazole-3-carboxamide **2v** in a 65% isolated yield. Compared with literature reports concerning acid-catalyzed cyclization of 2-nitrobenzyl compounds toward the synthesis of 2,1-benzisoxazoles,[15a−c] it implied that capturing of water molecule generated during the reaction by the cyano group might be crucial to the ease of the reaction reported herein (ambient temperature, instant reaction). Indeed, the yield of **2a** dropped to 38% if 1 equiv of water was added to the mixture of **1a** and TfOH (Scheme 2a). Besides, no reaction occurred when 2-(2-nitrophenyl)acetamide **3a**, methyl 2-(2-nitrophenyl)acetate **3b**, or 1-benzyl-2-nitrobenzene **3c** was subjected to the reaction conditions (Scheme 2b).

Based on the results of the experiments and literature reports,[15a] a plausible mechanism is depicted in Scheme 3. Acid-promoted enolization of **1** provided **A**, intramolecular cyclization of which gave **B**. An attack of the cyanide group by the hydroxyl group resulted in the formation of **C**. **2a**–**u** and **2v** were formed following a retro-Diels–Alder-type reaction and an elimination pathway, respectively.

CONCLUSIONS

In summary, we have developed a novel solvent-free, TfOH-promoted decyanative cyclization approach for the synthesis of 2,1-benzisoxazoles with a broad substrate scope. The reactions are complete instantly at room temperature to yield the desired products in moderate to excellent isolated yields.

EXPERIMENTAL SECTION

Melting points were determined on a hot-stage apparatus and were uncorrected. Infrared spectra were obtained using a Fourier transform infrared (FT-IR) spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer. Mass spectra were recorded on a Q-TOF micro spectrometer. Flash column chromatography was performed over a silica gel 200–300 mesh.

General Procedure for the Synthesis of Substrate 1a–r. To a suspension of potassium *tert*-butoxide (224 mg, 2.0 mmol, 2.0 equiv) in dimethylformamide (DMF) (5 mL) at 0 °C, acetonitrile (1.2 mmol, 1.2 equiv) was added over 5 min, followed by 2-fluoronitrobenzene (1.0 mmol). After addition, the reaction was heated at 90 °C until completion according to thin-layer chromatography (TLC) analysis. The cooled mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and then concentrated under vacuum. The residue was purified by column chromatography on a silica gel (200–300 mesh) to give **1a**–**r**.

General Procedure for the Synthesis of Substrate 1s–u. A mixture of 2-nitrophenylacetonitrile (1.0 mmol) and potassium carbonate (276 mg, 2.0 mmol, 2.0 equiv) in DMF (5 mL) was stirred at room temperature for 0.5 h. Alkyl iodine (1.1 mmol, 1.1 equiv) was added. The reaction was stirred at room temperature until completion according to TLC analysis, and then cooled to 0 °C and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and then concentrated under vacuum. The crude product was purified by column chromatography on a silica gel (200–300 mesh) to give **1s**–**u**.

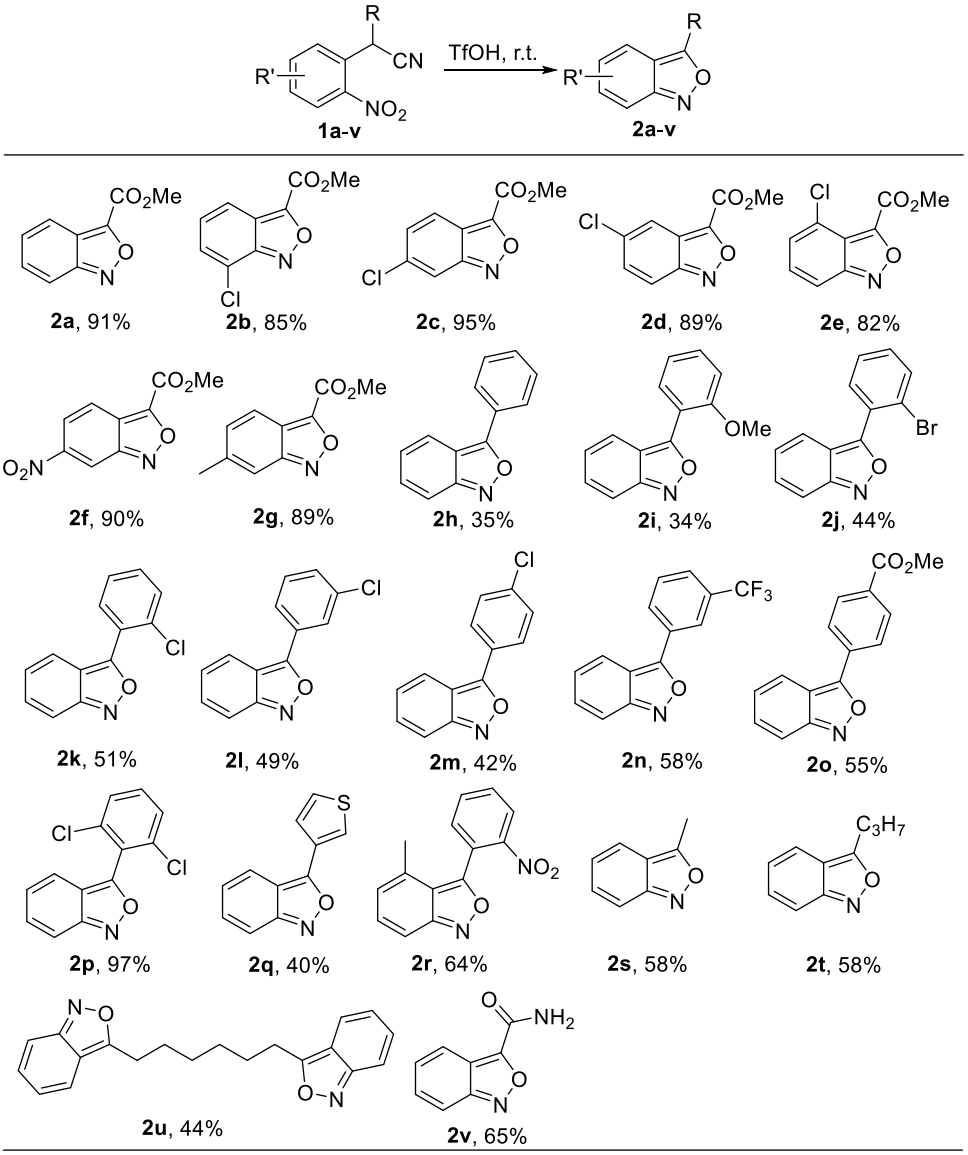
General Procedure for the Synthesis of 2,1-Benzisoxazoles 2a–v. TfOH (8.0 mmol, 8 equiv) was added to **1a**–**v** (1.0 mmol) at room temperature. After addition, the reaction was quenched immediately with saturated aqueous sodium carbonate (20 mL), and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to give **2a**–**v**.

Methyl benzo[*c*]isoxazole-3-carboxylate (2a). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 30/1). Yellow solid (161 mg, 91%); mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 9.1 Hz, 1H), 7.37 (ddd, J = 9.1, 6.4, 1.0 Hz, 1H), 7.22 (ddd, J = 8.8, 6.4, 0.6 Hz, 1H), 4.07 (s, 3H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 157.6, 157.6, 153.5, 131.33, 128.1, 120.5, 120.5, 116.2, 53.0 ppm; IR (neat): ν_{max} 1731, 1313, 1197 cm^{-1}; electrospray ionization-high-resolution mass spectrometry (ESI-HRMS): m/z [M + H]$^+$ calcd for $C_9H_8NO_3$: 178.0499, found: 178.0497.

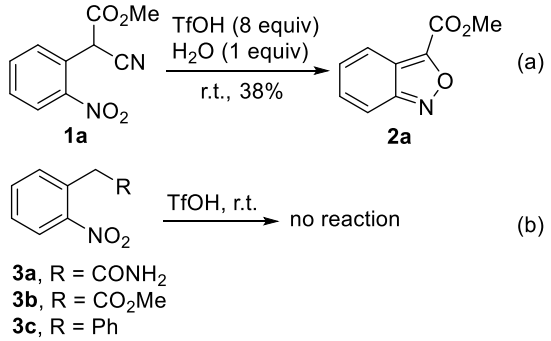
Methyl 7-chlorobenzo[*c*]isoxazole-3-carboxylate (2b). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 6/1). White solid (179 mg, 85%); mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, J = 8.8, 0.6 Hz, 1H), 7.40 (dd, J = 7.0, 0.6 Hz, 1H), 7.16 (dd, J = 8.8, 7.0 Hz, 1H),

https://doi.org/10.1021/acs.joc.1c00091
J. Org. Chem. 2021, 86, 7326–7332

Table 2. Substrate Scope



Scheme 2. Control Experiments



4.08 (s, 3H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.2, 156.1, 155.0, 130.5, 128.3, 122.3, 121.6, 119.4, 53.2 ppm; IR (neat): ν_{max} 1715, 1268, 1213 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_9H_7{}^{35}ClNO_3$: 212.0109, found: 212.0106.

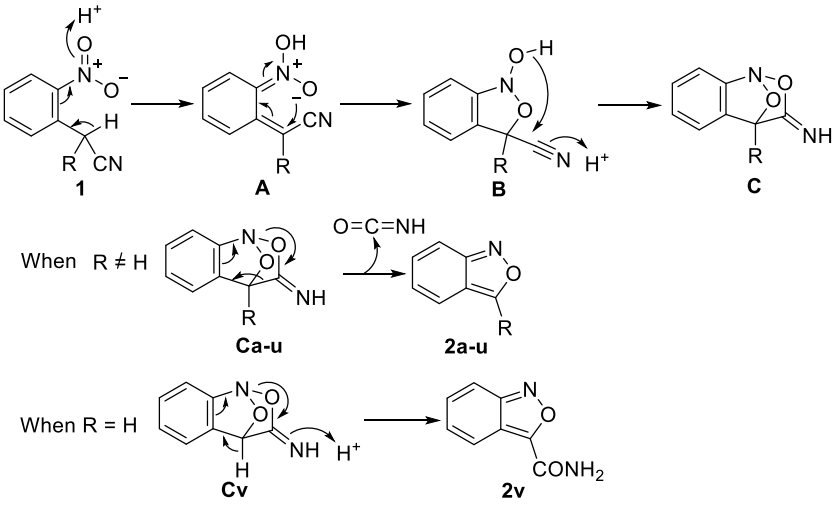
Methyl 6-chlorobenzo[*c*]isoxazole-3-carboxylate (2c). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 8/1). White solid (200 mg, 95%); mp 111−112 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 9.2 Hz, 1H), 7.70 (s, 1H), 7.15 (d, J = 9.2 Hz, 1H), 4.07 (s, 3H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.6, 157.2, 154.2, 137.8, 130.0, 121.9, 118.9, 114.7, 53.1 ppm; IR (neat): ν_{max} 1718, 1298, 1228, 1043 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_9H_7{}^{35}ClNO_3$: 212.0109, found: 212.0107.

Methyl 5-chlorobenzo[*c*]isoxazole-3-carboxylate (2d). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 8/1). White solid (188 mg, 89%); mp 111−112 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 7.67 (d, J = 9.4 Hz, 1H), 7.30 (dd, J = 9.4, 1.8 Hz, 1H), 4.08 (s, 3H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.3, 156.1, 153.2, 134.4, 133.4, 120.7, 119.0, 117.8, 53.1 ppm; IR (neat): ν_{max} 1728, 1279, 1193 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_9H_7{}^{35}ClNO_3$: 212.0109, found: 212.0110.

Methyl 4-chlorobenzo[*c*]isoxazole-3-carboxylate (2e). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 8/1). White solid (173 mg, 82%); mp 87−88 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, J = 8.5, 1.1 Hz, 1H), 7.24−7.19 (m, 2H), 4.03 (s, 3H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 158.6, 157.1, 154.8, 131.2, 128.4, 125.4, 118.4, 115.1, 53.3 ppm; IR (neat): ν_{max} 1733, 1262, 1181 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_9H_7{}^{35}ClNO_3$: 212.0109, found: 212.0106.

https://doi.org/10.1021/acs.joc.1c00091
J. Org. Chem. 2021, 86, 7326−7332

Scheme 3. Proposed Mechanism



Methyl 6-nitrobenzo[*c*]isoxazole-3-carboxylate (2f). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 8/1). Yellow solid (200 mg, 90%); mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (dd, J = 1.8, 0.9 Hz, 1H), 8.14 (dd, J = 9.5, 0.9 Hz, 1H), 8.01 (dd, J = 9.5, 1.8 Hz, 1H), 4.13 (s, 3H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 156.9, 156.4, 155.7, 150. 2, 123.2, 121.6, 121.0, 114.4, 53.5 ppm; IR (neat): ν_{max} 1720, 1268, 1213 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_9H_7N_2O_5$: 223.0349, found: 223.0357.

Methyl 6-methylbenzo[*c*]isoxazole-3-carboxylate (2g). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 10/1). Yellow solid (170 mg, 89%); mp 67−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 7.07 (d, J = 9.0 Hz, 1H), 4.07 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 158.3, 157.7, 153.0, 141.9, 131.6, 119.9, 119.5, 113.6, 52.9, 22.6 ppm; IR (neat): ν_{max} 1708, 1295, 1229 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{10}H_{10}NO_3$: 192.0655, found: 192.0654.

3-Phenylbenzo[*c*]isoxazole (2h). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 2/1). Yellow liquid (68 mg, 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03−8.00 (m, 2H), 7.83 (d, J = 8.9 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.57−7.53 (m, 2H), 7.51−7.46 (m, 1H), 7.32 (ddd, J = 9.1, 6.4, 0.8 Hz, 1H), 7.05 (ddd, J = 8.9, 6.4, 0.6 Hz, 1H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 164.5, 157.9, 130.8, 130.4, 129.4, 128.5, 126.7, 124.7, 120.7, 115.6, 114.5 ppm; IR (neat): ν_{max} 2924, 2852, 1632 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_{10}NO$: 196.0757, found: 196.0754.

3-(2-Methoxyphenyl)benzo[*c*]isoxazole (2i). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 10/1). Yellow liquid (77 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, J = 7.7, 1.7 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 7.49 (ddd, J = 9.1, 7.4, 1.7 Hz, 1H), 7.30 (ddd, J = 9.1, 6.4, 1.0 Hz, 1H), 7.13 (td, J = 7.7, 1.0 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.98 (ddd, J = 8.9, 6.4, 0.8 Hz, 1H), 3.94 (s, 3H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 163.5, 157.9, 156.5, 132.0, 130.6, 130.6, 123.4, 122.7, 121.2, 117.8, 116.1, 115.2, 111.8, 55.7 ppm; IR (neat): ν_{max} 2924, 2854, 1251, 1021 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{12}NO_2$: 226.0863, found: 226.0860.

3-(2-Bromophenyl)benzo[*c*]isoxazole (2j). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 10/1). Yellow liquid (120 mg, 44%); ^{1}H NMR (400 MHz, CD_3OD): δ = 9.40 (dd, J = 8.0, 1.0 Hz, 1H), 9.20 (dd, J = 7.7, 1.8 Hz, 1H), 9.17−9.11 (m, 3H), 9.07−9.02 (m, 1H), 8.97 (ddd, J = 9.1, 6.4, 1.0 Hz, 1H), 8.66 (ddd, J = 8.9, 6.4, 0.7 Hz, 1H) ppm; ^{13}C{1H} NMR (100 MHz, CD_3OD): δ = 165.9, 158.4, 135.2, 133.4, 133.1, 132.6, 130.3, 129.1, 126.0, 123.2, 121.8, 117.4, 115.7 ppm; IR (neat): ν_{max} 2976, 2842, 1267, 1030 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_9{}^{79}BrNO$: 273.9862, found: 273.9860.

3-(2-Chlorophenyl)benzo[*c*]isoxazole (2k). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 25/1). Yellow solid (117 mg, 51%); mp 67−68 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 9.29−9.27 (m, 1H), 9.24−9.22 (m, 1H), 9.19−9.16 (m, 2H), 9.14−9.07 (m, 2H), 8.98 (ddd, J = 9.0, 6.4, 1.0 Hz, 1H), 8.68 (ddd, J = 9.1, 6.4, 0.8 Hz, 1H) ppm; ^{13}C{1H} NMR (100 MHz, CD_3OD): δ = 164.6, 158.5, 134.0, 133.2, 132.8, 132.6, 132.0, 128.7, 128.2, 126.0, 121.9, 117.6, 115.7 ppm; IR (neat): ν_{max} 2956, 2852, 1251, 1021 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_9{}^{35}ClNO$: 230.0367, found: 230.0364.

3-(3-Chlorophenyl)benzo[*c*]isoxazole (2l). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 50/1). White solid (112 mg, 49%); mp 85−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.90−7.88 (m, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.50−7.43 (m, 2H), 7.33 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 7.09 (ddd, J = 8.9, 6.4, 0.7 Hz, 1H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 162.8, 158.0, 135.4, 130.9, 130.7, 130.3, 130.0, 126.5, 125.4, 124.7, 120.3, 115.8, 114.8 ppm; IR (neat): ν_{max} 2966, 2862, 1256, 1021 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_9{}^{35}ClNO$: 230.0367, found: 230.0364.

3-(4-Chlorophenyl)benzo[*c*]isoxazole (2m). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 10/1). White solid (96 mg, 42%); mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97−7.93 (m, 2H), 7.78 (d, J = 8.9 Hz, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.55−7.51 (m, 2H), 7.33 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 7.08 (ddd, J = 8.9, 6.4, 0.7 Hz, 1H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 163.3, 158.0, 136.5, 130.9, 129.7, 127.8, 126.9, 125.1, 120.4, 115.8, 114.6 ppm; IR (neat): ν_{max} 2926, 2852, 1250, 1022 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_9{}^{35}ClNO$: 230.0367, found: 230.0364.

3-(3-(Trifluoromethyl)phenyl)benzo[*c*]isoxazole (2n). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 10/1). Yellow solid (153 mg, 58%); mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1H), 8.21 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.76−7.68 (m, 2H), 7.65 (d, J = 9.1 Hz, 1H), 7.36 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 7.13 (ddd, J = 8.9, 6.4, 0.7 Hz, 1H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ = 162.7, 158.1, 132.0 (J_{F-C} = 32.7 Hz), 131.0, 130.0, 129.7 (J_{F-C} = 1.2 Hz), 129.2, 126.8 (J_{F-C} = 3.7 Hz), 125.7, 123.8 (J_{F-C} = 270.9 Hz), 123.4 (J_{F-C} = 3.9 Hz), 120.1, 116.0, 115.0 ppm; IR (neat): ν_{max} 2960, 2923, 2848, 1318, 1107 cm^{-1}; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_9F_3NO$: 264.0631, found: 264.0627.

Methyl 4-(benzo[*c*]isoxazol-3-yl)benzoate (2o). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 6/1). Yellow solid (139 mg, 55%); mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23−8.20 (m, 2H), 8.11−

https://doi.org/10.1021/acs.joc.1c00091
J. Org. Chem. 2021, 86, 7326−7332

8.08 (m, 2H), 7.85 (d, J = 8.9 Hz, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.35 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 7.12 (ddd, J = 8.9, 6.4, 0.8 Hz, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 166.4, 163.1, 158.0, 132.2, 131.3, 130.9, 130.6, 126.4, 125.6, 120.4, 116.0, 115.4, 52.6 ppm; IR (neat): ν_{max} 1719, 1277, 1102 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{12}NO_3$: 254.0812, found: 254.0811.

3-(2,6-Dichlorophenyl)benzo[*c*]isoxazole (2p). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 15/1). Yellow solid (254 mg, 97%); mp 101−102 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68−7.65 (m, 1H), 7.51−7.49 (m, 2H), 7.45−7.41 (m, 1H), 7.38−7.32 (m, 2H), 7.04 (ddd, J = 8.7, 6.4, 0.7 Hz, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 160.6, 157.2, 136.5, 132.4, 131.0, 128.7, 126.7, 124.9, 120.3, 117.7, 115.7 ppm; IR (neat): ν_{max} 2966, 2852, 1251, 1021 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_8{}^{35}Cl_2NO$: 263.9977, found: 263.9974.

3-(Thiophen-3-yl)benzo[*c*]isoxazole (2q). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 30/1). Yellow solid (80 mg, 40%); mp 89−90 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, J = 3.0, 1.2 Hz, 1H), 7.74−7.70 (m, 2H), 7.57 (d, J = 9.1 Hz, 1H), 7.50 (J = 5.1, 3.0 Hz, 1H), 7.30 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 7.03 (ddd, J = 8.8, 6.4, 0.7 Hz, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.3, 156.1, 153.2, 134.4, 133.4, 120.7, 119.0, 117.8, 53.1 ppm; IR (neat): ν_{max} 2922, 2850, 1250, 1021 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{11}H_8NOS$: 202.0321, found: 202.0320.

4-Methyl-3-(2-nitrophenyl)benzo[*c*]isoxazole (2r). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 10/1). White solid (163 mg, 64%); mp 110−111 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28−8.26 (m, 1H), 7.83−7.75 (m, 2H), 7.63−7.60 (m, 1H), 7.48 (d, J = 9.1 Hz, 1H), 7.22 (dd, J = 9.1, 6.5 Hz, 1H), 6.74 (d, J = 6.5 Hz, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.4, 157.9, 148.7, 133.3, 133.1, 131.8, 131.6, 130.4, 125.3, 124.3, 124.3, 117.4, 113.3, 19.3 ppm; IR (neat): ν_{max} 2924, 2852, 1630 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{11}N_2O_3$: 255.0764, found: 255.0766.

3-Methylbenzo[*c*]isoxazole (2s). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 8/1). Colorless oil (77 mg, 58%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.48 (m, 1H), 7.43−7.41 (m, 1H), 7.25 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 6.91 (dd, J = 8.8, 6.4 Hz, 1H), 2.78 (s, 3H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.8, 157.2, 130.9, 122.9, 120.0, 115.8, 115.0, 12.1 ppm; IR (neat): ν_{max} 2922, 2859, 1072 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for C_8H_8NO: 134.0600, found: 134.0596.

3-Propylbenzo[*c*]isoxazole (2t). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 30/1). Yellow oil (93 mg, 58%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52−7.49 (m, 1H), 7.47−7.44 (m, 1H), 7.25 (ddd, J = 9.1, 6.3, 1.0 Hz, 1H), 6.91 (ddd, J = 8.8, 6.3, 0.7 Hz, 1H), 3.12 (t, J = 7.4 Hz, 2H), 1.94−1.85 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.2, 130.9, 122.9, 120.1, 115.5, 115.1, 28.8, 21.5, 14.0 ppm; IR (neat): ν_{max} 2951, 2922, 2859, 1091 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{10}H_{12}NO$: 162.0913, found: 162.0910.

1,6-Bis(benzo[*c*]isoxazol-3-yl)hexane (2u). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 15/1). Yellow solid (141 mg, 44%); mp 69−70 °C; ^1H NMR (400 MHz, CD_3OD): δ = 7.57−7.54 (m, 2H), 7.45−7.43 (m, 2H), 7.33 (ddd, J = 9.1, 6.3, 1.0 Hz, 1H), 6.96 (ddd, J = 8.8, 6.3, 0.7 Hz, 1H), 3.18 (t, J = 7.4 Hz, 4H), 1.86−1.82 (m, 4H), 1.43−1.39 (m, 4H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, CD_3OD): δ = 171.5, 158.2, 132.7, 124.2, 121.3, 116.6, 115.1, 29.7, 28.7, 27.2 ppm; IR (neat): ν_{max} 2933, 2922, 2859, 1061 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_2$: 321.1598, found: 321.1596.

Benzo[*c*]isoxazole-3-carboxamide (2v). The crude product was purified by column chromatography on a silica gel (*n*-hexane/ethyl acetate = 6/1). White solid (105 mg, 65%); mp 209−210 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.64 (s, 1H), 8.18 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.49 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 7.26 (ddd, J = 8.8, 6.4, 0.9 Hz, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6): δ = 157.7, 157.2, 157.0, 131.9, 127.1, 121.0, 118.2, 115.2 ppm; IR (neat): ν_{max} 3380, 3170, 1698, 1670 cm^{-1}; ESI-HRMS: m/z $[M + H]^+$ calcd for $C_8H_7N_2O_2$: 163.0502, found: 163.0499.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00091.

^1H and ^{13}C NMR spectra for compounds **2a**−**v** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Chuanjun Song − *College of Chemistry and Green Catalysis Center, Zhengzhou University, Zhengzhou 450001, China;* orcid.org/0000-0001-7733-578X; Email: chjsong@zzu.edu.cn

Authors

Mengge Zhang − *College of Chemistry and Green Catalysis Center, Zhengzhou University, Zhengzhou 450001, China*

Yonggang Meng − *College of Chemistry and Green Catalysis Center, Zhengzhou University, Zhengzhou 450001, China*

Yangang Wu − *College of Chemistry and Green Catalysis Center, Zhengzhou University, Zhengzhou 450001, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00091

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to NSFC-Henan (U1804283) for financial support.

■ REFERENCES

(1) Li, J.; Wang, Z.; Xu, Y.; Lu, X.; Zhu, S.; Liu, L. Catalyst-free cyclization of anthranils and cyclic amines: one-step synthesis of rutaecarpine. *Chem. Commun.* **2019**, *55*, 12072−12075.

(2) (a) Zou, M.; Liu, J.; Tang, C.; Jiao, N. Rh-Catalyzed N−O Bond Cleavage of Anthranil: A C−H Amination Reagent for Simultaneous Incorporation of Amine and a Functional Group. *Org. Lett.* **2016**, *18*, 3030−3033. (b) Li, L.; Wang, H.; Yu, S.; Yang, X.; Li, X. Cooperative Co(III)/Cu(II)-Catalyzed C−N/N−N Coupling of Imidates with Anthranils: Access to 1*H*-Indazoles via C−H Activation. *Org. Lett.* **2016**, *18*, 3662−3665. (c) Jeon, M.; Park, J.; Dey, P.; Oh, Y.; Oh, H.; Han, S.; Um, S. H.; Kim, H. S.; Mishra, N. K.; Kim, I. S. Site-Selective Rhodium(III)-Catalyzed C−H Amination of 7-Azaindoles with Anthranils: Synthesis and Anticancer Evaluation. *Adv. Synth. Catal.* **2017**, *359*, 3471−3478. (d) Yu, S.; Tang, G.; Li, Y.; Zhou, X.; Lan, Y.; Li, X. Anthranil: An Aminating Reagent Leading to Bifunctionality for Both $C(sp^3)$−H and $C(sp^2)$−H under Rhodium(III) Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 8696−8700. (e) Li, H.; Jie, J.; Wu, S.; Yang, X.; Xu, H. Rh(iii)-Catalyzed direct C-7 amination of indolines with anthranils. *Org. Chem. Front.* **2017**, *4*, 250−254. (f) Hsu, Y.; Hsieh, S.; Liu, R. Gold-Catalyzed Annulations of N−Propargyl Ynamides with Anthranils with Two Distinct Chemoselectivities. *Chem. - Eur. J.* **2019**, *25*, 5288−5297. (g) Li, J.; Tan, E.; Keller, N.; Chen, Y.; Zehetmaier, P. M.; Jakowetz, A. C.; Bein, T.; Knochel, P. Cobalt-Catalyzed Electrophilic Aminations with Anthranils: An Expedient Route to Condensed Quinolines. *J. Am. Chem. Soc.* **2019**, *141*, 98−103. (h) Debbarma, S.; Maji, M. S. Cp*RhIII-Catalyzed Directed Amidation of Aldehydes with Anthranils. *Eur. J. Org. Chem.* **2017**, *2017*, 3699−3706. (i) Tang, C.; Zou, M.; Liu, J.; Wen, X.; Sun, X.; Zhang, Y.; Jiao, N. Rh-Catalyzed Direct Amination

of Unactivated C(sp^3)−H bond with Anthranils Under Mild Conditions. *Chem. - Eur. J.* **2016**, *22*, 11165−11169.
(3) (a) Singh, R. R.; Skaria, M.; Chen, L.; Cheng, M.; Liu, R. Gold-catalyzed (4+3)-annulations of 2-alkenyl-1-alkynylbenzenes with anthranils with alkyne-dependent chemoselectivity: skeletal rearrangement versus non-rearrangement. *Chem. Sci.* **2019**, *10*, 1201−1206. (b) Wang, Z.; Zhang, H.; Wang, D.; Xu, P.; Luo, Y. Lewis acid catalyzed diastereoselective [3+4]-annulation of donor−acceptor cyclopropanes with anthranils: synthesis of tetrahydro-1-benzazepine derivatives. *Chem. Commun.* **2017**, *53*, 8521−8524. (c) Feng, J.; Zhou, M.; Lin, X.; Lu, A.; Zhang, X.; Zhao, M. Base-Mediated [3+4]-Cycloaddition of Anthranils with Azaoxyallyl Cations: A New Approach to Multisubstituted Benzodiazepines. *Org. Lett.* **2019**, *21*, 6245−6248.
(4) (a) Tian, X.; Song, L.; Farshadfar, K.; Rudolph, M.; Rominger, F.; Oeser, T.; Ariafard, A.; Hashmi, A. S. K. Acyl Migration versus Epoxidation in Gold Catalysis: Facile, Switchable, and Atom-Economic Synthesis of Acylindoles and Quinoline Derivatives. *Angew. Chem., Int. Ed.* **2020**, *59*, 471−478. (b) Wu, X.; Xiao, Y.; Sun, S.; Yu, J.; Cheng, J. Rhodium-Catalyzed Reaction of Sulfoxonium Ylides and Anthranils toward Indoloindolones via a (4+1) Annulation. *Org. Lett.* **2019**, *21*, 6653−6657.
(5) (a) Wang, F.; Xu, P.; Wang, S.; Ji, S. Cu(II)/Ag(I)-Catalyzed Cascade Reaction of Sulfonylhydrazone with Anthranils: Synthesis of 2-Aryl-3-sulfonyl Substituted Quinoline Derivatives. *Org. Lett* **2018**, *20*, 2204−2207. (b) Sahani, R. L.; Liu, R. Gold-Catalyzed [4+2] Annulation/Cyclization Cascades of Benzisoxazoles with Propiolate Derivatives to Access Highly Oxygenated Tetrahydroquinolines. *Angew. Chem.* **2017**, *129*, 12910−12914. (c) Jin, H.; Tian, B.; Song, X.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Gold-Catalyzed Synthesis of Quinolines from Propargyl Silyl Ethers and Anthranils through the Umpolung of a Gold Carbene Carbon. *Angew. Chem. Int. Ed.* **2016**, *55*, 12688−12692. (d) Mokar, B. D.; Jadhav, P. D.; Pandit, Y. B.; Liu, R. Gold-catalyzed (4+2)-annulations between α-alkyl alkenylgold carbenes and benzisoxazoles with reactive alkyl groups. *Chem. Sci.* **2018**, *9*, 4488−4492. (e) Yu, S.; Li, Y.; Zhou, X.; Wang, H.; Kong, L.; Li, X. Access to Structurally Diverse Quinoline-Fused Heterocycles via Rhodium(III)-Catalyzed C−C/C−N Coupling of Bifunctional Substrates. *Org. Lett.* **2016**, *18*, 2812−2815. (f) Shi, L.; Wang, B. Rh(III)-Catalyzed C−H Amination/Annulation Reactions: Synthesis of Indoloquinoline Derivatives in Water. *Org. Lett* **2016**, *18*, 2820−2823. (g) Biswas, A.; Bera, S.; Poddar, P.; Dhara, D.; Samanta, R. Rh(iii)-Catalyzed tandem indole C4-arylamination/annulation with anthranils: access to indoloquinolines and their application in photophysical studies. *Chem. Commun.* **2020**, *56*, 1440−1443. (h) Hu, Y.; Wang, T.; Liu, Y.; Nie, R.; Yang, N.; Wang, Q.; Li, G.; Wu, Y. Practical Synthesis of Benzimidazo[1,2-a]quinolines via Rh(III)-Catalyzed C−H Activation Cascade Reaction from Imidamides and Anthranils. *Org. Lett.* **2020**, *22*, 501−504.
(6) (a) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Gold-Catalyzed C−H Annulation of Anthranils with Alkynes: A Facile, Flexible, and Atom-Economical Synthesis of Unprotected 7-Acylindoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 794−797. (b) Kim, S.; Han, S. H.; Mishra, N. K.; Chun, R.; Jung, Y. H.; Kim, H. S.; Park, J. S.; Kim, I. S. Dual Role of Anthranils as Amination and Transient Directing Group Sources: Synthesis of 2-Acyl Acridines. *Org. Lett.* **2018**, *20*, 4010−4014.
(7) Chaker, A.; Najahi, E.; Chatriant, O.; Valentin, A.; Tene, N.; Treilhou, M.; Chabchoub, F.; Nepveu, F. New 3-substituted-2,1-benzisoxazoles: Synthesis and antimicrobial activities. *Arabian J. Chem.* **2017**, *10*, S2464−S2470.
(8) Massarotti, A.; Theeramunkong, S.; Mesenzani, O.; Caldarelli, A.; Genazzani, A. A.; Tron, G. C. Identification of Novel Antitubulin Agents by Using a Virtual Screening Approach Based on a 7-Point Pharmacophore Model of the Tubulin Colchi-Site. *Chem. Biol. Drug Des.* **2011**, *78*, 913−922.
(9) Parish, C. A.; Smith, S. K.; Calati, K.; Zink, D.; Wilson, K.; Roemer, T.; Jiang, B.; Xu, D.; Bills, G.; Platas, G.; Peláez, F.; Díez, M. T.; Tsou, N.; McKeown, A. E.; Ball, R. G.; Powles, M. A.; Yeung, L.; Liberator, P.; Harris, G. Isolation and Structure Elucidation of Parnafungins, Antifungal Natural Products that Inhibit mRNA Polyadenylation. *J. Am. Chem. Soc.* **2008**, *130*, 7060−7066.
(10) Pierce, A. C.; Jacobs, M.; Stuver-Moody, C. Docking Study Yields Four Novel Inhibitors of the Protooncogene Pim-1 Kinas. *J. Med. Chem.* **2008**, *51*, 1972−1975.
(11) (a) Więcław, M.; Bobin, M.; Kwast, A.; Bujok, R.; Wróbel, Z.; Wojciechowski, K. General synthesis of 2,1-benzisoxazoles (anthranils) from nitroarenes and benzylic C−H acids in aprotic media promoted by combination of strong bases and silylating agents. *Mol. Divers.* **2015**, *19*, 807−816. (b) Rezazadeh, M.; Pordel, M.; Davoodnia, A.; Saberi, S. New fluorescent 3H-imidazo[4,5-*e*][2,1]-benzoxazoles: synthesis, spectroscopic characterization, and antibacterial activity. *Chem. Heterocycl. Compd.* **2015**, *51*, 918−922. (c) Pokhodylo, N. T.; Teslenko, Y. O.; Matiychuk, V. S.; Obushak, M. D. Synthesis of 2,1-Benzisoxazoles by Nucleophilic Substitution of Hydrogen in Nitroarenes Activated by the Azole Ring. *Synthesis* **2009**, *2009*, 2741−2748. (d) Ghaemi, M.; Pordel, M. Isoxazolo[4,3-*e*]indazole as a new heterocyclic system: design, synthesis, spectroscopic characterization, and antibacterial activity. *Chem. Heterocycl. Compd.* **2016**, *52*, 52−57. (e) Beier, P.; Pastýříková, T. Synthesis of SF_5-containing benzisoxazoles, quinolines, and quinazolines by the Davis reaction of nitro-(pentafluorosulfanyl)-benzenesSimple and scalable electrochemical synthesis of 2,1-benzisoxazoles and quinoline N-oxides. *Beilstein J. Org. Chem.* **2013**, *9*, 411−416. (f) Davis, R. B.; Pizzini, L. C. Condensation of Aromatic Nitro Compounds with Acrylacetonitriles.[1,2] II. Some p-Substituted Nitrobenzenes. *J. Org. Chem.* **1960**, *25*, 1884−1888. (g) Bakavoli, M.; Pordel, M.; Rahimizadeh, M.; Jahandari, P.; Seresht, E. R. Sulfuric Acid Mediated Heterocyclization of *ortho*-Cyanomethylnitroarenes to Benzo[*c*]isoxazoles and Fused Benzo[*c*]isoxazoles. *Heterocycles* **2008**, *75*, 165−171.
(12) (a) Arcadi, A.; Chiarini, M.; Vecchio, L. D.; Marinelli, F.; Michelet, V. Silver-versus gold-catalyzed sequential oxidative cyclization of unprotected 2-alkynylanilines with oxone. *Chem. Commun.* **2016**, *52*, 1458−1461. (b) Arcadi, A.; Chiarini, M.; Vecchio, L. D.; Marinelli, F.; Michelet, V. Sequential Silver-Catalyzed Oxidative Cyclization Reactions of Unprotected 2-Alkynylanilines to Anthranils. *Eur. J. Org. Chem.* **2017**, *2017*, 2214−2222. (c) Asao, N.; Sato, K.; Yamamoto, Y. $AuBr_3$-catalyzed cyclization of o-(alkynyl)-nitrobenzenes. Efficient synthesis of isatogens and anthranils. *Tetrahedron Lett.* **2003**, *44*, 5675−5677. (d) Cikotiene, I. Intramolecular Iodine-Mediated Oxygen Transfer from Nitro Groups to C≡C Bonds. *Eur. J. Org. Chem.* **2012**, *2012*, 2766−2773. (e) Zheng, M.; Chen, K.; Zhu, S. One-Pot Synthesis of Indole Derivatives from the Reaction of Nitroalkynes and Alkynes via a Mercury-Carbene Intermediate. *Synthesis* **2017**, *49*, 4173−4182. (f) Li, X.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. Intramolecular Oxygen Transfer from Nitro Groups to C:C Bonds Mediated by Iridium Hydrides. *Organometallics* **2005**, *24*, 3066−3073.
(13) (a) Kim, B. H.; Jin, Y.; Jun, Y. M.; Han, R.; Baik, W.; Lee, B. M. Indium mediated reductive heterocyclization of 2-nitroacylbenzenes or 2-nitroiminobenzenes toward 2,1-benzisoxazoles in aqueous media. *Tetrahedron Lett.* **2000**, *41*, 2137−2140. (b) Marti, L.; Sanchez, L. M.; Climent, M. J.; Corma, A.; Iborra, S.; Romanelli, G. P.; Concepcion, P. Chemoselective Reductive Heterocyclization by Controlling the Binomial Architecture of Metal Particles and Acid−Base Properties of the Support. *ACS Catal.* **2017**, *7*, 8255−8262. (c) Rodrigo, E.; Baunis, H.; Suna, E.; Waldvogel, S. R. Simple and scalable electrochemical synthesis of 2,1-benzisoxazoles and quinoline N-oxides. *Chem. Commun.* **2019**, *55*, 12255−12258. (d) Byeong, H. K.; Young, M. J.; Tae, K. K.; Yoon, S. L.; Woonphil, B.; Byung, M. L. 2-Bromo-2-nitropropane/Zn Promoted Reductive Cyclization of *Ortho*-substituted Nitroarenes Toward 2,1-benzisoxazole Derivatives. *Heterocycles* **1997**, *45*, 235−240. (e) Haggam, R. A.; El-Sayed, H. A. Microwave-promoted syntheses of fluoren-9-ones and benzisoxazoles. *Res. Chem. Intermed.* **2015**, *41*, 8159−8172.
(14) (a) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. Intramolecular Fe(II)-Catalyzed N−O or N−N Bond

https://doi.org/10.1021/acs.joc.1c00091
J. Org. Chem. 2021, 86, 7326−7332

Formation fromAryl Azides. *Org. Lett.* **2010**, *12*, 2884−2887. (b) Odinokov, A. V.; Plekhovich, S. D.; Budruev, A. V. Synthesis of 3-phenylbenzo[*c*]isoxazoles by thermocyclization of 2-azidobenzophenones. *Russ. Chem. Bull.* **2019**, *68*, 1298−1300. (c) Gaywood, A. P.; McNab, H. Methylene Meldrum's Acid Derivatives of Indoxyl and Their Cyclization Reactions under Flash Vacuum Pyrolysis Conditions. *Synthesis* **2010**, *8*, 1361−1364. (d) Wang, Y.; Yu, P.; Ren, Q.; Jia, F.; Chen, Y.; Wu, A. Synthesis of 2,1-Benzoisoxazole-Containing 1,2,3-Triazoles through Copper-Catalyzed Three-Component Domino Reactions of *o*-Bromoacetophenones, Aldehydes, and Sodium Azide. *J. Org. Chem.* **2020**, *85*, 2688−2696. (e) Su, H.; Bao, M.; Pei, C.; Hu, W.; Qiu, L.; Xu, X. Gold-catalyzed dual annulation of azide-tethered alkynes with nitriles: expeditious synthesis of oxazolo[4,5-*c*]quinolones. *Org. Chem. Front.* **2019**, *6*, 2404−2409.

(15) (a) Bullen, J. V.; Ridd, J. H.; Sabek, O. The Cyclisation and Rearrangement of the Nitro Derivatives of Aromatic Hydrocarbons in Trifluoromethanesulphonic Acid(*). *Gazz. Chim. Ital.* **1990**, *120*, 291−296. (b) Duffy, K. J.; Tennant, G. The scope and mechanism of a novel synthesis of 3,4-fused isoxazoles. *J. Chem. Soc., Chem. Commun.* **1995**, 2457−2459. (c) Barrow, P.; Bullen, J. V.; Dent, A.; Murphy, T.; Ridd, J. H.; Sabek, O. The Rearrangement of Aromatic Nitro-compounds in Strongly Acidic Media. *J. Chem. Soc., Chem. Commun.* **1986**, 1649−1650. (d) Sulikowski, D.; Makosza, M. Synthesis of 3-Phenyl-2,1-benzisoxazoles via Conversion of Diethyl α-(*o*-Nitroaryl)benzylphosphonates. *Acta Chim. Slov.* **2009**, *56*, 680−683. (e) Zhu, J. S.; Son, J.; Teuthorn, A. P.; Haddadin, M. J.; Kurth, M. J.; Tantillo, D. J. Diverting Reactive Intermediates Toward Unusual Chemistry: Unexpected Anthranil Products from Davis−Beirut Reaction. *J. Org. Chem.* **2017**, *82*, 10875−10882. (f) Wróbel, Z. Facile Synthesis of 3-Substituted 2,1-Benzisoazoles (Anthranils). *Synthesis* **1997**, *1997*, 753−755.

(16) (a) Chen, P.; Meng, Y.; Yang, Q.; Wu, J.; Xiao, Y.; Gorja, D. R.; Song, C.; Chang, J. Selective synthesis of 2,5-disubstituted furan-3-carboxylates and the isomeric 2,4-disubstituted furan-3-carboxylates. *RSC. Adv.* **2015**, *5*, 79906−79914. (b) Zhu, C.; Zhao, P.; Qiao, Y.; Xiao, K.; Song, C.; Chang, J. Methylenecyclopropane Ring Formation/Opening Cascade for the Synthesis of Indolizines. *J. Org. Chem.* **2017**, *82*, 7045−7049. (c) Zhang, Q.; Song, C.; Huang, H.; Zhang, K.; Chang, J. Cesium carbonate promoted cascade reaction involving DMF as a reactant for the synthesis of dihydropyrrolizino[3,2-b]indol-10-ones. *Org. Chem. Front.* **2018**, *5*, 80−87. (d) Xiao, K.; Zhu, C.; Lin, M.; Song, C.; Chang, J. Base-Promoted Cycloisomerization for the Synthesis of Indolizines and Related Heterocycles. *ChemistrySelect* **2018**, *3*, 11270−11272. (e) Zhang, L.; Xiao, K.; Qiao, Y.; Li, X.; Song, C.; Chang, J. Base-Promoted Cycloisomerization for the Synthesis of Oxazoles and Imidazoles. *Eur. J. Org. Chem.* **2018**, 6913−6918. (f) Xu, H.; Sun, L.; Song, C. Base-Mediated N-Arylation for the Synthesis of 9H-Pyrrolo[1,2-*a*]indol-9-ones and 10H-Indolo[1,2-a]indol-10-ones. *Helv. Chim. Acta* **2019**, *102*, No. e1800195. (g) Wu, Y.; Meng, Y.; Liu, Z.; Zhang, M.; Song, C. $AlCl_3$-promoted three-component cascade reaction for rapid access to [1,2,3]triazolo[5,1-*a*]-isoquinolines. *Tetrahedron Lett.* **2019**, *60*, No. 151287.

https://doi.org/10.1021/acs.joc.1c00091
J. Org. Chem. 2021, 86, 7326−7332