JOC The Journal of Organic Chemistry

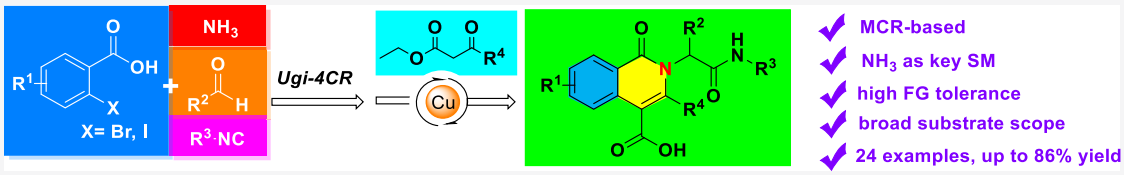
pubs.acs.org/joc Article

Isoquinolone-4-Carboxylic Acids by Ammonia-Ugi-4CR and Copper-Catalyzed Domino Reaction

Qian Wang, Kumchok C. Mgimpatsang, Xin Li, and Alexander Dömling*

Cite This: J. Org. Chem. 2021, 86, 9771−9780 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Highly substituted isoquinolone-4-carboxylic acid is an important bioactive scaffold; however, it is challenging to access it in a general and short way. A Cu-catalyzed cascade reaction was successfully designed involving the Ugi postcyclization strategy by using ammonia and 2-halobenzoic acids as crucial building blocks. Privileged polysubstituted isoquinolin-1(2*H*)-ones were constructed in a combinatorial format with generally moderate to good yields. The protocol, with a ligand-free catalytic system, shows a broad substrate scope and good functional group tolerance toward excellent molecular diversity. Free 4-carboxy-isoquinolone is now for the first time generally accessible by a convergent multicomponent reaction protocol.

INTRODUCTION

Isoquinolin-1(2*H*)-one has attracted considerable attention as a privileged structure presented in numerous natural products of pharmaceutical interest such as ruprechstyril,[1] pancratistatin,[2] and gusanlung D[3] (Figure 1A); it exhibits various biological activities, including antimicrobial,[4] antifungal,[5] analgesic,[6] and antihypertensive[7] activities. They also act as useful NK3 antagonists,[8] 5-HT_3 receptor antagonists,[9] chemoattractant receptor antagonist,[10] and JNK inhibitors.[11] In addition, the isoquinolin-1(2*H*)-one pharmacophore is employed to battle stomach tumors and human brain cell diseases.[12] Interestingly, amide derivatives in the 4 position of this scaffold exhibit promising biological properties.[5,6,13] As an intermediate in organic synthesis, substituted isoquinolin-1(2*H*)-ones are investigated on their further transformation to indenoisoquinolines, protoberberines, and dibenzoquinolizines as building blocks and key intermediates.[14]

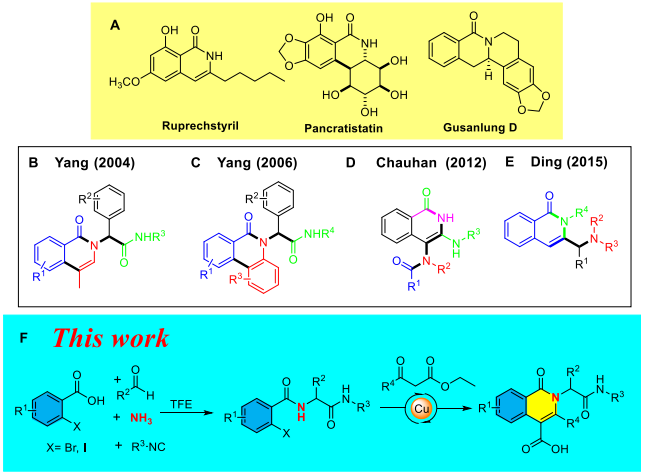


Figure 1. (A) Isoquinolin-1(2*H*)-one alkaloids; (B) Ugi-4CR/Heck sequence; (C) Ugi 4CR/Pd-catalyzed intramolecular arylation; (D) Ugi-4CR/Pd-catalyzed cascade reaction; (E) Ugi-4CR/Wittig sequence; and (F) *Our work:* Ammonia-Ugi 4-CR/Cu-catalyzed domino reaction.

Owning to the critical biological profiles, several procedures have been developed to obtain isoquinolin-1(2*H*)-one derivatives.[15] However, the reported protocols suffer from a reduced precursor scope with only a few points of diversity and from a lengthy, sequential, overall low-yielding multistep synthesis.[16] Based on the Ugi postcyclization strategy as a powerful tool to create structurally diverse heterocycles and large compound numbers in an atom and step economic, green manner,[17] there are several reports on the synthesis of isoquinolone derivatives via the sequence of Ugi-MCR/post-condensation transformation.[18] In 2004, the Yang group reported a synthesis of isoquinolones via the Ugi-4CR/Heck reaction (Figure 1B).[18a] Two years later, another Ugi-4CR and subsequent Pd-catalyzed intramolecular arylation reaction were published by them (Figure 1C).[18b] In 2012, the Chauhan

Received: May 19, 2021
Published: June 29, 2021

© 2021 The Authors. Published by American Chemical Society

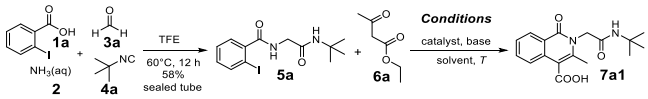
group developed a ligand-free Pd-catalyzed cascade reaction to achieve diverse isoquinolone derivatives based on Ugi reaction (Figure 1D).[16] Furthermore, Ding and co-workers provided a one-pot synthetic approach of isoquinolin-1(2*H*)-ones by a sequential Ugi-4CC/Wittig process (Figure 1E).[18c] However, none of them allow for the preparation of the target structure isoquinolone-4-carboxylic acid.

Based on prior intermolecular C−C coupling work[19] and our experience in constructing diverse heterocyclic scaffolds via MCR chemistry,[20] we envisaged that if Ugi reaction using the *o*-halobenzoic acids and ammonia as the starting materials and Cu-catalyzed C−C coupling/annulation reaction of the corresponding Ugi adducts and *β*-keto esters could be performed sequentially, it should lead to isoquinolin-1(2*H*)-ones alternatively (Figure 1F). We have previously shown a successful application of this strategy for the generation of tetraheterocyclic indenoisoquinolinones.[20d] It is the first report on the efficient synthesis of multisubstituted isoquinolone-4-carboxylic acid from readily accessible starting materials. Derivatization of the carboxyl group at this position is a hot spot in medicinal chemistry.[5,6,13c]

RESULTS AND DISCUSSION

Ullmann-type condensations allow a variety of heterocycles to be constructed practically, representing efficient tools in the formation of C−heteroatom and C−C bonds.[19,21] As the starting point of our work, the model Ugi reaction among *o*-iodobenzoic acid **1a**, paraformaldehyde **3a**, and *tert*-butyl isocyanide **4a** in equimolar quantities and excessive ammonia water (25%) **2** was performed in trifluoroethanol under 60 °C for 12 h, affording the Ugi product **5a** in 58% isolated yield. Thereafter, we investigated a copper-catalyzed tandem reaction involving acetoacetate to explore and optimize the Cu-catalyzed C−C coupling/annulation reaction conditions (Table 1). When the reaction of Ugi adduct **5a** (0.3 mmol) with ethyl acetoacetate **6a** (0.45 mmol) was carried out in dioxane (3.0 mL) at 80 °C for 12 h in a 10 mL round-bottom flask in the presence of $CuSO_4$ (10 mol %) and Cs_2CO_3 (0.6 mmol), it led to the target product **7a1**, albeit in low yield (32%, entry 1). Then, other copper catalysts were also evaluated (entries 2−4). Replacing the catalyst with $CuCl_2$ or CuBr resulted in higher yields of 40 and 72%, respectively (entries 2−3). Gratifyingly, it was found that when CuI was employed, the yield of **7a1** increased to 82% (entry 4). As expected, without addition of a base, no product **7a1** can be detected (entry 5). Cs_2CO_3 was found to be better than K_2CO_3 (entry 4 vs entry 6) and was selected as the model base to further determine the scope and limitation of this methodology. The yield of **7a1** did not improve by increasing the amount of **6a** to 2.0 equiv (entry 7). A variety of solvents were also examined. A diminished yield was obtained (42%) when CH_3CN medium was employed (entry 8), while better yields were obtained when toluene and dimethylformamide were used (entries 9 and 10). For solvent selection, dioxane proved to be optimal in the outcome of this reaction (entry 4 vs entries 8−10). Moreover, only a trace amount of the product was detected without heating, even when the reaction time was extended to 18 h (entry 11). However, increasing the reaction temperature to 120 °C did not improve the yield (entry 12). Microwave irritation was also useful, but it produced isoquinolone-4-carboxylic acid **7a1** in a relatively lower yield (32%, entry 13). Thus, it can be concluded that the optimal conditions for the reaction of Ugi adduct **5a** (1.0 equiv) and ethyl acetoacetate **6a** (1.5 equiv) with Cs_2CO_3 (2.0 equiv) are as follows: in the presence of 10 mol % CuI, in dioxane (0.1 M), and at 80 °C for 12 h (entry 4).

Table 1. Optimization of Reaction Conditions[ab]



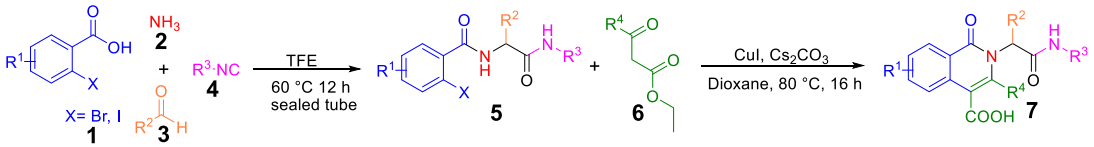
entry	6 (equiv)	catalyst	base	solvent	T (°C)	yield 7a1[c] (%)
1	1.5	$CuSO_4$	Cs_2CO_3	dioxane	80	32
2	1.5	$CuCl_2$	Cs_2CO_3	dioxane	80	40
3	1.5	CuBr	Cs_2CO_3	dioxane	80	72
4	1.5	CuI	Cs_2CO_3	dioxane	80	82
5	1.5	CuI		dioxane	80	N.D.[d]
6	1.5	CuI	K_2CO_3	dioxane	80	53
7	2.0	CuI	Cs_2CO_3	dioxane	80	81
8	1.5	CuI	Cs_2CO_3	MeCN	80	42
9	1.5	CuI	Cs_2CO_3	toluene	80	60
10	1.5	CuI	Cs_2CO_3	DMF	80	75
11[e]	1.5	CuI	Cs_2CO_3	dioxane	r.t.	trace
12	1.5	CuI	Cs_2CO_3	dioxane	120	84
13[f]	1.5	CuI	Cs_2CO_3	dioxane	100	32

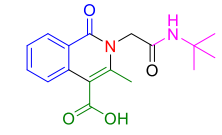
[a]Reaction conditions: **5a** (0.3 mmol), **6a**, catalyst (10 mmol %), base (0.6 mmol), solvent (3 mL), 12 h. [b]TFE = 2,2,2-trifluoroethanol. [c]Isolated yields. [d]N.D. = not detected. [e]Reaction time is 18 h. [f]Under microwave irritation for 1 h.

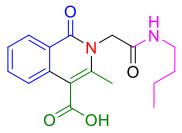
Having established the optimized conditions, we synthesized several Ugi products to evaluate the substrate scope and limitations of the tandem reaction by reacting substituted 2-halogen benzoic acids with different aldehydes, isocyanides, and ammonia solution in TFE, followed by CuI-catalyzed cascade reaction, to give the corresponding isoquinolone-4-carboxylic acid derivatives **7a−t** in fair to very good yields (Scheme 1). Paraformaldehyde was employed in several cases and underwent efficient domino reaction to give the desired products (**7a-c**, **7n**, **7r-s**) in moderate to good yields. With regard to the aliphatic aldehyde **3**, we were pleased to see that a wide variety of substituents R^2 (Scheme 1), including methyl (**7d-e**), isopropyl (**7o**), *n*-propyl (**7f**), 2-methylpropyl (**7g**), cyclopentyl (**7h**), 2-phenylethyl (**7p**), and 2-(methylthio)ethyl (**7q**), irrespective of the sterically hindered effect, could be installed to effectively deliver corresponding products. Subsequently, reactivity of aromatic aldehydes was examined. Aromatic aldehydes bearing an electron-donating *para*-methoxy group (**7l**) resulted in yields of isoquinolone derivatives that are similar to those obtained from aromatic aldehydes bearing an electron-withdrawing *para*-bromo group (**7j**). When benzaldehyde with a strong electron-withdrawing cyano substituent and unsubstituted benzaldehyde was employed, the yield of the desired compounds **7i** and **7k** decreased slightly to 63 and 66%, respectively. Also aldehyde possessing a heteroaromatic ring (**7m**) was an effective substrate for the reaction. For 2-halobenzoic acid substrates, electron-rich methoxy and methyl groups as well as nitro group were tolerated under the reaction conditions, and moderate to good yields were obtained (**7n-s**). It is noteworthy that when cyclopentanone (**7t**) was employed in the cascade reaction, only a trace amount of the desired product was observed by mass spectrometry (MS) analysis (Supporting Information), putatively due to steric hindrance.

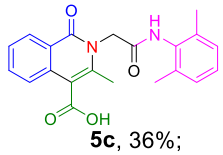
https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780

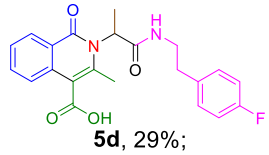
Scheme 1. Copper-Catalyzed Domino Synthesis of Isoquinolone-4-Carboxylic Acid Derivatives[abcde]

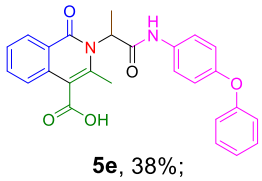


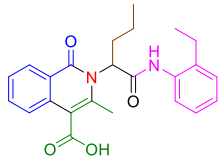

5a, 58%;
7a1, 82%

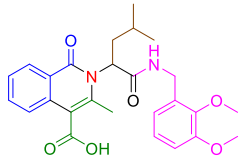

5b, 49%;
7b, 75%

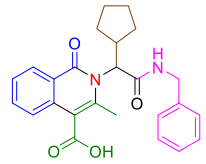

5c, 36%;
7c, 80%

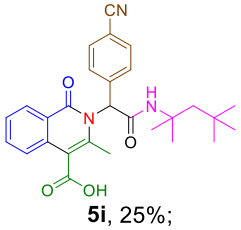

5d, 29%;
7d, 62%

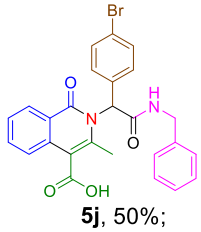

5e, 38%;
7e, 76%

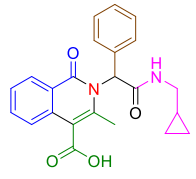

5f, 54%;
7f, 68%

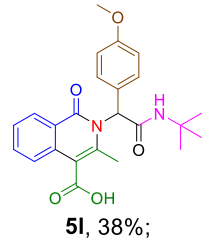

5g, 39%;
7g, 70%

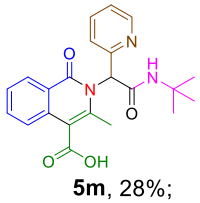

5h, 62%;
7h, 79%

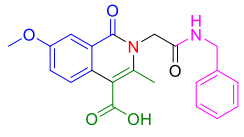

5i, 25%;
7i, 63%

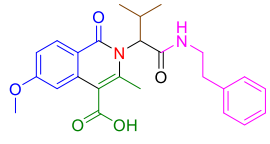

5j, 50%;
7j, 78%

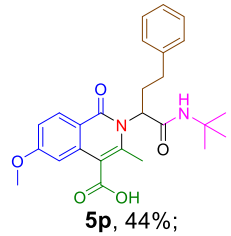

5k, 35%;
7k, 66%

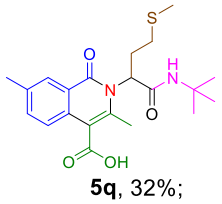

5l, 38%;
7l, 75%

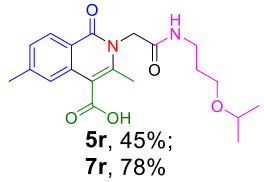

5m, 28%;
7m, 64%

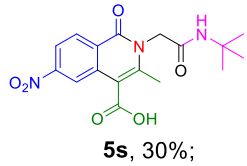

5n, 42%;
7n, 83%

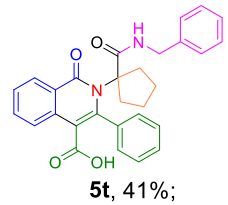

5o, 36%;
7o, 74%

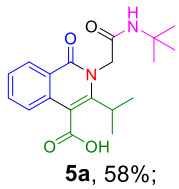

5p, 44%;
7p, 65%

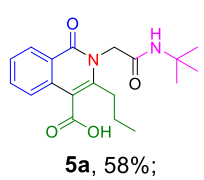

5q, 32%;
7q, 60%

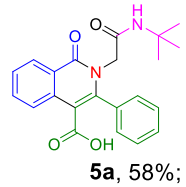

5r, 45%;
7r, 78%

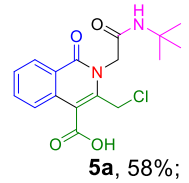

5s, 30%;
7s, 86%


5t, 41%;
7t, trace


5a, 58%;
7a2, 52%


5a, 58%;
7a3, 58%


5a, 58%;
7a4, 40%


5a, 58%;
7a5, N.D.

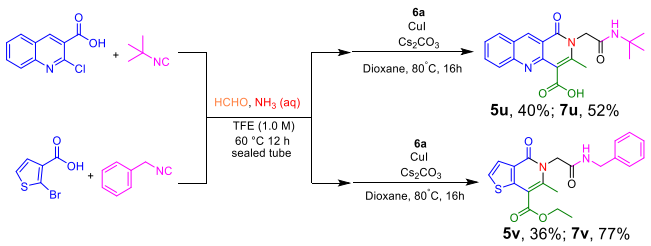
[a]The ammonia, aldehyde, carboxylic acid, isocyanide, and β-keto ester components are depicted with red, brown, blue, pink, and green, respectively. [b]The Ugi reaction was carried out using **1** (2.0 mmol), **2** (2.2 mmol), **3** (2.0 mmol), and **4** (2.0 mmol) in CF_3CH_2OH (1.0 M) for 12 h at 60 °C. [c]Reaction conditions: **5** (0.3 mmol), **6** (0.45 mmol), Cs_2CO_3 (0.6 mmol), CuI (0.03 mmol), dioxane (3 mL), 80 °C, 12 h. [d]Isolated yield. [e]N.D. = not detected.

https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780

Next, we investigated the reactivity of an array of Ugi adducts **5** derived from various isocyanides for the cascade reaction by reacting with ethyl acetoacetate **6a** under the optimal conditions, as shown in Scheme 1. The reactions of Ugi adducts containing benzyl (**7h**, **7j**, and **7n**) and 2,3-dimethoxy benzyl groups (**7g**) with **6a** gave the target products smoothly with 79, 78, 83, and 70% yields, respectively. Additionally, valuable functional groups such as 2,6-dimethyl-, 4-anisole-, and 2-ethyl-substituted isocyanobenzene can be expediently converted to isoquinolone-4-carboxylic acid derivatives (**7c**, **7e**, and **7f**, respectively). Moreover, (2-isocyanoethyl)benzene (**7o**) and 1-fluoro-4-(2-isocyanoethyl)-benzene (**7d**) also furnished the different isoquinolone products in 74 and 62% yields, respectively. Furthermore, substrates bearing alkyl groups on the isocyanide component such as *n*-butyl (**7b**), cyclopropylmethyl (**7k**) *tert*-butyl (**7a**, **7l**, **7m**, **7p**, **7q**, and **7s**), *tert*-octyl (**7i**), and 3-isopropoxypropyl (**7r**) could be well-accommodated. Lastly, the scope of *β*-keto esters was examined. The reactions also proceeded with the *β*-keto esters containing bigger isopropyl, propyl, and phenyl groups, but the yields of the corresponding products **7a2**, **7a3**, and **7a4** were lower, which illustrates that steric hindrance is a key factor. Of particular note is the fact that no reaction occurred when ethyl 4-chloroacetoacetate was subjected to the reaction conditions (**7a5**). The diversity of successful reactions shown in Scheme 1 clearly demonstrates that many functional groups in all four building blocks are compatible with the overall reaction sequence.

To further extend the scope of the product structures, we also performed this protocol with heteroaromatic 2-halo carboxylic acids. As shown in Scheme 2, product **5u** derived

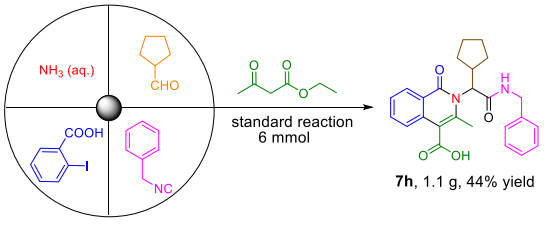
Scheme 2. Heteroaromatic 2-Halocarboxylic Acids in the Ugi-4CR/Copper-Catalyzed Cascade Reaction



from 2-chloro-3-quinolinecarboxylic acid reacted effectively with ethyl acetoacetate **6a** under the present protocol, leading to the corresponding triheterocycle **7u** in 52% yield. By contrast, the thiophene substrate **5v** afforded the uncleaved **7v** in good 77% yield.

Next, the ability to conduct the Ugi-4CR/copper-catalyzed cascade sequence reaction on a gram scale was accessed (Scheme 3, Supporting Information). A Ugi four-component

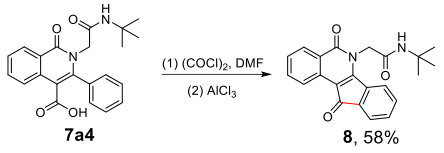
Scheme 3. Gram-Scale Reaction



reaction was conducted by reacting 2-iodobenzoic acid, ammonia, and cyclopentanecarbaldehyde with benzyl isocyanide on a 6 mmol scale. The Ugi product precipitated during the reaction and was filtered without further purification. It was reacted with ethyl acetoacetate, and we were pleased to observe the formation of 1.1 g of isoquinolone **7h** (44% overall yield).

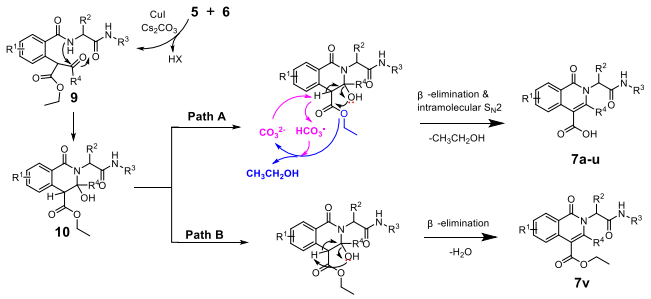
Lastly, we showed a synthetic application of the isoquinolone-4-carboxylic acids described herein. In situ acid chloride formation from **7a4** with oxalyl chloride and Friedel-Crafts cyclization provided indenoisoquinoline **8** in 58% yield (Scheme 4). This represents an efficient procedure to convert **7** into a medicinally relevant tetracyclic scaffold that has been reported as an inhibitor of topoisomerase I.[22]

Scheme 4. Transformation of 7a4



Our hypothesized reaction mechanism for the cascade reaction is proposed as follows (Scheme 5). In the presence of

Scheme 5. Proposed Reaction Mechanism



a Cu(I) catalyst, *ortho*-directed Ullmann-type C−C coupling affords intermediate **9**, which followed by the intramolecular condensation to form **10**. The isoquinolone-4-carboxylic acids **7a-u** could be generated through pathway **A**, and it involves the carbonate ion attacking the proton, which leads to the isoquinolin-1(2*H*)-one scaffold after the hydroxide ion leaves, followed by a final intramolecular S_N2 reaction to the carboxylic acid product **7a-u**, along with the formation of ethanol. In another case, the cascade reaction may also proceed through pathway **B**, through which **10** undergoes dehydration to give the product **7v**.

CONCLUSIONS

In summary, we have developed an unprecedented, highly efficient approach to synthesize structurally very diverse isoquinolone-4-carboylic acids via a sequence of ammonia-Ugi-4CR/Cu-catalyzed domino reaction. The protocol has the advantages of being step economic, affording good yields, absence of ligands, and environmental friendliness, leading to its possible application in combinatorial and medicinal chemistry. Considering the operation easiness and the availability and simplicity of the starting materials of the protocol, we believe that this methodology will provide a promising method to access isoquinolin-1(2*H*)-one derivatives.

https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780

Attempts to apply our recently developed automated nanosynthesis to this two-step sequence are ongoing and will be reported in due course.[23]

EXPERIMENTAL SECTION

General Information. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shifts for ^{1}H NMR were reported relative to TMS (δ 0 ppm) or internal solvent peak ($CDCl_3$ δ 7.26 ppm, CD_3OD δ 3.31 ppm or D_2O δ 4.79 ppm), and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dt = double triplet, ddd = doublet of double doublet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm relative to the solvent peak ($CDCl_3$ δ 77.23 ppm, DMSO δ 39.52 ppm, CD_3OD δ 49.00 ppm). Filtrations were performed on a silica bed (Screening Devices BV, 60−200 μm, 60 Å). Flash chromatography was performed on a Grace Reveleris X2 using Grace Reveleris Silica columns (12 g), and a gradient of petroleum ether/ethyl acetate (0−100%) or dichloromethane/methanol (0−20%) was applied. Thin-layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μm). Reagents were available from commercial suppliers and used without any purification, unless otherwise noted. All isocyanides were homemade by performing the Ugi,[24] Hoffman,[25] or Leukart−Wallach reductive amination procedure.[26] Other reagents were purchased from Sigma Aldrich, ABCR, Acros, Fluorochem, and AK Scientific and were used without further purification. Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 × 250 mm, 5 μm particle size) and reported as (m/z). High-resolution mass spectra (HRMS) were recorded using a LTQ-Orbitrap-XL (Thermo Fisher Scientific; ESI pos. mode) at a resolution of 60,000@m/z400. Melting points were obtained on a melting point apparatus and were uncorrected. Yields given refer to chromatographically purified compounds, unless otherwise stated. Compounds **5a, 5b, 5e, 5f, 5g, 5h, 5l, 5n, 5q, 5s**, and **5u** were all prepared following the reported literature protocols.[20d]

General Experimental Procedure and Characterization. *Procedure A.* A calculated volume of 25% ammonia solution (0.17 mL; 2.2 mmol; 1.1 equiv) was added to a stirred solution or suspension of the carboxylic acid (2 mmol; 1.0 equiv) in 2,2,2-trifluoroethanol (2 mL). The aldehyde (2 mmol; 1.0 equiv) and isocyanide (2 mmol; 1.0 equiv) were then introduced, and stirring was continued at 60 °C in a 4 mL screwed close vial in a heating metal block overnight. Solvent was removed by rotary evaporation, and the crude product was purified by column chromatography to give the desired product **5**.

Procedure B. Ugi adduct 5 (0.3 mmol; 1.0 equiv), β−keto ester 6 (0.45 mmol; 1.5 equiv), Cs_2CO_3 (0.6 mmol; 2.0 equiv), and CuI (0.03 mmol; 0.1 equiv) were added to a 10 mL round-bottom flask equipped with a magnetic stir bar, and 3 mL of dioxane was added. The mixture was heated to 80 °C and reacted in an oil bath for 12 h. After the reaction was completed, solvent was removed by rotary evaporation, and the crude product was purified by column chromatography to give the desired product 7.

*Gram-Scale Reaction Procedure of **7h**.* A 20 mL screwed close vial equipped with a magnetic stir bar was charged with a calculated volume of 25% ammonia solution (6.6 mmol; 1.1 equiv) and 2-iodobenzoic acid (0.51 mL; 6 mmol; 1.0 equiv) in 2,2,2-trifluoroethanol (6 mL). Then, cyclopentanecarbaldehyde (6 mmol; 1.0 equiv) and benzyl isocyanide (6 mmol; 1.0 equiv) were added to the solution, and the reaction was stirred at 60 °C in a sand bath overnight. The reaction mixture was washed with petroleum ether and filtered. The residue (1.78 g) was added to ethyl acetoacetate 6a (6 mmol) and Cs_2CO_3 (8 mmol) in dioxane (25 mL) and heated to 80 °C for 5 min, and then CuI (0.4 mol) was added and reacted in an oil bath for 12 h. The progress of the reaction was monitored by thin-layer chromatography. After the reaction was completed, solvent was removed by rotary evaporation and the crude product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate = 3:2) to afford the product **7h** (1.1 g, 44% two-step yield).

Procedure C. Under an Ar atmosphere, **7a4** (56 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (0.5 mL). At 0 °C, oxalyl chloride (32 ul, 0.3 mmol) and DMF (1 drop) were added, and the mixture was stirred for 2 h at rt. The reaction mixture was diluted with CH_2Cl_2 (0.5 mL), $AlCl_3$ (49 mg, 0.36 mmol) was added, and it was further stirred for 1 h at rt. The mixture was diluted with sat. Rochelle salt (5 mL), the layers were separated, and the organic layer was dried over $MgSO_4$, filtrated, and concentrated in vacuo. The remaining residue was purified by column chromatography (silica gel, petroleum ether: ethyl acetate = 3:2) to afford the product **8** as a red solid (31 mg, 58%).

*N-(2-((2,6-Dimethylphenyl)amino)-2-oxoethyl)-2-iodobenzamide **5c**.* It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5c** (294 mg, 36%) as a yellow solid; mp: 176−177 °C; R_f = 0.39 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.95 (dd, J = 7.9, 1.1 Hz, 1H), 7.54 (dd, J = 7.7, 1.8 Hz, 1H), 7.48 (td, J = 7.6, 1.1 Hz, 1H), 7.21 (td, J = 7.7, 1.8 Hz, 1H), 7.13 (d, J = 2.4 Hz, 3H), 4.26 (s, 2H), 2.29 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, Methanol-d_4) δ 171.6, 168.7, 142.0, 139.6, 139.5, 135.7, 133.7, 130.9, 128.2, 127.7, 127.1, 91.8, 42.6, 17.2, 17.1. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{18}IN_2O_2$, 409.0413; found, 409.0415.

*N-(1-((4-Fluorophenethyl)amino)-1-oxopropan-2-yl)-2-iodobenzamide **5d**.* It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5d** (255 mg, 29%) as a yellow solid; mp: 165−166 °C; R_f = 0.42 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.83−7.77 (m, 1H), 7.42 (t, J = 5.8 Hz, 1H), 7.34−7.28 (m, 2H), 7.19 (d, J = 7.8 Hz, 1H), 7.12−7.04 (m, 3H), 6.91 (t, J = 8.7 Hz, 2H), 4.78 (p, J = 7.0 Hz, 1H), 3.53−3.42 (m, 1H), 3.41−3.33 (m, 1H), 2.75 (td, J = 7.2, 2.3 Hz, 2H), 1.43 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-d) δ 172.1, 169.1, 161.5 (d, J = 244.2 Hz), 141.3, 139.9, 134.5 (d, J = 3.2 Hz), 131.3, 130.2 (d, J = 7.8 Hz), 128.2 (d, J = 14.4 Hz), 115.3, 115.2, 92.6, 49.4, 40.9, 34.7, 18.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{19}FIN_2O_2$, 441.0475; found, 441.0487.

*N-(1-(4-Cyanophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)-2-iodobenzamide **5i**.* It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5i** (259 mg, 25%) as a yellow solid; mp: 162−163 °C; R_f = 0.48 (30% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.92−7.85 (m, 1H), 7.71−7.62 (m, 4H), 7.58 (d, J = 7.0 Hz, 1H), 7.40 (dd, J = 7.0, 1.6 Hz, 2H), 7.15 (ddd, J = 8.0, 6.6, 2.6 Hz, 1H), 6.52 (s, 1H), 5.91 (d, J = 7.0 Hz, 1H), 1.69−1.54 (m, 2H), 1.27 (d, J = 17.2 Hz, 6H), 0.80 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-d) δ 169.0, 166.9, 143.2, 140.9, 140.1, 132.6, 131.6, 128.3, 128.2, 118.5, 112.1, 92.4, 57.5, 56.1, 51.5, 31.4, 31.2, 29.0, 28.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{29}IN_3O_2$, 518.1304; found, 518.1307.

*N-(2-(Benzylamino)-1-(4-bromophenyl)-2-oxoethyl)-2-iodobenzamide **5j**.* It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5j** (547 mg, 50%) as a yellow solid; mp: 172−173 °C; R_f = 0.49 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (dd, J = 8.2, 3.1 Hz, 1H), 8.84 (q, J = 5.8 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.61−7.56 (m, 2H), 7.51 (dd, J = 8.9, 3.0 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.39−7.34 (m, 1H), 7.30 (t, J = 7.4 Hz, 2H), 7.27−7.15 (m, 4H), 5.72 (dd, J = 8.4, 4.4 Hz, 1H), 4.33 (qd, J = 15.3, 5.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 169.6, 169.0, 142.6, 139.4, 138.2, 131.7, 131.5, 131.4, 130.3, 130.2 (d, J = 21.5 Hz), 128.9, 128.8, 128.3, 127.6, 127.3, 121.4, 94.0, 56.7, 42.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{19}BrIN_2O_2$, 548.9675; found, 548.9676.

*N-(2-((Cyclopropylmethyl)amino)-2-oxo-1-phenylethyl)-2-iodobenzamide **5k**.* It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5k** (304 mg, 35%) as a yellow solid; mp: 183−184 °C; R_f = 0.78 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.88 (d, J = 7.9 Hz, 1H), 7.56 (dd, J = 6.9, 1.8 Hz, 2H), 7.43 (dd, J = 7.6, 1.8 Hz, 2H), 7.40−7.32 (m, 4H), 7.12 (td, J = 7.7, 1.8 Hz, 1H), 6.61 (t, J = 5.5 Hz, 1H), 5.87 (d, J = 7.2 Hz, 1H), 3.34−2.69 (m, 2H), 0.86 (tt, J = 7.5, 4.8 Hz, 1H), 0.39 (dd,

https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780

J = 8.2, 1.5 Hz, 2H), 0.19−0.10 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 169.5, 168.7, 141.2, 140.0, 137.8, 131.4, 128.9, 128.5, 128.4, 128.1, 127.5, 92.5, 57.5, 44.7, 10.4, 3.4 (d, J = 3.6 Hz). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}IN_2O_2$, 435.0569; found, 435.0576.

N-(2-(Tert-butylamino)-2-oxo-1-(pyridin-2-yl)ethyl)-2-iodobenzamide ***5m***. It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5m** (245 mg, 28%) as a white solid; mp: 193−194 °C; R_f = 0.26 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, Chloroform-d) δ 8.57 (dt, J = 4.7, 1.5 Hz, 1H), 7.94 (dt, J = 7.9, 1.7 Hz, 1H), 7.86 (d, J = 5.7 Hz, 1H), 7.74 (tt, J = 7.8, 1.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.54 (dd, J = 7.7, 1.7 Hz, 1H), 7.43 (ddt, J = 7.5, 6.2, 1.6 Hz, 1H), 7.28−7.24 (m, 1H), 7.16 (td, J = 7.6, 1.7 Hz, 1H), 7.11 (s, 1H), 5.63 (d, J = 5.6 Hz, 1H), 1.34 (d, J = 1.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 169.0, 167.0, 155.8, 148.8, 141.2, 140.2, 137.2, 131.5, 128.6, 128.2, 123.0, 121.2, 92.6, 58.8, 51.8, 28.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{21}IN_3O_2$, 438.0678; found, 438.0680.

2-Bromo-4-methoxy-N-(3-methyl-1-oxo-1-(phenethylamino)-butan-2-yl)benzamide ***5o***. It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5o** (311 mg, 36%) as a brown solid; mp: 164−165 °C; R_f = 0.46 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, Chloroform-d) δ 7.53 (d, J = 8.6 Hz, 1H), 7.34−7.28 (m, 2H), 7.26−7.18 (m, 3H), 7.13 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 8.6, 2.5 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H), 4.49−4.38 (m, 1H), 3.84 (s, 3H), 3.62 (dt, J = 13.4, 6.7 Hz, 1H), 3.54 (dt, J = 13.4, 6.6 Hz, 1H), 2.85 (t, J = 7.1 Hz, 2H), 2.21 (q, J = 6.7 Hz, 1H), 1.00 (dd, J = 6.8, 1.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 170.7, 167.1, 161.3, 138.7, 131.3, 129.1, 128.8, 128.7, 126.6, 120.2, 118.8, 113.4, 59.3, 55.7, 40.7, 35.7, 31.2, 19.4, 18.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{26}BrN_2O_3$, 433.1127; found, 433.1129.

N-(1-(Tert-butylamino)-1-oxo-4-phenylbutan-2-yl)-2-iodo-4-methoxybenzamide ***5p***. It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5p** (393 mg, 44%) as a yellow solid; mp: 160−161 °C; R_f = 0.45 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, Chloroform-d) δ 7.49 (d, J = 8.6 Hz, 1H), 7.35−7.26 (m, 2H), 7.25−7.19 (m, 3H), 7.13 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.6, 2.5 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.17 (s, 1H), 4.59 (td, J = 7.5, 6.0 Hz, 1H), 3.84 (s, 3H), 2.78 (ddd, J = 13.3, 9.6, 6.2 Hz, 2H), 2.27 (ddt, J = 13.9, 9.8, 6.3 Hz, 1H), 2.09 (dddd, J = 13.6, 9.7, 7.3, 6.1 Hz, 1H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 170.1, 167.0, 161.3, 141.0, 131.0, 129.2, 128.5, 128.4, 126.1, 120.3, 118.7, 113.4, 55.7, 53.9, 51.6, 34.2, 31.8, 28.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}IN_2O_3$, 447.1283; found, 447.1288.

2-Bromo-N-(2-((3-isopropoxypropyl)amino)-2-oxoethyl)-4-methylbenzamide ***5r***. It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5r** (333 mg, 45%) as a yellow solid; mp: 199−200 °C; R_f = 0.36 (100% EtOAc). ^1H NMR (500 MHz, Chloroform-d) δ 7.44 (dd, J = 7.7, 4.0 Hz, 1H), 7.41 (t, J = 1.6 Hz, 1H), 7.19−7.12 (m, 1H), 7.11−7.07 (m, 1H), 6.93 (t, J = 5.5 Hz, 1H), 4.11 (dd, J = 5.0, 2.3 Hz, 2H), 3.58−3.51 (m, 1H), 3.51−3.46 (m, 2H), 3.39 (q, J = 6.2 Hz, 2H), 2.35 (d, J = 2.6 Hz, 3H), 1.77 (ddt, J = 12.4, 8.1, 4.4 Hz, 2H), 1.16−1.10 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 168.1, 167.8, 142.2, 133.9, 133.1, 129.6, 128.3, 119.3, 71.8, 66.7, 43.6, 38.3, 29.3, 22.1, 21.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{24}BrN_2O_3$, 371.0970; found, 371.0989.

N-(1-(Benzylcarbamoyl)cyclopentyl)-2-iodobenzamide ***5t***. It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5t** (367 mg, 41%) as a yellow solid; mp: 175−176 °C; R_f = 0.52 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (d, J = 2.9 Hz, 1H), 8.05 (q, J = 5.2 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 4.5 Hz, 4H), 7.22 (q, J = 4.2 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 4.36 (d, J = 6.0 Hz, 2H), 2.13 (t, J = 6.4 Hz, 4H), 1.83−1.73 (m, 2H), 1.68 (t, J = 5.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 173.7, 169.4, 143.2, 140.5, 139.3, 139.1, 131.1, 129.2, 128.6, 127.3, 126.9, 93.9, 67.4, 42.9, 36.5, 24.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}IN_2O_2$, 449.0726; found, 449.0733.

N-(2-(Benzylamino)-2-oxoethyl)-2-bromothiophene-3-carboxamide ***5v***. It was synthesized according to procedure **A** on a 2 mmol scale, which afforded **5v** (253 mg, 36%) as a white solid; mp: 165−166 °C; R_f = 0.25 (80% EtOAc/petroleum ether). ^1H NMR (500 MHz, Chloroform-d) δ 7.58 (t, J = 4.9 Hz, 1H), 7.33 (dt, J = 6.9, 1.4 Hz, 1H), 7.32−7.27 (m, 5H), 7.23−7.18 (m, 2H), 4.49 (d, J = 5.7 Hz, 2H), 4.23 (d, J = 5.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 168.5, 162.4, 137.8, 134.7, 129.0, 128.7, 127.8, 127.6, 126.3, 113.9, 43.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{14}BrN_2O_2S$, 352.9959; found, 352.9957.

2-(2-(Tert-butylamino)-2-oxoethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7a1***. It was synthesized according to procedure **B** on 0.3 mmol scale, which afforded **7a1** (78 mg, 82%) as a white solid; mp: 257−258 °C; R_f = 0.41 (40% EtOAc/petroleum ether). ^1H NMR (500 MHz, Chloroform-d) δ 8.35 (dd, J = 7.6, 1.4 Hz, 1H), 7.72−7.58 (m, 2H), 7.37 (ddd, J = 8.0, 5.8, 2.4 Hz, 1H), 5.57 (s, 1H), 4.70 (s, 2H), 2.66 (s, 3H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-d) δ 183.0, 170.0, 165.7, 163.1, 134.0, 133.3, 129.6, 125.4, 124.2, 122.5, 100.1, 51.8, 43.4, 28.8, 25.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_4$, 317.1501; found, 317.1502.

2-(2-(Butylamino)-2-Oxoethyl)-3-Methyl-1-Oxo-1,2-Dihydroisoquinoline-4-Carboxylic Acid ***7b***. It was synthesized according to procedure **B** on 0.3 mmol scale, which afforded **7b** (71 mg, 75%) as a white solid; mp: 248−249 °C; R_f = 0.35 (40% EtOAc/dichloromethane). ^1H NMR (500 MHz, DMSO-d_6) δ 9.18 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.75 (t, J = 5.7 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 6.84 (t, J = 7.4 Hz, 1H), 4.54 (s, 2H), 3.04 (q, J = 6.6 Hz, 2H), 2.39 (s, 3H), 1.37 (q, J = 7.2 Hz, 2H), 1.29 (p, J = 7.2 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 194.1, 169.0, 164.4, 140.9, 131.9, 127.4, 127.2, 123.3, 119.2 (d, J = 12.7 Hz), 117.9, 96.9, 42.6, 38.7, 34.3, 31.8, 20.0, 14.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_4$, 317.1501; found, 317.1502.

2-(2-((2,6-Dimethylphenyl)amino)-2-oxoethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7c***. It was synthesized according to procedure **B** on 0.3 mmol scale, which afforded **7c** (87 mg, 80%) as a yellow solid; mp: 260−261 °C; R_f = 0.32 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1H), 9.21 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.04 (s, 3H), 6.85 (t, J = 7.3 Hz, 1H), 4.81 (s, 2H), 2.44 (s, 3H), 2.19 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 194.1, 168.1, 164.5, 140.9, 135.9, 135.8, 131.9, 127.9, 127.4, 127.3, 126.6, 123.4, 119.2, 117.9, 96.9, 42.7, 18.7, 18.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_4$, 365.1501; found, 365.1505.

2-(1-((4-Fluorophenethyl)amino)-1-oxopropan-2-yl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7d***. It was synthesized according to procedure **B** on 0.3 mmol scale, which afforded **7d** (74 mg, 62%) as a yellow solid; mp: 274−275 °C; R_f = 0.38 (70% EtOAc/petroleum ether). ^1H NMR (500 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.91 (s, 1H), 7.21 (s, 4H), 7.01 (s, 2H), 6.84 (s, 1H), 5.53 (s, 1H), 3.26 (s, 1H), 3.12 (s, 1H), 2.64 (s, 2H), 2.40 (s, 3H), 1.56−0.90 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 194.3, 171.7, 164.1, 161.1 (d, J = 241.1 Hz), 140.9, 136.6, 131.9, 130.9 (d, J = 7.8 Hz), 127.4 (d, J = 20.6 Hz), 123.2, 119.2, 118.2, 115.3 (d, J = 20.6 Hz), 97.3, 48.7, 41.1, 34.9, 34.4, 15.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}FN_2O_4$, 397.1564; found, 397.1549.

3-Methyl-1-oxo-2-(1-oxo-1-((4-phenoxyphenyl)amino)propan-2-yl)-1,2-dihydroisoquinoline-4-carboxylic Acid ***7e***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7e** (101 mg, 76%) as a yellow solid; mp: 268−269 °C; R_f = 0.34 (40% EtOAc/petroleum ether). ^1H NMR (500 MHz, Acetone-d_6) δ 9.31 (d, J = 8.6 Hz, 1H), 9.20 (s, 1H), 8.04 (dd, J = 7.9, 1.6 Hz, 1H), 7.68 (dd, J = 8.8, 2.3 Hz, 2H), 7.35 (dd, J = 8.6, 7.3 Hz, 2H), 7.29 (ddd, J = 8.6, 6.6, 1.5 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 7.00−6.93 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 5.89 (q, J = 6.7 Hz, 1H), 2.48 (s, 3H), 1.54 (d, J = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, Acetone-d_6) δ 194.5, 171.3, 164.4, 164.1, 158.1, 152.1, 141.2, 135.9, 131.4, 129.7, 127.3 (d, J = 10.4 Hz), 123.4, 122.7, 121.5 (d, J = 21.2 Hz), 119.2, 118.7, 118.2, 117.9, 97.4, 49.7, 33.5, 14.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_5$, 443.1607; found, 443.1612.

https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780

2-(1-((2-Ethylphenyl)amino)-1-oxopentan-2-yl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7f***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7f** (83 mg, 68%) as a yellow solid; mp: 271−272 °C; R_f = 0.49 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.65 (dq, *J* = 19.0, 10.9, 9.4 Hz, 3H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.24−7.15 (m, 3H), 7.11 (t, *J* = 7.5 Hz, 1H), 5.83 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.66 (s, 3H), 2.56 (q, *J* = 7.6 Hz, 2H), 2.45−2.22 (m, 2H), 1.43−1.31 (m, 2H), 1.16 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 183.5, 170.1, 167.8, 163.7, 135.0, 134.9, 133.9, 133.5, 129.7, 128.6, 126.7, 125.7, 125.4, 124.2, 123.5, 122.6, 100.0, 55.9, 30.4, 25.2, 24.4, 19.8, 14.0, 13.8. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_4$, 407.1971; found, 407.1969.

2-(1-((2,3-Dimethoxybenzyl)amino)-4-methyl-1-oxopentan-2-yl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7g***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7 g** (98 mg, 70%) as a yellow solid; mp: 242−243 °C; R_f = 0.34 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.73−7.57 (m, 2H), 7.37 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H), 7.02 (t, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.25 (t, *J* = 5.7 Hz, 1H), 5.72 (dd, *J* = 9.8, 5.0 Hz, 1H), 4.65−4.38 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.64 (s, 3H), 2.24 (ddd, *J* = 14.2, 9.8, 4.6 Hz, 1H), 2.01 (ddd, *J* = 14.0, 9.2, 5.1 Hz, 1H), 1.44 (q, *J* = 4.8 Hz, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 183.1, 170.1, 169.5, 163.3, 152.5, 147.1, 133.9, 133.3, 131.7, 129.7, 125.5, 124.2, 124.2, 122.7, 121.4, 111.8, 100.1, 60.7, 55.7, 53.5, 39.2, 37.4, 25.5, 25.2, 23.3, 22.1. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{26}H_{31}N_2O_6$, 467.2182; found, 467.2185.

2-(2-(Benzylamino)-1-cyclopentyl-2-oxoethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7h***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7 h** (99 mg, 79%) as red oil; R_f = 0.36 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.76−7.57 (m, 2H), 7.41−7.35 (m, 1H), 7.34−7.30 (m, 2H), 7.30−7.23 (m, 3H), 6.31 (s, 1H), 5.46 (d, *J* = 10.5 Hz, 1H), 4.58 (dd, *J* = 14.9, 6.1 Hz, 1H), 4.42 (dd, *J* = 15.0, 5.3 Hz, 1H), 3.26−3.03 (m, 1H), 2.65 (s, 3H), 2.18 (dq, *J* = 13.8, 7.3 Hz, 1H), 1.72 (ddd, *J* = 7.9, 5.3, 2.8 Hz, 2H), 1.61 (dq, *J* = 12.3, 4.3, 3.0 Hz, 1H), 1.54−1.41 (m, 3H), 1.22−1.03 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 183.3, 170.1, 169.4, 163.7, 138.3, 133.9, 133.4, 129.7, 128.6, 127.6, 127.4, 125.5, 124.2, 122.6, 99.9, 60.3, 43.6, 38.3, 32.1, 30.2, 25.7, 25.2, 24.7. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{27}N_2O_4$, 419.1971; found, 419.1974.

2-(1-(4-Cyanophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)-amino)ethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7i***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7i** (89 mg, 63%) as a yellow solid; mp: 263−264 °C; R_f = 0.44 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.72−7.66 (m, 2H), 7.65 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.42−7.34 (m, 1H), 6.58 (s, 1H), 5.44 (s, 1H), 2.64 (s, 3H), 1.69 (d, *J* = 15.0 Hz, 1H), 1.56 (d, *J* = 15.0 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 0.90 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 183.1, 169.9, 165.0, 163.2, 140.4, 133.8, 133.6, 132.6, 131.0, 129.7, 125.7, 124.3, 122.7, 118.3, 112.7, 100.4, 59.6, 56.2, 53.0, 31.5, 31.4, 28.4 (d, *J* = 9.1 Hz), 25.1. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{28}H_{32}N_3O_4$, 474.2393; found, 474.2397.

2-(2-(Benzylamino)-1-(4-bromophenyl)-2-oxoethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7j***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7j** (118 mg, 78%) as a yellow solid; mp: 255−256 °C; R_f = 0.46 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.42−8.25 (m, 1H), 7.73−7.56 (m, 4H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.42−7.24 (m, 6H), 6.65 (s, 1H), 6.01 (q, *J* = 5.4, 4.9 Hz, 1H), 4.59 (dd, *J* = 15.1, 6.0 Hz, 1H), 4.49 (dd, *J* = 15.1, 5.6 Hz, 1H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 182.9, 169.9, 167.1, 163.2, 138.0, 133.9, 133.8, 133.5, 132.3, 132.2, 129.7, 128.7, 127.7, 127.5, 125.6, 124.2, 123.4, 122.8, 100.5, 58.7, 44.0, 25.1. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{26}H_{22}BrN_2O_4$, 505.0763; found, 505.0763.

2-(2-((Cyclopropylmethyl)amino)-2-oxo-1-phenylethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7k***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7k** (77 mg, 66%) as a white solid; mp: 241−242 °C; R_f = 0.26 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (dd, *J* = 8.7, 1.2 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.41−7.37 (m, 2H), 7.32−7.24 (m, 4H), 7.22−7.16 (m, 1H), 6.84 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 6.67 (s, 1H), 3.07−2.86 (m, 2H), 2.39 (s, 3H), 0.99−0.78 (m, 1H), 0.33 (dtd, *J* = 8.2, 3.4, 2.0 Hz, 2H), 0.14 (dd, *J* = 4.9, 3.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 194.5, 169.6, 164.4, 164.3, 140.9, 138.5, 132.2, 129.8, 128.0, 127.6 (d, *J* = 23.3 Hz), 127.1, 123.2, 119.4 (d, *J* = 15.5 Hz), 118.0, 97.2, 79.8 (d, *J* = 11.0 Hz), 57.4 (d, *J* = 17.4 Hz), 43.5, 34.3 (d, *J* = 5.0 Hz), 11.4 (d, *J* = 9.2 Hz), 3.55. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{23}H_{23}N_2O_4$, 391.1658; found, 391.1660.

2-(2-(Tert-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7l***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7l** (95 mg, 75%) as a yellow solid; mp: 268−270 °C; R_f = 0.35 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.63−7.56 (m, 2H), 7.35 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.52 (s, 1H), 5.56 (s, 1H), 3.83 (s, 3H), 2.62 (s, 3H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 182.4, 170.1, 166.9, 163.2, 159.9, 133.9, 133.1, 131.9, 129.7, 127.4, 125.4, 124.1, 123.1, 114.4, 100.5, 59.4, 55.3, 51.7, 28.6, 25.0. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_5$, 423.1920; found, 423.1920.

2-(2-(Tert-butylamino)-2-oxo-1-(pyridin-2-yl)ethyl)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7m***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7m** (76 mg, 64%) as a yellow solid; mp: 248−249 °C; R_f = 0.22 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.71 (s, 1H), 8.61 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.37 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.76−7.55 (m, 3H), 7.39 (ddd, *J* = 8.1, 5.4, 2.9 Hz, 1H), 7.27−7.24 (m, 1H), 7.10 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.75 (s, 1H), 2.67 (s, 3H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 182.9, 170.2, 164.6, 163.3, 156.0, 147.6, 137.5, 134.1, 133.4, 129.9, 125.5, 124.2, 122.8, 122.2, 120.9, 100.4, 57.3, 51.3, 28.7, 25.2. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{22}H_{24}N_3O_4$, 394.1767; found, 394.1763.

2-(2-(Benzylamino)-2-oxoethyl)-7-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7n***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7n** (95 mg, 83%) as a yellow solid; mp: 250−251 °C; R_f = 0.42 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (d, *J* = 9.3 Hz, 1H), 8.29 (s, 1H), 7.42 (d, *J* = 3.1 Hz, 1H), 7.31 (d, *J* = 6.2 Hz, 4H), 7.23 (td, *J* = 6.0, 2.7 Hz, 1H), 6.97 (dd, *J* = 9.3, 3.1 Hz, 1H), 4.64 (s, 2H), 4.28 (d, *J* = 6.0 Hz, 2H), 3.74 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 193.4, 169.5, 164.1, 164.0, 152.9, 140.2, 135.3, 128.6, 127.6, 127.0, 125.5, 121.3, 118.5, 108.2, 96.4, 42.9, 42.4, 40.7, 34.3. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_5$, 381.1450; found, 381.1454.

6-Methoxy-3-methyl-2-(3-methyl-1-oxo-1-(phenethylamino)-butan-2-yl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7o***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7o** (97 mg, 74%) as a brown solid; mp: 275−276 °C; R_f = 0.36 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.8 Hz, 1H), 7.11 (tdd, *J* = 9.5, 6.3, 3.5 Hz, 5H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.23 (s, 1H), 5.15 (d, *J* = 10.3 Hz, 1H), 3.95 (s, 3H), 3.64 (dq, *J* = 13.2, 6.6 Hz, 1H), 3.49−3.37 (m, 1H), 2.93 (dp, *J* = 10.3, 6.6 Hz, 1H), 2.88−2.73 (m, 2H), 2.67 (s, 3H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 183.7, 170.4, 169.0, 163.7, 163.4, 138.9, 135.8, 132.1, 128.7, 128.4, 126.2, 115.9, 111.6, 109.3, 99.8, 55.6, 40.6, 35.5, 26.4, 25.4, 21.5, 19.1. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{29}N_2O_5$, 437.2076; found, 437.2085.

2-(1-(Tert-butylamino)-1-oxo-4-phenylbutan-2-yl)-6-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7p***. It was

https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780

synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7p** (88 mg, 65%) as a yellow solid; mp: 244−245 °C; R_f = 0.34 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.8 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.14−7.06 (m, 3H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.3 Hz, 1H), 5.66−5.57 (m, 1H), 5.46 (s, 1H), 3.93 (s, 3H), 2.79−2.69 (m, 1H), 2.63 (s, 3H), 2.62−2.57 (m, 1H), 2.56−2.47 (m, 2H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 183.3, 170.3, 168.4, 163.5, 163.0, 140.9, 135.8, 132.0, 128.3 (d, *J* = 2.3 Hz), 125.9, 116.0, 111.5, 109.4, 100.1, 55.6, 55.3, 51.5, 32.8, 29.6, 28.7, 25.3. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{26}H_{31}N_2O_5$, 451.2233; found, 451.2238.

2-(1-(Tert-butylamino)-4-(methylthio)-1-oxobutan-2-yl)-3,7-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7q***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7q** (73 mg, 60%) as a yellow solid; mp: 269−270 °C; R_f = 0.39 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.66 (dd, *J* = 8.8, 5.2 Hz, 1H), 5.45 (s, 1H), 2.64 (s, 3H), 2.60−2.55 (m, 1H), 2.55−2.50 (m, 1H), 2.46−2.43 (m, 3H), 2.44−2.41 (m, 1H), 2.39−2.37 (dt, *J* = 8.7, 4.4 Hz, 1H), 2.08 (s, 3H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 182.6, 170.0, 168.0, 163.5, 135.6, 134.6, 131.2, 129.6, 124.2, 122.5, 100.0, 54.5, 51.6, 31.3, 28.7, 28.0, 25.1, 20.8, 15.5. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{29}N_2O_4S$, 405.1848; found, 405.1850.

2-(2-((3-Isopropoxypropyl)amino)-2-oxoethyl)-3,6-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7r***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7r** (88 mg, 78%) as a white solid; mp: 239−240 °C; R_f = 0.55 (10% MeOH/ dichloromethane). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.17 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 6.69 (dd, *J* = 8.1, 1.7 Hz, 1H), 4.69 (s, 2H), 3.48 (p, *J* = 6.1 Hz, 1H), 3.40 (t, *J* = 6.1 Hz, 2H), 3.25 (q, *J* = 6.2 Hz, 2H), 2.51 (s, 3H), 2.31 (s, 3H), 1.67 (t, *J* = 6.4 Hz, 2H), 1.05 (d, *J* = 6.0 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, Acetone-d_6) δ 194.6, 170.2, 164.6, 141.1 (d, *J* = 2.1 Hz), 127.3, 127.2, 123.3, 120.4, 120.3, 115.8, 97.0, 71.0 (d, *J* = 6.9 Hz), 65.4, 43.5, 36.5, 36.3, 33.5, 29.9, 21.6. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{27}N_2O_5$, 375.1920; found, 375.1908.

2-(2-(Tert-butylamino)-2-oxoethyl)-3-methyl-6-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7s***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7s** (93 mg, 86%) as a yellow solid; mp: 271−272 °C; R_f = 0.25 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Methanol-d_4) δ 10.12 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.73 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.75 (s, 2H), 2.62 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Methanol-d_4) δ 197.7, 168.7, 165.1, 164.3, 160.0, 150.8, 140.4, 128.4, 121.3, 113.2, 98.1, 50.7, 42.9, 31.9, 27.7. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{20}N_3O_6$, 362.1352; found, 362.1354.

2-(2-(Tert-butylamino)-2-oxoethyl)-3-isopropyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic Acid ***7a2***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7a2** (54 mg, 52%) as a yellow solid; mp: 245−246 °C; R_f = 0.52 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.59 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 4.78 (s, 2H), 4.13 (s, 1H), 1.38 (s, 9H), 1.17 (d, *J* = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, Methanol-d_4) δ 207.6, 169.1, 165.4, 163.4, 140.2, 132.2, 127.0, 122.9, 120.0, 117.6, 97.8, 50.6, 43.1, 27.8 (d, *J* = 15.1 Hz), 19.5, 19.0. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_4$, 345.1814; found, 345.1811.

2-(2-(Tert-butylamino)-2-oxoethyl)-1-oxo-3-propyl-1,2-dihydroisoquinoline-4-carboxylic Acid ***7a3***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7a3** (60 mg, 58%) as a white solid; mp: 231−232 °C; R_f = 0.55 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.64 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 5.60 (s, 1H), 4.70 (s, 2H), 2.93−2.84 (m, 2H), 1.98−1.85 (m, 2H), 1.38 (s, 9H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 186.4, 170.1, 165.7, 163.1, 133.9, 133.3, 129.5, 125.4, 124.2, 122.6, 99.7, 51.8, 43.5, 38.6, 28.8, 19.6, 14.1. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_4$, 345.1814; found, 345.1816.

2-(2-(Tert-butylamino)-2-oxoethyl)-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylic Acid ***7a4***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7a4** (45 mg, 40%) as a yellow solid; mp: 261−262 °C; R_f = 0.42 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.57 (dtd, *J* = 7.0, 4.0, 3.4, 1.4 Hz, 3H), 7.51−7.45 (m, 2H), 7.23 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.16 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 6.85 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.61 (s, 1H), 4.75 (s, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.4, 170.4, 165.7, 163.2, 136.0, 133.5, 132.1, 131.5, 129.1, 128.9, 128.7, 125.7, 125.6, 122.7, 99.2, 51.9, 43.5, 28.9. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_4$, 379.1658; found, 379.1660.

2-(2-(Tert-butylamino)-2-oxoethyl)-3-methyl-1-oxo-1,2-dihydrobenzo[b][1,6]naphthyridine-4-carboxylic Acid ***7u***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7u** (57 mg, 52%) as a yellow solid; mp: 248−249 °C; R_f = 0.49 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 7.97−7.93 (m, 1H), 7.88 (ddd, *J* = 8.5, 7.1, 1.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 5.58 (s, 1H), 4.71 (s, 2H), 2.79 (s, 3H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 200.9, 166.3, 163.6, 161.1, 150.0, 143.5, 138.1, 135.2, 130.2, 126.0, 122.5, 118.7, 117.3, 95.6, 51.7, 43.4, 32.1, 28.9. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_4$, 368.1610; found, 368.1612.

Ethyl 5-(2-(benzylamino)-2-oxoethyl)-6-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-7-carboxylate ***7v***. It was synthesized according to procedure **B** on a 0.3 mmol scale, which afforded **7v** (89 mg, 77%) as a yellow solid; mp: 267−268 °C; R_f = 0.38 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 5.5 Hz, 1H), 7.32 (d, *J* = 5.5 Hz, 1H), 7.28−7.19 (m, 6H), 4.91 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.41 (d, *J* = 5.8 Hz, 2H), 2.89 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 167.2, 165.5, 159.5, 148.0, 147.3, 137.8, 128.6, 127.7, 127.5, 127.4, 126.8, 124.3, 107.7, 61.8, 48.3, 43.6, 18.6, 14.3. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_4S$, 385.1222; found, 385.1229.

N-(Tert-butyl)-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide ***8***. It was synthesized according to procedure **C** on a 0.15 mmol scale, which afforded **8** (31 mg, 58%) as a red solid; mp: 255−257 °C; R_f = 0.54 (60% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 8.1 Hz, 1H), 8.35 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.79−7.74 (m, 1H), 7.61 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.52−7.44 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 6.45 (s, 1H), 5.07 (s, 2H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 190.6, 166.1, 164.2, 155.8, 137.1, 134.5, 134.4, 133.6, 132.5, 131.1, 128.6, 127.4, 123.7, 123.3, 123.2, 123.1, 109.2, 52.0, 49.6, 28.6. HRMS (ESI) *m/z*: [M + H]$^+$calcd for $C_{22}H_{21}N_2O_3$, 361.1552; found, 361.1549.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01170.

^{1}H and ^{13}C{^{1}H} NMR spectra for compounds **5**, **7**, and **8** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Alexander Dömling − *Department of Drug Design, University of Groningen, Groningen 9713 AV, The Netherlands;* orcid.org/0000-0002-9923-8873; Email: a.s.s.domling@rug.nl

Authors

Qian Wang − *Department of Drug Design, University of Groningen, Groningen 9713 AV, The Netherlands*

Kumchok C. Mgimpatsang − *Department of Drug Design, University of Groningen, Groningen 9713 AV, The Netherlands*

Xin Li − *Department of Drug Design, University of Groningen, Groningen 9713 AV, The Netherlands*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01170

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.D. was supported by the National Institute of Health (NIH) (2R01GM097082-05), the European Lead Factory (IMI) under grant agreement number 115489, and the Qatar National Research Foundation (NPRP6-065-3-012). Moreover, funding was received through ITN "Accelerated Early stage drug dIScovery" (AEGIS, grant agreement No 675555) and COFUND ALERT (grant agreement No 665250), Hartstichting (ESCAPE-HF, 2018B012), and KWF Kankerbestrijding grant (grant agreement No 10504). The authors thank Walid Maho (University of Groningen) and Marcel de Vries (University of Groningen) for their help with HRMS analysis. Q.W. and X.L. acknowledge the China Scholarship Council for supporting.

■ REFERENCES

(1) Pettit, G. R.; Meng, Y. H.; Herald, D. L.; Graham, K. A. N.; Pettit, R. K.; Doubek, D. L. Isolation and Structure of Ruprechstyril from *Ruprechtia tangarana*[†,1]. *J. Nat. Prod.* **2003**, *66*, 1065−1069.

(2) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. Total Synthesis of (+)-Narciclasine and (+)-Pancratistatin. *J. Am. Chem. Soc.* **2000**, *122*, 6624−6628.

(3) Chrzanowska, M.; Dreas, A.; Rozwadowska, M. D. Asymmetric Synthesis of (R)-(+)-and (S)-(−)-2,3-Methylenedioxy-8-Xoberbine (Gusanlung D). *Tetrahedron: Asymmetry* **2004**, *15*, 1113−1120.

(4) Capilla, A. S.; Romero, M.; Pujol, M. D.; Caignard, D. H.; Renard, P. Synthesis of Isoquinolines and Tetrahydroisoquinolines as Potential Antitumour Agents. *Tetrahedron* **2001**, *57*, 8297−8303.

(5) Mood, A. D.; Premachandra, I. D. U. A.; Hiew, S.; Wang, F.; Scott, K. A.; Oldenhuis, N. J.; Liu, H. Potent Antifungal Synergy of Phthalazinone and Isoquinolones with Azoles Against *Candida albicans*. *ACS Med. Chem. Lett.* **2017**, *8*, 168−173.

(6) Kawamoto, Y.; Seo, R.; Murai, N.; Hiyama, H.; Oka, H. Identification of Potent Lysophosphatidic Acid Receptor 5 (LPA5) Antagonists as Potential Analgesic Agents. *Bioorg. Med. Chem.* **2018**, *26*, 257−265.

(7) (a) Pettit, G. R.; Melody, N. Antineoplastic Agents. 527. Synthesis of 7-Deoxynarcistatin, 7-Deoxy-Trans-Dihydronarcistatin, and Trans-Dihydronarcistatin 1. *J. Nat. Prod.* **2005**, *68*, 207−211. (b) Pettit, G. R.; Eastham, S. A.; Melody, N.; Orr, B.; Herald, D. L.; McGregor, J.; Knight, J. C.; Doubek, D. L.; Pettit, G. R.; Garner, L. C.; Bell, J. A. Isolation and Structural Modification of 7-Deoxynarciclasine and 7-Deoxy-Trans-Dihydronarciclasine, 1. *J. Nat. Prod.* **2006**, *69*, 7−13. (c) Pettit, G. R.; Ducki, S.; Eastham, S. A.; Melody, N. Antineoplastic Agents. 454. Synthesis of the Strong Cancer Cell Growth Inhibitors Trans-Dihydronarciclasine and 7-Deoxy-Trans-Dihydronarciclasine. *J. Nat. Prod.* **2009**, *72*, 1279−1282.

(8) Simonsen, K.B.; Kehler, J.; Juhl, K.; Khanzhin, N.; Nielsen, S.M. Patent WO2008131779A1.

(9) Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C. H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. 2-(Quinuclidin-3-yl)pyrido[4,3-*b*]indol-1-ones and Isoquinolin-1-ones. Potent Conformationally Restricted 5-HT3 Receptor Antagonists. *J. Med. Chem.* **1993**, *36*, 2645−2657.

(10) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. Discovery of Isoquinolinone Indole Acetic Acids as Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* **2014**, *57*, 1299−1322.

(11) Asano, Y.; Kitamura, S.; Ohra, T.; Itoh, F.; Kajino, M.; Tamura, T.; Kaneko, M.; Ikeda, S.; Igata, H.; Kawamoto, T.; Sogabe, S.; Matsumoto, S.; Tanaka, T.; Yamaguchi, M.; Kimura, H.; Fukumoto, S. Discovery, Synthesis and Biological Evaluation of Isoquinolones as Novel and Highly Selective JNK Inhibitors (2). *Bioorg. Med. Chem.* **2008**, *16*, 4699−4714.

(12) Glushkov, V. A.; Shklyaev, Y. V. Synthesis of 1(2*H*)-Isoquinolones. *Chem. Heterocycl. Compd.* **2001**, *37*, 663−687.

(13) (a) Furber, M.; Alcaraz, L.; Luckhurst, C.; Bahl, A.; Beaton, H.; Bowers, K.; Collington, J.; Denton, R.; Donald, D.; Kinchin, E.; MacDonald, C. Discovery and Evolution of Phenoxypiperidine Hydroxyamide Dual CCR3/H1 Antagonists. Part II: Optimising in Vivo Clearance. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7707−7710. (b) Song, L. I.; Zhang, H. J.; Deng, A. J.; Li, J.; Li, X.; Li, Z. H.; Zhang, Z. H.; Wu, L. Q.; Wang, S. Q.; Qin, H. L. Syntheses and Structure-Activity Relationships on Antibacterial and Antiulcerative Colitis Properties of Quaternary 13-Substituted Palmatines and 8-Oxo-13-Substituted Dihydropalmatines. *Bioorg. Med. Chem.* **2018**, *26*, 2586−2598. (c) Francis, S.; Croft, D.; Schüttelkopf, A. W.; Parry, C.; Pugliese, A.; Cameron, K.; Claydon, S.; Drysdale, M.; Gardner, C.; Gohlke, A.; Goodwin, G. Structure-Based Design, Synthesis and Biological Evaluation of a Novel Series of Isoquinolone and Pyrazolo[4,3-*c*]pyridine Inhibitors of Fascin 1 as Potential Antimetastatic Agents. *Bioorg. Med. Chem.* **2019**, *29*, 1023−1029.

(14) Coelho, F.; Veronese, D.; Lopes, E. C.; Rossi, R. C. An Approach to Substituted Dihydroisoquinolin-1(2*H*)-ones from Baylis−Hillman Adducts. *Tetrahedron Lett.* **2003**, *44*, 5731−5735.

(15) (a) RaoáBatchu, V.; KumaráBarange, D.; AmarenderáReddy, E. Tandem C−C Coupling−Intramolecular Acetylenic Schmidt Reaction Under Pd/C−Cu Catalysis. *Chem. Commun.* **2007**, *43*, 1966−1968. (b) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. A Simple and Efficient Approach to Quinazolinones Under Mild Copper-Catalyzed Conditions. *Angew. Chem. Int. Ed.* **2009**, *48*, 348−351. (c) Guimond, N.; Gouliaras, C.; Fagnou, K. Rhodium (III)-Catalyzed Isoquinolone Synthesis: the N−O Bond as a Handle for C−N Bond Formation and Catalyst Turnover. *J. Am. Chem. Soc.* **2010**, *132*, 6908−6909. (d) Liu, C. C.; Parthasarathy, K.; Cheng, C. H. Synthesis of Highly Substituted Isoquinolone Derivatives by Nickel-Catalyzed Annulation of 2-Halobenzamides with Alkynes. *Org. Lett.* **2010**, *12*, 3518−3521. (e) Guimond, N.; Gorelsky, S. I.; Fagnou, K. Rhodium (III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies. *J. Am. Chem. Soc.* **2011**, *133*, 6449−6457.

(16) Tyagi, V.; Khan, S.; Giri, A.; Gauniyal, H. M.; Sridhar, B.; Chauhan, P. M. A Ligand-Free Pd-Catalyzed Cascade Reaction: An Access to the Highly Diverse Isoquinolin-1(2*H*)-one Derivatives via Isocyanide and Ugi-MCR Synthesized Amide Precursors. *Org. Lett.* **2012**, *14*, 3126−3129.

(17) Wang, Y.; Patil, P.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Dömling, A. Diverse Isoquinoline Scaffolds by Ugi/Pomeranz−Fritsch and Ugi/Schlittler−Müller Reactions. *Org. Lett.* **2019**, *21*, 3533−3537.

(18) (a) Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. Concise Synthesis of Isoquinoline via the Ugi and Heck reactions. *Org. Lett.* **2004**, *6*, 3155−3158. (b) Ma, Z.; Xiang, Z.; Luo, T.; Lu, K.; Xu, Z.; Chen, J.; Yang, Z. Synthesis of Functionalized Quinolines via Ugi and Pd-Catalyzed Intramolecular Arylation Reactions. *J. Comb. Chem.* **2006**, *8*, 696−704. (c) Duan, Z.; Gao, Y.; Yuan, D.; Ding, M. W. One-Pot Synthesis of Isoquinolin-1(2*H*)-ones by a Sequential Ugi 4CC/Wittig Process. *Synlett* **2015**, *26*, 2598−2600.

(19) (a) Xu, G. D.; Huang, Z. Z. A Cascade Dehydrogenative Cross-Coupling/Annulation Reaction of Benzamides with β-Keto Esters for the Synthesis of Isoquinolinone Derivatives. *Org. Lett.* **2017**, *19*, 6265−6267. (b) Jiang, M.; Li, J.; Wang, F.; Zhao, Y.; Zhao, F.; Dong, X.; Zhao, W. A Facile Copper-Catalyzed One-pot Domino Synthesis of 5,12-Dihydroindolo[2,1-*b*]quinazolines. *Org. Lett.* **2012**, *14*, 1420−1423. (c) Kavala, V.; Wang, C. C.; Barange, D. K.; Kuo, C. W.; Lei, P. M.; Yao, C. F. Synthesis of Isocoumarin Derivatives via the Copper-Catalyzed Tandem Sequential Cyclization of 2-Halo-*N*-phenyl Benzamides and Acyclic 1,3-Diketones. *J. Org. Chem.* **2012**, *77*, 5022−5029.

(20) (a) Rudrakshula, M.; Wang, Q.; Dömling, A. With Unprotected Amino Acids to Tetrazolo Peptidomimetics. *Chem. Commun.* **2017**, *53*, 8549−8552. (b) Wang, Q.; Osipyan, A.; Konstantinidou, M.; Butera, R.; Mgimpatsang, K. C.; Shishkina, S. V.; Dömling, A. Pd-Catalyzed de Novo Assembly of Diversely Substituted Indole-Fused Polyheterocycles. *J. Org. Chem.* **2019**, *84*, 12148−12156. (c) Wang, Q.; Mgimpatsang, K. C.; Konstantinidou, M.; Shishkina, S. V.; Dömling, A. 1,3,4-Oxadiazoles by Ugi-Tetrazole and Huisgen Reaction. *Org. Lett.* **2019**, *21*, 7320−7323. (d) Wang, Q.; Tuinhof, J.; Mgimpatsang, K. C.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Dömling, A. Copper-Catalyzed Modular Assembly of Polyheterocycles. *J. Org. Chem.* **2020**, *85*, 9915−9927.

(21) (a) Wang, Z. L.; Zhao, L.; Wang, M. X. Caryl−Calkyl Bond Formation from $Cu(ClO_4)_2$-Mediated Oxidative Cross Coupling Reaction Between Arenes and Alkyllithium Reagents Through Structurally Well-Defined Ar−Cu(III) Intermediates. *Chem. Commun.* **2012**, *48*, 9418−9420. (b) Yang, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. A Simple Copper-Catalyzed Cascade Synthesis of 2-Amino-1*H*-indole-3-carboxylate Derivatives. *Adv. Synth. Catal.* **2010**, *352*, 1033−1038. (c) Li, C.; Zhang, L.; Shu, S.; Liu, H. A Simple Copper-Catalyzed Two-Step One-Pot Synthesis of Indolo[1,2-*a*]quinazoline. *Beilstein J. Org. Chem.* **2014**, *10*, 2441−2447. (d) Jiang, H.; Yang, J.; Tang, X.; Wu, W. Divergent Syntheses of Isoquinolines and Indolo[1,2-*a*]quinazolines by Copper-Catalyzed Cascade Annulation from 2-Haloaryloxime Acetates with Active Methylene Compounds and Indoles. *J. Org. Chem.* **2016**, *81*, 2053−2061.

(22) Pommier, Y.; Cushman, M. The Indenoisoquinoline Non-camptothecin Topoisomerase I Inhibitors: Update and Perspectives. *Mol. Cancer Ther.* **2009**, *8*, 1008−1014.

(23) (a) Wang, Y.; Shaabani, S.; Ahmadianmoghaddam, M.; Gao, L.; Xu, R.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Olechno, J.; Ellson, R.; Kossenjans, M.; Helan, V.; Groves, M.; Dömling, A. Acoustic Droplet Ejection Enabled Automated Reaction Scouting. *ACS Cent. Sci.* **2019**, *5*, 451−457. (b) Neochoritis, C. G.; et al. Rapid Approach to Complex Boronic Acids. *Sci. Adv.* **2019**, *5*, No. eaaw4607.

(24) (a) Obrecht, R.; Herrmann, R.; Ugi, I. Isocyanide synthesis with phosphoryl chloride and diisopropylamine. *Synthesis* **1985**, *1985*, 400−402. (b) Skorna, G.; Ugi, I. Isocyanide Synthesis with Diphosgene. *Agnew. Chem. Int. Ed. Engl.* **1977**, *16*, 259−260. (c) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. Isonitrile syntheses. *Agnew. Chem. Int. Ed. Engl.* **1965**, *4*, 472−484. (d) Ugi, I.; Meyr, R. o-Tolyl Isocyanide. *Organic Synth.* **1961**, 101−101.

(25) (a) Gokel, G. W.; Widera, R. P.; Weber, W. P. Phase-Transfer Hofmann Carbylamine Reaction: *tert*-Butyl Isocyanide: Propane, 2-isocyano-2-methyl. *Organic Synth.* **2003**, *55*, 96−96. (b) Weber, W. P.; Gokel, G. W.; Ugi, I. K. Phase transfer catalysis in the Hofmann carbylamine reaction. *Agnew. Chem. Int. Ed. Engl.* **1972**, *11*, 530−531.

(26) Neochoritis, C. G.; Zarganes-Tzitzikas, T.; Stotani, S.; Dömling, A.; Herdtweck, E.; Khoury, K.; Dömling, A. Leuckart−Wallach route toward isocyanides and some applications. *ACS Comb. Sci.* **2015**, *17*, 493−499.

https://doi.org/10.1021/acs.joc.1c01170
J. Org. Chem. 2021, 86, 9771−9780