JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Bicyclic Piperidines *via* [2 + 2] Photocycloaddition

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c02355 Read Online

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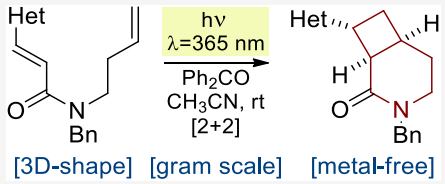
ABSTRACT: A synthetic strategy to fused bicyclic piperidines—building blocks for medicinal chemistry—is developed. The key step was an intramolecular [2 + 2]-photocyclization. The photochemical step was performed on a gram scale. Crystallographic analysis of the obtained compounds revealed that they occupy a novel chemical space and can be considered as elongated analogues of 3-substituted piperidines.



INTRODUCTION

Piperidine is one among the top three most popular rings in drugs and bioactive agents (Figure 1).[1,2] At the same time, recent trends in medicinal chemistry like "escape from flatland"[3] and "conformational restriction"[4] have already changed the way how medicinal chemists think. These days, they prefer to use small F(sp^3)-rich cyclic molecules in their research.[5,6] It is not surprising, therefore, that the intrinsically conformationally restricted bicyclic piperidines became interesting in drug discovery programs.[7] For example, the recently launched antiviral drugs Ledipasvir and Nelfinavir contain the saturated bicyclic piperidine fragment (Figure 1).

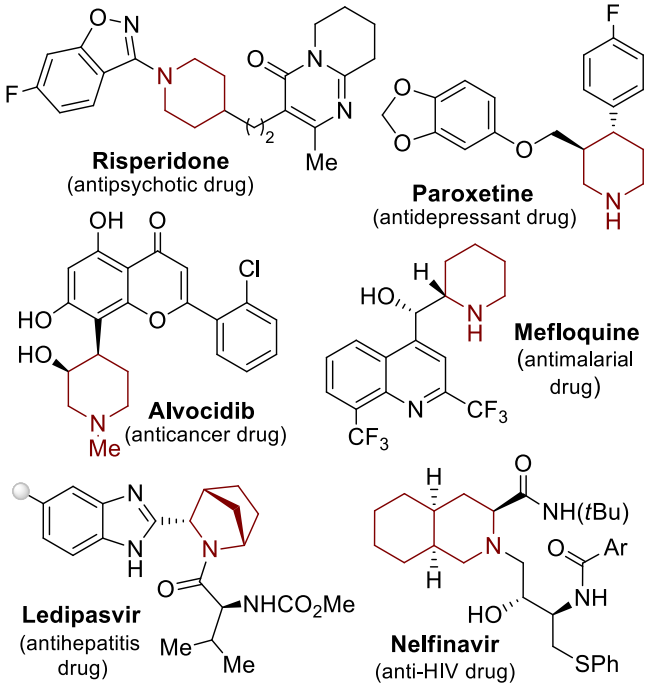


Figure 1. Bioactive derivatives of mono- and bicyclic piperidines.

During the past decade, photochemistry proved to be a powerful tool for preparing the cyclobutane-containing molecules.[8] Moreover, chemists at pharmaceutical companies extensively use it for making cyclobutane-containing building blocks.[9] For example, a number of medchem-relevant bicyclic pyrrolidines were synthesized recently *via* a photochemical [2 + 2]-cycloaddition.[10−12] At the same time, bicyclic cyclobutyl piperidines, in spite of conceptual interest, unexpectedly, have been remaining in the shadow. While tri-, tetra-, and polycyclic cores A[13] and B[14] are well-known in the literature (Scheme 1), bicyclic core C is much less studied.

In 1981, Hanaoka and co-workers performed the photochemical cycloaddition of cyclic alkene **1** with vinyl acetate (**2**) to obtain a non-separable mixture of products **3** and **4** (7/1), each one being a mixture of two stereoisomers (Scheme 1).[15] In 1983, Kaneko and colleagues realized photochemical cycloaddition of pyridone **5** with ethylene (**6**) to produce cyclobutane **7** (Scheme 1).[16] The corresponding reaction with the substituted allyl alcohol (**8**) gave bicyclic piperidone **9** as a mixture of isomers. In 1989, Sato used these transformations in his research.[17] In 1989, Ghosez developed a very interesting approach to bicyclic piperidines.[18] Compound **10** reacted with $(CF_3SO_2)_2O$/collidine to form the intermediate keteniminium salt that underwent an intramolecular [3 + 2] cycloaddition into the bicyclic ketone **11** in 65% yield. In spite of high synthetic potential, this method unexpectedly received no further development. In 2007, Ohno developed a stereoselective thermal cyclization of compounds **12** into bicyclic

Received: October 5, 2020

https://dx.doi.org/10.1021/acs.joc.0c02355
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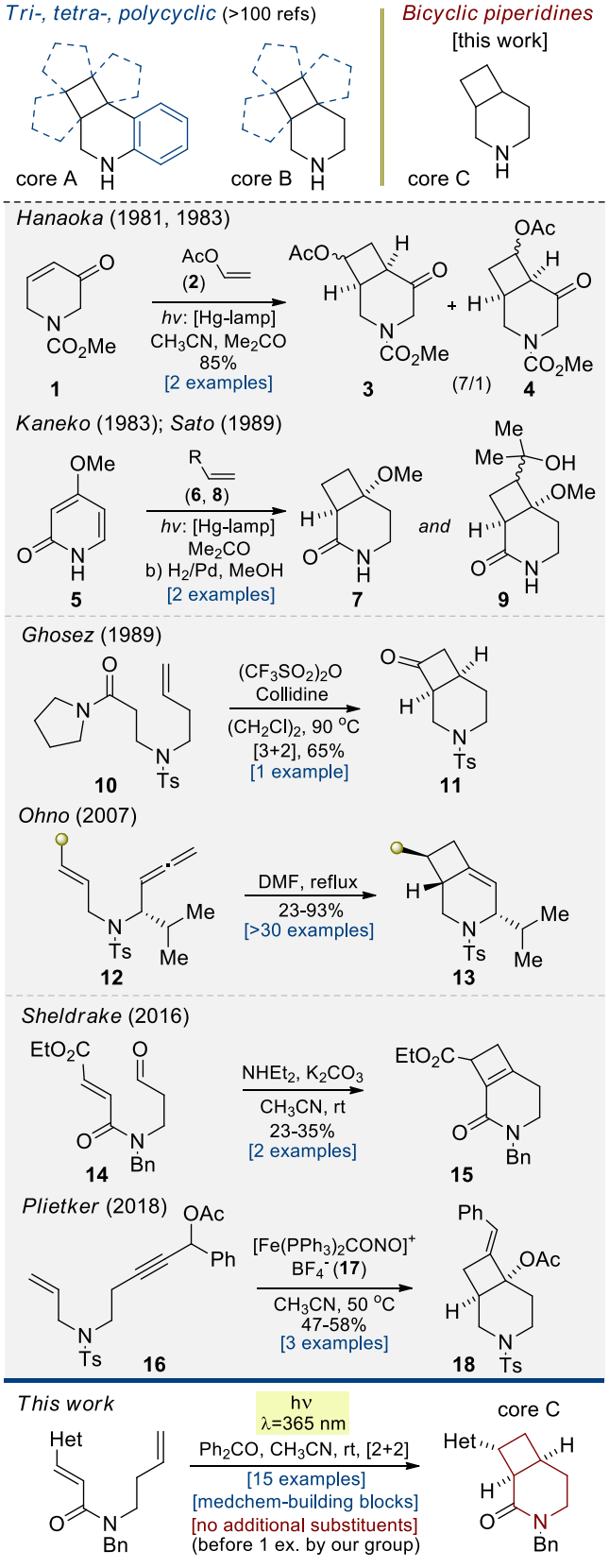
Scheme 1. Approaches to Bicyclic Piperidines



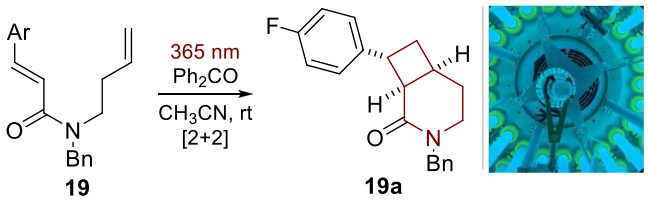
alkenes **13**.[19] In 2016, Sheldrake demonstrated that aldehyde **14** reacted with diethylamine at room temperature using K_2CO_3 as a base to form the bicyclic alkene **15**.[20] Finally, in 2018, Plietker and co-workers developed a cyclization of substrates **16** in the presence of iron catalyst **17** into bicyclic products of type **18**.[21]

In spite of many precedents in the literature on assembling the disubstituted core C (Scheme 1), we needed a modular approach to prepare various bicyclic piperidines with only one additional substituent (the second variation point is a nitrogen atom).[22] An approach should also rely on available starting materials. During the synthesis of bicyclic pyrrolidines,[11a] we mentioned that the same tactic could theoretically also be used for the preparation of piperidines. In this work, we report on the practical synthesis and crystallographic evaluation of novel bicyclic piperidines for medicinal chemistry (Scheme 1).[11a]

RESULTS AND DISCUSSION

Based on our previous results on photochemical synthesis of azaheterocycles,[11a,b] we became interested if compound **19** could undergo an intramolecular photochemical [2 + 2]-cyclization into the bicyclic piperidone **19a** (Table 1). Indeed,

Table 1. Optimization of the Synthesis of 19a



entry	deviation from above	yield (%)[a,b]
1	none	87 (82)[c]
2	419 nm	4
3	313 nm	7
4	254 nm	45
5	broad wavelength Hg lamp	39
6	PhCOMe instead of Ph_2CO	24
7	$(p\text{-MeOC}_6H_4)_2CO$ instead of Ph_2CO	65
8	$p\text{-FC}_6H_4)_2CO$ instead of Ph_2CO	51
9	CH_2Cl_2	63
10	acetone	17
11	toluene	39
12	EtOAc	41
13	no light, rt	0
14	no light, reflux	0

[a]2 mmol scale reaction. [b]Yield by ^1H NMR, CH_2Br_2 as an internal standard. [c]Isolated yield.

after some experimentation, we found that this reaction can be performed in acetonitrile under irradiation at 365 nm using benzophenone as a triplet sensitizer (Table 1). Product **19a** was obtained in 82% yield as a single stereoisomer. Irradiation with other standard wavelengths (254, 313, and 419 nm) or a broad wavelength mercury lamp gave lower yields of the product (Table 1, entries 2−5). Other triplet sensitizers—acetophenone or *para*-disubstituted benzophenones—also gave lower efficiency (entries 6−8). Also, the reaction did require irradiation as it did not proceed without light at room temperature or under heating (Table 1, entries 13, 14).

The whole synthesis scheme looked as follows. Benzaldehyde reacted with amine **20** in the presence of $NaBH(OAc)_3$ to afford the secondary amine **21** in 78% yield (Scheme 2). The standard acylation of the amine with *para*-fluorocinnamic acid **22** (easily obtained from *para*-fluoro-benzaldehyde and malonic acid) gave amide **19** in 85% yield. Importantly, the

https://dx.doi.org/10.1021/acs.joc.0c02355
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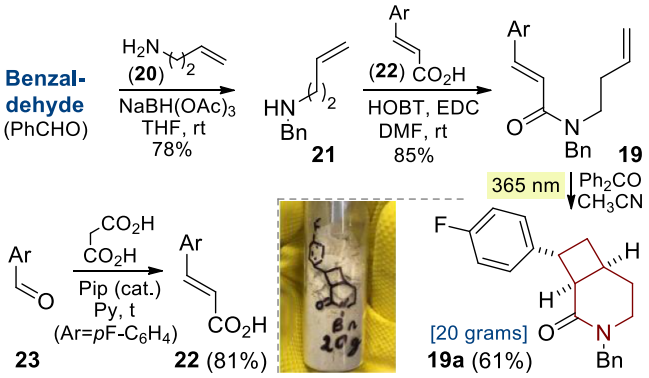
Scheme 2. Gram-Scale Synthesis of Compound 19a



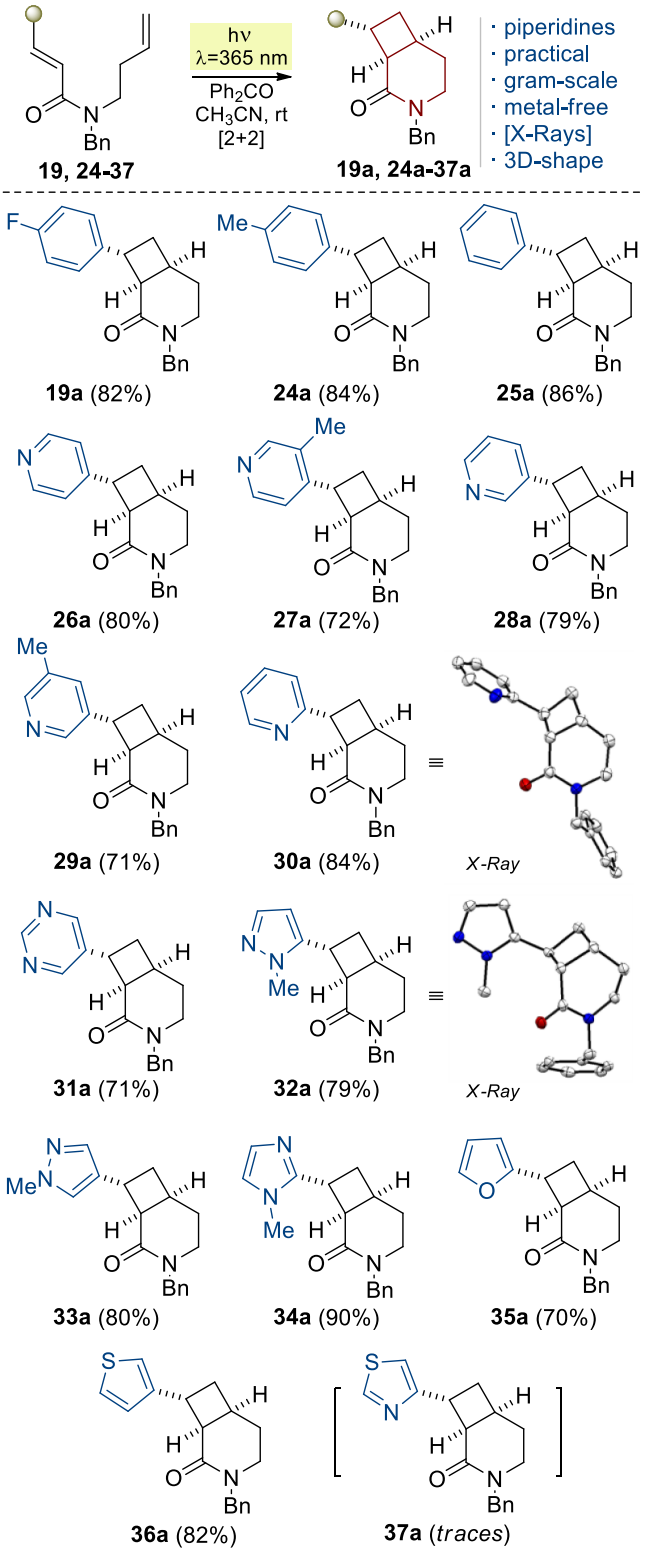
next photochemical step was also performed on a gram scale, although in a lower yield of 61%. Nevertheless, product **19a** was obtained on 20 g scale.

Having an optimized procedure in hand, we next studied its scope. In our previous projects,[11a,b] we paid attention to the synthesis of aryl-substituted bicyclic scaffolds. At the same time, the heterocyclic substituents are more interesting for medicinal chemistry. Aromatic products **24a** and **25a** were also synthesized in 84−86% yield. However, next we focused our attention onto the incorporation of the more interesting heterocyclic substituents. Pyridine has a very popular ring in bioactive compounds.[1] We were pleased to see that all 2-, 3-, and 4-pyridyl containing substrates **26**−**30** smoothly underwent the cyclization into the desired bicyclic piperidines **26a**−**30a** in 71−84% yield. The structure of compound **30a** was proven by X-ray analysis.[23] Similarly, pyrimidine-containing product **31a** was obtained in 71% yield. The fragment of pyrazole is popular in agrochemicals;[24] therefore, we also tried to prepare cyclization of substrates **32** and **33**. The reaction proceeded well, and the corresponding bicyclic products **32a** and **33a** were synthesized in 79−80% yield. The structure of bicyclic compound **32a** was also proven by X-ray analysis.[23] Analogously, products containing imidazole (**34a**), furan (**35a**), and thiophene (**36a**) were synthesized in 70−90% yield (Scheme 3). The developed procedure was not without limitations, however. Substrate **37** bearing the highly electron-deficient thiazole substituent gave only traces of the desired product **37a**. Instead, extensive polymerization was observed.

Next, we wanted to demonstrate how the obtained products could be transformed into the corresponding building blocks for medicinal chemistry. Reduction of the representative compound **19a** with $LiAlH_4$ followed by hydrogenolysis of the *N*-Bn protecting group smoothly gave the desired amine **38** in 84% yield (Scheme 4). Importantly, the synthesis was scaled-up, and 10 g of the product was obtained. It is worth mentioning that amine **38** is a homologue of the corresponding pyrrolidine-containing fragment—a key component of the antischizophrenia agent Belaperidone (Scheme 4). Two other representative amines **39** and **40** were alternatively synthesized from compounds **25a** and **35a**, correspondingly (Scheme 4). *N*-Benzoyl protection of amine **40** followed by oxidation of the furane ring with $NaIO_4/RuCl_3$ (cat.) gave interesting bicyclic conformationally rigid amino acid **41** in 31% yield (Scheme 5).

Finally, we planned to compare the geometric parameters of bicyclic piperidine C with those of 3-substituted piperidines. For that we used an exit vector plots tool, introduced recently

Scheme 3. Scope of Substituents in the Reaction



by our colleagues.[25] In this approach, the substituents mounted onto the disubstituted scaffold were simulated by two exit vectors *n***1** and *n***2** (Figure 2). Relative spatial arrangement of these vectors can be described by four geometric parameters: the distance between C- and N-variation points *r*, the plane angles $\varphi 1$ (between vectors *n***1** and N-atom) and $\varphi 2$ (between *n***2** and C-atom), and the dihedral angle θ defined by vectors

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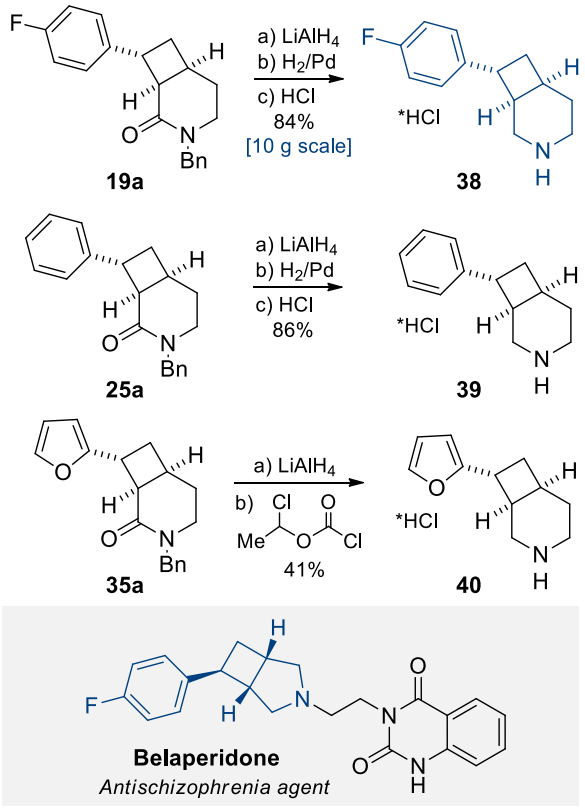
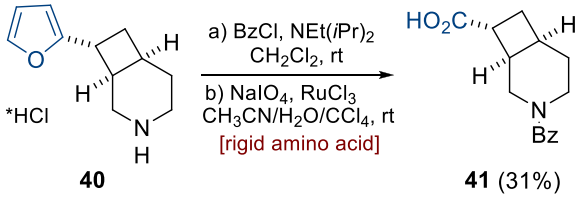
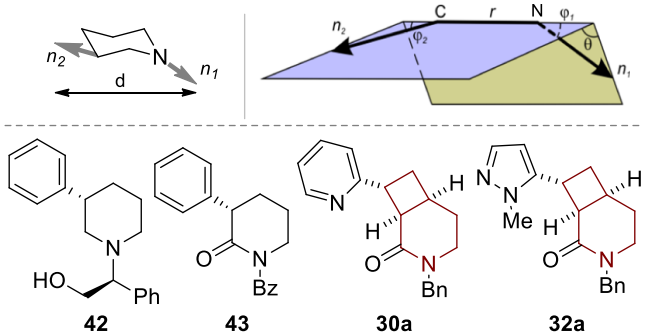
Scheme 4. Synthesis of Amines 38−40



Scheme 5. Synthesis of Conformationally Rigid Amino Acid 41





Compound	d (Å)	r (Å)	φ1 (°)	φ2 (°)	θ (°)
42	4.982(4)	2.521(3)	34.9(2)	37.0(2)	38.0(5)
43	4.945(3)	2.498(3)	28.0(1)	42.0(1)	53.5(4)
30a	6.018(4)	3.598(4)	34.9(2)	40.1(2)	64.9(5)
32a	5.593(3)	3.176(2)	37.0(1)	36.6(1)	51.0(3)

Figure 2. Definition of vectors *n*1, *n*2 (3-disubstituted piperidine is shown as an example). Definition of geometric parameters *d*, *r*, *φ*1, *φ*2, and *θ*. Geometric parameters *d*, *r*, *φ*1, *φ*2, and *θ* for 3-substituted piperidin(on)es **42**, **43**, bicyclic piperidones **30a**, **32a**.

*n*1, N−C, and *n*2. Additionally, the final key parameter—distance *d* between two substituents (Figure 2)—was also measured. We calculated the values of *d*, *r*, *φ*1, *φ*2, and *θ* from the X-ray data for compounds **30a** and **32a**. As reference models for 3-substituted piperidines/ones, we chose compounds **42** and **43** crystal data of which were reported in the literature (Figure 2).[26,27] Analysis of the data showed that angles *φ*1 (28−37°) and *φ*2 (37−42°) were similar in both cores—piperidine (**42**, **43**) and bicyclic piperidine (**30a**, **32a**). Planarity, as measured by dihedral angle *θ*, was also alike in both cores: 38−54° (**42**, **43**) versus 51−65° (**30a**, **32a**). However, in bicyclic piperidines distance *r* was up to 1 Å longer than that in 3-substituted piperidines: 2.50−2.52 Å (**42**, **43**) versus 3.18−3.60 Å (**30a**, **32a**). Also, the distance between the substituents (*d*) differed significantly: 4.95−4.98 Å (**42**, **43**) versus 5.59−6.02 Å (**30a**, **32a**).

As a short summary, angles *φ*1, *φ*2, and *θ* are similar in bicyclic piperidines (core C) and 3-substituted piperidines (Figure 2). However, distances *r* and *d* in bicyclic piperidines are up to 1 Å longer than those in 3-substituted piperidines. Therefore, the products obtained in this work (core C) could be considered as extended, elongated analogues of 3-substituted piperidines, to complement them in medicinal chemistry projects.

CONCLUSIONS

In this work, photochemical synthesis of bicyclic piperidines was developed. The compounds were designed as 3D-shaped building blocks for medicinal chemistry. The photochemical step was performed on a gram scale. X-ray crystallographic analysis revealed that the obtained compounds could be considered as elongated extended analogues of 3-substituted piperidines with a similar angular model.

EXPERIMENTAL SECTION

General Considerations. All chemicals were provided by Enamine Ltd (www.enamine.net). All solvents were treated according to standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC-\ characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100−200 mesh). ^{1}H NMR spectra were recorded at 400 or 500 MHz (Varian); and ^{13}C NMR spectra were recorded at 100, 126, or 151 MHz (Varian). ^{1}H NMR chemical shifts are calibrated using residual undeuterated solvents $CHCl_3$ (δ = 7.26 ppm), DMSO (δ = 2.50 ppm), or H_2O (δ = 4.79 ppm). ^{13}C NMR chemical shifts for ^{13}C NMR are reported relative to the central $CHCl_3$ (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm). Coupling constants are given in Hz. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Photochemical reactions were performed in a standard chemical glassware (no quarz) at 366 nm. Distance to the irradiation vessel−ca. 10−15 cm.

General Procedure for Synthesis of 19 and 24−37 (19 as an Example). *(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(4-fluorophenyl)-acrylamide (**19**).* 3-(4-Fluorophenyl)acrylic acid (83 g, 0.5 mol, 1 equiv) was dissolved in DMF (500 mL). The solution was cooled to 0 °C, and hydroxybenzotriazole (HOBt, 81 g, 0.6 mol, 1.2 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 93 g, 0.6 mol, 1.2 equiv) were added. The mixture was stirred for 1 h at 0 °C, and compound **21** (80.5 g, 0.5 mol, 1 equiv) was added. The resulting mixture was stirred overnight and then concentrated under reduced pressure. The residue was dissolved in methyl *tert*-butyl ether (MTBE). The mixture was washed with water (2 times), dried over

https://dx.doi.org/10.1021/acs.joc.0c02355
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Na_2SO_4, filtered through SiO_2, and concentrated under reduced pressure. Yield: 131.3 g, 85%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 7.74, 7.69 (2 × d, J = 15.7 Hz, 1H), 7.53−7.44 (m, 1H), 7.42−7.15 (m, 6H), 7.05 (t, J = 8.3 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 6.81, 6.70 (2 × d, J = 15.4 Hz, 1H), 5.90−5.63 (m, 1H), 5.17−4.96 (m, 2H), 4.71 (s, 1H), 4.67 (s, 1H), 3.53 (t, J = 7.1 Hz, 1H), 3.44 (t, J = 8.0 Hz, 1H), 2.35 (br s, 2H) ppm. ^{13}C {^{1}H} of both amide rotamers NMR (126 MHz, $CDCl_3$): δ 166.9, 166.5, 163.6 (d, J = 250 Hz), 163.6 (d, J = 250 Hz), 142.1, 142.0, 137.8, 137.3, 135.5, 134.4, 131.6, 129.8, 129.7, 129.1, 128.7, 128.2, 127.8, 127.5, 126.5, 117.8, 117.5, 117.2, 116.9, 116.1 (d, J = 14 Hz), 115.9 (d, J = 14 Hz), 51.7, 49.5, 46.9, 46.6, 33.8, 32.3 ppm. LCMS (m/z): 310 (M + H$^+$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{21}FNO$, 310.1607; found, 310.1602.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(p-tolyl)acrylamide ***(24)***. Yield: 24.4 g, 80%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 7.76, 7.72 (2 × d, J = 15.79 Hz, 1H), 7.47−7.03 (m, 9H), 6.85, 6.75 (2 × d, 15.3 Hz, 1H), 5.90−5.63 (m, 1H), 5.16−4.97 (m, 2H), 4.71 (s, 1H), 4.66 (s, 1H), 3.52 (t, J = 7.2 Hz, 1H), 3.43 (t, J = 7.3 Hz, 1H), 2.46−2.21 (m, 5H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 167.2, 166.8, 143.2, 143.2, 140.0, 139.9, 137.8, 137.3, 135.5, 134.4, 132.6, 132.5, 129.6, 129.5, 128.9, 128.6, 128.1, 127.8, 127.7, 127.4, 126.5, 117.6, 116.7, 116.5, 116.3, 51.6, 49.4, 46.8, 46.5, 33.7, 32.3, 21.4 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{24}NO$, 306.1858; found, 306.1852.

(E)-N-Benzyl-N-(but-3-en-1-yl)cinnamamide ***(25)***. Yield: 27.1 g, 93%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 7.81, 7.76 (2 × d, J = 15.6 Hz, 1H), 7.57−7.16 (m, 10H), 6.91, 6.81 (2 × d, J = 15.4 Hz, 1H), 5.93−5.65 (m, 1H), 5.13−5.00 (m, 2H), 4.73, 4.67 (2 × s, 2H), 3.55 (t, J = 7.2 Hz, 1H), 3.44 (t, J = 7.3 Hz, 1H), 2.43−2.28 (m, 2H) ppm. ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$): δ 166.9, 166.5, 143.1, 143.0, 137.7, 137.1, 135.4, 135.2, 135.1, 134.2, 129.6, 129.5, 128.9, 128.8, 128.7, 128.5, 128.0, 127.8, 127.6, 127.3, 126.4, 117.6, 117.5, 117.3, 116.7, 51.5, 49.3, 46.7, 46.4, 33.6, 32.2 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{22}NO$, 292.1701; found, 292.1704.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(pyridin-4-yl)acrylamide ***(26)***. Yield: 27.1 g, 73%, yellow oil. ^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$): δ 8.64, 8.57 (2 × d, J = 4.6 Hz, 1H), 7.69, 7.63 (2 × d, J = 15.4 Hz, 1H), 7.41−7.20 (m, 8H), 7.07, 7.65 (2 × d, J = 15.4 Hz, 1H), 5.91−5.66 (m, 1H), 5.19−5.00 (m, 2H), 4.74 (s, 1H), 4.69 (s, 1H), 3.57 (t, J = 7.3 Hz, 1H), 3.46 (t, J = 7.2 Hz, 1H), 2.37 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.2, 150.7, 150.6, 140.5, 140.3, 135.3, 134.2, 129.2, 128.8, 128.3, 128.0, 127.7, 126.4, 122.4, 122.1, 121.8, 118.1, 117.1, 51.8, 49.6, 47.0, 46.8, 33.8, 32.3 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1650.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(3-methylpyridin-4-yl)-acrylamide ***(27)***. Yield: 27.1 g, 82%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, DMSO-d_6): δ 8.50−8.24 (m, 2H), 7.70 (t, J = 14.2 Hz, 1H), 7.62, 7.47 (2 × d, J = 4.8 Hz, 1H), 7.38−7.08 (m, 6H), 5.90−5.69 (m, 1H), 5.12−4.98 (m, 2H), 4.79 (s, 1H), 4.64 (s, 1H), 3.53 (t, J = 7.1 Hz, 1H), 3.44 (t, J = 7.3 Hz, 1H), 2.60−2.23 (m, 5H) ppm. ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$): δ 166.9, 166.3, 151.9, 151.8, 147.9, 147.8, 138.5, 138.3, 137.5, 137.0, 135.3, 134.1, 131.8, 131.7, 129.2, 128.8, 128.3, 128.0, 127.7, 126.4, 123.0, 122.6, 119.8, 118.1, 117.1, 51.8, 49.6, 47.0, 46.8, 33.7, 32.3, 16.69, 16.65 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{23}N_2O$, 307.1810; found, 307.1812.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(pyridin-3-yl)acrylamide ***(28)***. Yield: 26.3 g, 90%, yellow oil. ^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$): δ 8.77, 8.65 (2 × s, 1H), 8.58, 8.52 (2 × d, J = 3.8 Hz, 1H), 7.83−7.63 (m, 2H), 7.42−7.21 (m, 6H), 6.98, 6.85 (2 × d, J = 15.5 Hz, 1H), 5.90−5.67 (m, 1H), 5.17−4.98 (m, 2H), 4.74 (s, 1H), 4.69 (s, 1H), 3.57 (t, J = 7.3 Hz, 1H), 3.46 (t, J = 7.3 Hz, 1H), 2.47−2.27 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.4, 166.0, 150.5, 150.4, 149.4, 149.4, 139.7, 139.5, 137.6, 137.1, 135.4, 134.5, 134.4, 134.2, 131.2, 131.1, 129.2, 128.8, 128.2, 127.9, 127.6, 126.4, 123.8, 123.7, 119.9, 119.6, 118.0, 117.0, 51.8, 49.5, 47.0, 46.8, 33.8, 32.3 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1658.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(5-methylpyridin-3-yl)-acrylamide ***(29)***. Yield: 26.9 g, 88%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 8.56, 8.44 (2 × s, 1H), 8.39, 8.34 (2 × s, 1H), 7.72, 7.67 (2 × d, J = 15.6 Hz, 1H), 7.57, 7.47 (2 × s, 1H), 7.41−7.09 (m, 5H), 6.93, 6.82 (2 × d, J = 15.4 Hz, 1H), 5.90−5.62 (m, 1H), 5.12−4.93 (m, 2H), 4.71 (s, 1H), 4.67 (s, 1H), 3.54 (t, J = 7.3 Hz, 1H), 3.44 (t, J = 7.3 Hz, 1H), 2.37−2.22 (m, 5H) ppm. ^{13}C NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.5, 166.1, 151.13, 151.08, 146.7, 146.6, 139.9, 139.8, 137.6, 137.1, 135.4, 135.0, 134.8, 134.3, 133.4, 133.3, 130.7, 130.6, 129.1, 128.8, 128.2, 127.9, 127.6, 126.5, 119.6, 119.3, 117.9, 117.0, 51.8, 49.5, 47.0, 46.7, 33.8, 32.3, 18.5, 18.4 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{23}N_2O$, 307.1810; found, 307.1807.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(pyridin-2-yl)acrylamide ***(30)***. Yield: 26.6 g, 91%, yellow oil. ^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$): δ 8.64, 8.57 (2 × d, J = 4.1 Hz, 1H), 7.79−7.65 (m, 2H), 7.56, 7.50 (2 × d, J = 14.9 Hz, 1H), 7.40−7.19 (m, 7H), 5.88−5.69 (m, 1H), 5.16−5.01 (m, 2H), 4.76 (br s, 2H), 3.57−3.47 (m, 2H), 2.45−2.31 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.9, 166.6, 153.7, 153.6, 150.1, 141.8, 136.9, 136.9, 135.5, 134.4, 129.0, 128.7, 128.2, 127.8, 127.5, 126.9, 125.0, 124.9, 124.0, 123.9, 121.8, 121.6, 117.8, 116.9, 51.7, 49.5, 46.9, 46.1, 33.8, 32.2 ppm. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1652.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(pyrimidin-5-yl)acrylamide ***(31)***. Yield: 26.9 g, 92%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 9.13, 9.07 (2 × s, 1H), 8.83 (s, 1H), 8.70 (s, 1H), 7.69−7.53 (m, 1H), 7.36−7.15 (m, 5H), 7.01, 6.87 (2 × d, J = 15.6 Hz, 1H), 5.84−5.62 (m, 1H), 5.15−4.94 (m, 2H), 4.69 (s, 1H), 4.66 (s, 1H), 3.55 (t, J = 7.3 Hz, 1H), 3.43 (t, J = 7.3 Hz, 1H), 2.42−2.27 (m, 2H) ppm. ^{13}C NMR of both amide rotamers (151 MHz, $CDCl_3$): δ 165.8, 165.4, 158.7, 158.6, 155.5, 155.4, 137.2, 136.7, 135.8, 135.6, 135.1, 134.0, 129.2, 128.8, 128.2, 128.0, 127.7, 126.3, 121.9, 121.6, 118.5, 118.1, 117.1, 110.3, 51.8, 49.6, 46.9, 33.6, 32.2 ppm. LCMS (m/z): 294 (M + H$^+$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}N_3O$, 294.1606; found, 294.1609.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(1-methyl-1H-pyrazol-5-yl)-acrylamide ***(32)***. Yield: 23.9 g, 81%, yellow oil. ^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$): δ 7.71, 7.66 (2 × d, J = 15.1 Hz, 1H), 7.50−7.17 (m, 6H), 6.82, 6.70 (2 × d, J = 15.1 Hz, 1 H), 6.54, 6.38 (2 × s, 1H), 5.87−5.66 (m, 1H), 5.17−5.00 (m, 2H), 4.73 (s, 1H), 4.67 (s, 1H), 3.97, 3.91 (2 × s, 3H), 3.56 (t, J = 7.1 Hz, 1H), 3.44 (t, J = 7.2 Hz, 1H), 2.46−2.25 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.4, 166.0, 139.0, 138.9, 138.8, 138.7, 137.6, 137.1, 135.4, 134.2, 129.1, 128.8, 128.7, 128.6, 128.2, 127.9, 127.6, 126.5, 119.8, 119.6, 118.0, 117.0, 105.0, 104.8, 51.7, 49.7, 47.0, 46.8, 37.0, 33.8, 32.3 ppm. LCMS (m/z): 296 (M + H$^+$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{22}N_3O$, 296.1763; found, 296.1765.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(1-methyl-1H-pyrazol-4-yl)-acrylamide ***(33)***. Yield 27 g, 92%, yellow oil. ^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.71−7.19 (m, 5H), 6.63, 6.52 (2 × d, J = 15.3 Hz, 1H), 5.86−5.69 (m, 1H), 5.15−4.96 (m, 2H), 4.71 (s, 1H), 4.65 (s, 1H), 3.91 (s, 1H), 3.86 (s, 1H), 3.52 (t, J = 7.3 Hz, 1H), 3.41 (t, J = 7.4 Hz, 1H), 2.95, 2.88 (2 × s, 3H), 2.42−2.22 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 167.3, 167.0, 162.6, 138.4, 138.3, 137.9, 137.4, 135.6, 134.5, 133.7, 133.6, 130.3, 130.2, 129.0, 128.7, 128.2, 127.7, 127.4, 126.5, 119.3, 119.2, 117.6, 116.8, 115.2, 114.9, 51.6, 49.4, 46.8, 46.5, 39.2, 36.6, 33.8, 32.4, 31.6 ppm. LCMS (m/z): 296 (M + H$^+$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{22}N_3O$, 296.1763; found, 296.1766.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(1-methyl-1H-imidazole-2-yl)-acrylamide ***(34)***. Yield 26.3 g, 89%, yellow oil. ^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$): δ 7.65, 7.60 (2 × d, J = 15.2 Hz, 1H), 7.54−7.17 (m, 7H), 6.77, 6.64 (2 × d, J = 15.3 Hz, 1H), 5.88−5.68 (m, 1H), 5.14−4.98 (m, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 3.72, 3.63 (2 × s, 3H), 3.57 (t, J = 7.2 Hz, 1H), 3.44 (t, J = 7.5 Hz, 1H),

https://dx.doi.org/10.1021/acs.joc.0c02355
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2.45−2.25 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.8, 166.4, 140.3, 137.7, 137.3, 135.5, 134.3, 130.8, 130.5, 129.6, 129.1, 129.0, 128.8, 128.3, 128.2, 127.9, 127.6, 126.5, 117.9, 117.0, 116.2, 116.0, 51.8, 49.7, 47.0, 46.9, 33.8, 32.4, 32.1 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{22}N_3O$, 296.1763; found, 296.1760.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(furan-2-yl)acrylamide (**35**). Yield 24.4 g, 87%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 7.54, 7.46 (2 × d, *J* = 14.6 Hz, 1H), 7.40−7.10 (m, 6H), 6.79, 6.72 (2 × d, *J* = 15.1 Hz, 1H), 6.54, 6.50 (2 × d, *J* = 2.8 Hz, 1H), 6.44, 6.39 (2 × s, 1H), 5.86−5.64 (m, 1H), 5.12−4.91 (m, 2H), 4.70 (s, 1H), 4.66 (s, 1H), 3.50 (t, *J* = 7.3 Hz, 1H), 3.42 (t, *J* = 7.4 Hz, 1H), 2.42−2.28 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 166.8, 166.4, 151.7, 151.7, 144.0, 143.9, 137.8, 137.2, 135.4, 134.3, 129.9, 128.9, 128.6, 128.1, 127.6, 127.3, 126.6, 117.6, 116.7, 115.1, 114.9, 114.0, 113.9, 112.2, 112.1, 51.5, 49.4, 46.8, 46.3, 33.7, 32.2 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2$, 282.1494; found, 282.1489.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(thiophen-3-yl)acrylamide (**36**). Yield 27.6 g, 93%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 7.77, 6.72 (2 × d, *J* = 15.7 Hz, 1H), 7.49−7.09 (m, 8H), 6.72, 6.61 (d, *J* = 15.2 Hz, 1H), 5.86−5.66 (m, 1H), 5.12−4.95 (m, 2H), 4.71 (s, 1H), 4.65 (s, 1H), 3.52 (t, *J* = 7.0 Hz, 1H), 3.41 (t, *J* = 7.1 Hz, 1H), 2.40−2.25 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (126 MHz, $CDCl_3$): δ 167.2, 166.8, 138.4, 138.4, 137.9, 137.3, 137.0, 136.9, 135.5, 134.4, 129.0, 128.7, 128.2, 127.8, 127.4, 127.2, 127.1, 126.8, 126.7, 126.7, 126.5, 125.3, 125.2, 117.7, 117.3, 117.0, 116.8, 51.7, 49.5, 46.9, 46.6, 33.8, 32.3 ppm. LCMS (*m/z*): 298 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}NOS$, 298.1266; found, 298.1266.

(E)-N-Benzyl-N-(but-3-en-1-yl)-3-(thiazol-4-yl)acrylamide (**37**). Yield 25.3 g, 85%, yellow oil. ^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$): δ 8.80, 8.83 (2 × s, 1H), 7.75, 7.72 (d, *J* = 11.1 Hz, 1H), 7.43−7.14 (m, 7H), 5.89−5.61 (m, 1H), 5.14−4.92 (m, 2H), 4.71 (s, 1H), 4.69 (s, 1H), 3.56−3.33 (m, 2H), 2.39−2.28 (m, 2H) ppm. ^{13}C {^{1}H} NMR of both amide rotamers (101 MHz, $CDCl_3$): δ 167.0, 166.7, 153.7, 153.3, 137.8, 137.1, 135.5, 134.8, 134.4, 129.0, 128.7, 128.2, 127.8, 127.5, 126.8, 120.5, 120.4, 120.3, 120.1, 117.8, 116.9, 51.6, 49.5, 46.8, 46.2, 33.8, 32.2 ppm. LCMS (*m/z*): 299 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{19}N_2OS$, 299.1218; found, 299.1223.

General Procedure for [2 + 2] Photocycloaddition (Synthesis of Compounds 19a and 24a−37a). Benzophenone (0.1 equiv) was added to 0.05 M solution of the starting material (1.0 equiv) in dry acetonitrile. The reaction mixture was degassed by bubbling of argon for 15 min and irradiated at 365 nm. Irradiation of aromatic substrates (**19a**, **24a**, **25a**) was performed during 72 h. Irradiation of heteroaromatic substrates (**26a**−**37a**) was performed during 144 h. Thereafter, the reaction mixture was concentrated. The final product was purified *via* column chromatography.

3-Benzyl-8-(4-fluorophenyl)-3-azabicyclo[4.2.0]octan-2-one (**19a**). 1st run: yield 2.1 g (72 h irradiation), 82%. 2nd run: yield 20.1 g, 61% (96 h irradiation), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.37 (m, 2H), 7.38−7.13 (m, 5H), 7.01 (t, *J* = 8.7 Hz, 2H), 4.66 (q, *J* = 14.6 Hz, 2H), 3.87−3.63 (m, 1H), 3.43−3.20 (m, 2H), 3.21 (t, *J* = 8.7 Hz, 1H), 2.80−2.58 (m, 1H), 2.46−2.29 (m, 1H), 2.18 (t, *J* = 9.6 Hz, 1H), 2.09−1.95 (m, 1H), 1.94−1.76 (m, 1H) ppm. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.0, 161.5 (d, *J* = 243.8 Hz), 140.1 (d, *J* = 3.0 Hz), 137.4, 128.8, 128.3 (d, *J* = 7.9 Hz), 128.1, 127.6, 115.1 (d, *J* = 21.2 Hz), 50.5, 46.0, 44.9, 42.2, 30.9, 29.5, 28.5 ppm. LCMS (*m/z*): 310 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}FNO$, 310.1607; found, 310.1611.

3-Benzyl-8-(p-tolyl)-3-azabicyclo[4.2.0]octan-2-one (**24a**). Yield 2.6 g, 84%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.21 (m, 8H), 7.11 (d, *J* = 7.7 Hz, 1H), 4.64 (q, *J* = 19.0 Hz, 2H), 3.81−3.66 (m, 1H), 3.40−3.17 (m, 3H), 2.74−2.60 (m, 1H), 2.44−2.34 (m, 1H), 2.31 (s, 3H), 2.21−2.07 (m, 1H), 2.04−1.89 (m, 1H), 1.90−1.71 (m, 1H) ppm. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.2, 141.5, 137.6, 135.7, 129.1, 128.8, 128.2, 127.5, 126.7, 50.5, 45.9, 45.1, 42.5, 30.9, 29.8, 28.6, 21.2 ppm. LCMS (*m/z*): 306 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO$, 306.1858; found, 306.1860.

3-Benzyl-8-phenyl-3-azabicyclo[4.2.0]octan-2-one (**25a**). Yield 2.5 g, 86%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.14 (m, 10H), 4.70 (d, 1H), 4.62 (d, 1H), 3.80 (q, *J* = 8.8 Hz, 1H), 3.44−3.32 (m, 1H), 3.32−3.19 (m, 2H), 2.75−2.62 (m, 1H), 2.45−2.34 (m, 1H), 2.24−2.11 (m, 1H), 2.04−1.93 (m, 1H), 1.93−1.73 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 144.5, 137.5, 128.7, 128.4, 128.2, 127.5, 126.7, 126.2, 50.4, 45.9, 44.8, 42.7, 30.8, 29.9, 28.6 ppm. LCMS (*m/z*): 292 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{22}NO$, 292.1701; found, 292.1706.

3-Benzyl-8-(pyridin-4-yl)-3-azabicyclo[4.2.0]octan-2-one (**26a**). Yield 2.3 g, 80%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 3.5 Hz, 2H), 7.40 (d, *J* = 4.5 Hz, 2H), 7.35−7.22 (m, 5H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.61 (d, *J* = 14.6 Hz, 1H), 3.87−3.72 (m, 1H), 3.37−3.14 (m, 2H), 2.73−2.62 (m, 1H), 2.42−2.26 (m, 1H), 2.19 (t, *J* = 10.4 Hz, 1H), 2.13−1.97 (m, 1H), 1.92−1.73 (m, 2H) ppm. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.4, 153.5, 149.7, 137.3, 128.8, 128.2, 127.6, 122.2, 50.5, 46.1, 44.1, 42.0, 30.3, 30.1, 28.6 ppm. LCMS (*m/z*): 293 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1652.

3-Benzyl-8-(3-methylpyridin-4-yl)-3-azabicyclo[4.2.0]octan-2-one (**27a**). Yield 2.2 g, 72%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 4.9 Hz, 1H), 8.29 (s, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.32−7.23 (m, 5H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.57 (d, *J* = 14.6 Hz, 1H), 3.84 (q, *J* = 8.8 Hz, 1H), 3.42−3.27 (m, 3H), 2.76−2.62 (m, 1H), 2.26−2.22 (m, 1H), 2.20 (s, 3H), 2.06−1.97 (m, 1H), 1.92−1.83 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.3, 150.7, 150.5, 148.0, 137.4, 131.2, 128.8, 128.3, 127.7, 120.9, 50.5, 46.0, 42.3, 40.8, 31.3, 30.1, 28.4, 16.6 ppm. LCMS (*m/z*): 307 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_2O$, 307.1810; found, 307.1804.

3-Benzyl-8-(pyridin-3-yl)-3-azabicyclo[4.2.0]octan-2-one (**28a**). Yield 2.3 g, 79%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.41 (d, *J* = 4.3 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.31−7.18 (m, 6H), 4.64 (d, *J* = 14.6 Hz, 1H), 4.58 (d, *J* = 14.6 Hz, 1H), 3.77 (q, *J* = 8.9 Hz, 1H), 3.35−3.21 (m, 2H), 3.19 (t, *J* = 8.7 Hz, 1H), 2.72−2.61 (m, 1H), 2.42−2.30 (m, 1H), 2.18 (t, *J* = 10.4 Hz, 1H), 2.03−1.94 (m, 1H), 1.90−1.78 (m, 1H) ppm. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.3, 148.0, 147.5, 139.6, 137.2, 134.7, 128.6, 128.0, 127.4, 123.3, 50.3, 45.9, 44.3, 40.4, 30.4, 30.2, 28.4 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1658.

3-Benzyl-8-(5-methylpyridin-3-yl)-3-azabicyclo[4.2.0]octan-2-one (**29a**). Yield 2.1 g, 71%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.26 (s, 1H), 7.72 (s, 1H), 7.32−7.23 (m, 5H), 4.64 (q, *J* = 14.7 Hz, 2H), 3.76 (q, *J* = 8.9 Hz, 1H), 3.39−3.14 (m, 3H), 2.78−2.64 (m, 1H), 2.42−2.33 (m, 1H), 2.30 (s, 3H), 2.23−2.15 (m, 1H), 2.07−1.95 (m, 1H), 1.93−1.78 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 148.2, 145.3, 139.2, 137.4, 135.5, 132.9, 128.8, 128.2, 127.6, 50.5, 46.1, 44.5, 40.6, 30.7, 30.4, 28.6, 18.6 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_2O$, 307.1810; found, 307.1815.

3-Benzyl-8-(pyridin-2-yl)-3-azabicyclo[4.2.0]octan-2-one (**30a**). Yield 2.5 g, 84%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, *J* = 4.4 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.36−7.23 (m, 5H), 7.15−7.06 (m, 1H), 4.65 (s, 2H), 3.83 (q, *J* = 8.6 Hz, 1H), 3.45−3.32 (m, 2H), 3.32−3.25 (m, 1H), 2.81−2.71 (m, 1H), 2.70−2.60 (m, 1H), 2.13 (t, *J* = 9.6 Hz, 1H), 2.07−1.99 (m, 1H), 1.90−1.76 (m, 1H) ppm. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.0, 162.7, 149.3, 137.5, 136.5, 128.7, 128.2, 127.5, 122.7, 121.6, 50.4, 46.0, 44.7, 43.6, 30.0, 29.6, 28.8 ppm. LCMS (*m/z*): 293 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O$, 293.1654; found, 293.1650.

3-Benzyl-8-(pyrimidin-5-yl)-3-azabicyclo[4.2.0]octan-2-one (**31a**). Yield 2.1 g, 71%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.60 (d, *J* = 5.2 Hz, 1H), 7.55 (d, *J* = 4.5 Hz, 1H), 7.34−7.22 (m, 5H), 4.63 (s, 2H), 3.86−3.71 (m, 1H), 3.43−3.20 (m, 3H), 2.82−2.68 (m, 1H), 2.67−2.55 (m, 1H), 2.18−2.07 (m, 1H), 2.07−1.96 (m, 1H), 1.91−1.77 (m, 1H) ppm. ^{13}C {^{1}H} NMR of both

https://dx.doi.org/10.1021/acs.joc.0c02355
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amide rotamers (126 MHz, $CDCl_3$): δ 171.4, 171.1, 158.9, 157.0, 137.3, 128.8, 128.2, 127.7, 120.3, 50.5, 46.1, 44.1, 43.0, 30.3, 29.0, 28.8 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$, 294.1606; found, 294.1610.

*3-Benzyl-8-(1-methyl-1H-pyrazol-5-yl)-3-azabicyclo[4.2.0]octan-2-one (**32a**).* Yield 2.3 g, 79%, white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39−7.16 (m, 6H), 6.20 (s, 1H), 4.60 (q, *J* = 14.6 Hz, 2H), 3.79 (s, 3H), 3.67−3.57 (m, 1H), 3.38−3.31 (m, 1H), 3.29−3.19 (m, 1H), 3.08 (t, *J* = 7.9 Hz, 1H), 2.80−2.71 (m, 1H), 2.37−2.27 (m, 1H), 2.24−2.13 (m, 1H), 1.98−1.88 (m, 1H), 1.82−1.69 (m, 1H) ppm. ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.9, 145.1, 137.8, 137.1, 128.6, 127.9, 127.4, 103.8, 103.2, 50.3, 45.4, 44.3, 36.5, 33.8, 29.6, 27.7 ppm. LCMS (*m/z*): 296 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{22}N_3O$, 296.1763; found, 296.1766.

*3-Benzyl-8-(1-methyl-1H-pyrazol-4-yl)-3-azabicyclo[4.2.0]octan-2-one (**33a**).* Yield 2.4 g, 80%, white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59−7.10 (m, 7H), 4.60 (d, *J* = 7.7 Hz, 2H), 3.81 (s, 3H), 3.65−3.54 (m, 1H), 3.33−3.15 (m, 2H), 3.01 (t, *J* = 8.3 Hz, 1H), 2.69−2.59 (m, 1H), 2.29−2.15 (m, 1H), 2.08 (t, *J* = 9.4 Hz, 1H), 1.99−1.88 (m, 1H), 1.85−1.71 (m, 1H) ppm. ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.8, 137.4, 137.1, 128.7, 128.1, 128.0, 127.4, 125.4, 50.2, 46.0, 45.8, 38.8, 34.3, 31.2, 30.3, 28.3 ppm. LCMS (*m/z*): 296 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{22}N_3O$, 296.1763; found, 296.1755.

*3-Benzyl-8-(1-methyl-1H-imidazole-2-yl)-3-azabicyclo[4.2.0]-octan-2-one (**34a**).* Yield 2.7 g, 90%, white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.20 (m, 5H), 6.92 (s, 1H), 6.77 (s, 1H), 4.60 (s, 2H), 3.66−3.62 (m, 1H), 3.61 (s, 3H), 3.40−3.30 (m, 1H), 3.29−3.13 (m, 2H), 3.03−2.90 (m, 1H), 2.88−2.77 (m, 1H), 2.12−2.03 (m, 1H), 1.98−1.86 (m, 1H), 1.78−1.66 (m, 1H) ppm. ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.6, 149.5, 137.3, 128.7, 128.0, 127.5, 127.0, 121.4, 50.5, 45.7, 44.1, 34.2, 32.7, 29.7, 28.3, 27.8 ppm. LCMS (*m/z*): 296 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{22}N_3O$, 296.1763; found, 296.1760.

*3-Benzyl-8-(furan-2-yl)-3-azabicyclo[4.2.0]octan-2-one (**35a**).* Yield 2 g, 70%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.21 (m, 6H), 6.33−6.30 (m, 1H), 6.18 (d, *J* = 3.0 Hz, 1H), 4.66 (s, 2H), 3.76−3.65 (m, 1H), 3.42−3.20 (m, 3H), 2.82−2.69 (m, 1H), 2.55−2.42 (m, 1H), 2.13−2.05 (m, 1H), 2.04−1.91 (m, 1H), 1.87−1.72 (m, 1H) ppm. ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.7, 156.7, 141.7, 137.3, 128.8, 128.3, 127.6, 110.4, 105.4, 50.5, 45.7, 43.4, 36.7, 29.8, 29.7, 28.2 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2$, 282.1494; found, 282.1490.

*3-Benzyl-8-(thiophen-3-yl)-3-azabicyclo[4.2.0]octan-2-one (**36a**).* Yield 2.4 g, 82%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.11 (m, 8H), 4.66 (q, *J* = 14.6 Hz, 2H), 3.85−3.64 (m, 1H), 3.40−3.23 (m, 2H), 3.20 (t, *J* = 8.5 Hz, 1H), 2.79−2.62 (m, 1H), 2.45−2.29 (m, 1H), 2.23−2.09 (m, 1H), 2.03−1.93 (m, 1H), 1.91−1.77 (m, 1H) ppm ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.1, 142.1, 137.1, 128.6, 128.5, 128.1, 127.3, 125.4, 120.7, 50.6, 44.2, 44.1, 36.0, 29.2, 27.7, 26.0 ppm. LCMS (*m/z*): 298 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}NOS$, 298.1266; found, 298.1264.

General Procedure for the Synthesis of 38, 39 (38 as an Example). *8-(4-Fluorophenyl)-3-azabicyclo[4.2.0]octane Hydrochloride (**38**).* A solution of **19a** (18.5 g, 0.06 mol, 1 equiv) in THF (150 mL) was added dropwise to 2 M suspension of LiAlH4 (4.6 g, 0.12 mol, 2 equiv) in THF (300 mL) at rt. The reaction mixture was heated at reflux for 5 h using an oil bath and Ika thermocouple, then cooled to −20 °C, and treated dropwise with 40% aqueous KOH solution. Formed suspension was filtered through Na_2SO_4. The solution was concentrated. The obtained product was distilled (0.1 mmHg) and dissolved in methanol to get a 1 M solution. 10% Palladium on charcoal (2 g) and 2 M aqueous HCl (50 mL) were added. The resultant reaction mixture was stirred under hydrogen atmosphere (50 atm) overnight at 50 °C using an oil bath and Ika thermocouple, then filtered, and concentrated under reduced pressure. The residue was dissolved in cold EtOAc, and 5 M HCl in dioxane was added dropwise to achieve a slightly acidic pH. The precipitate was filtered and dried. Yield 12.2 g, 84%, white solid, mp 206−207 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.37 (br s, 2H), 7.35 (t, *J* = 6.2 Hz, 2H), 7.12 (t, *J* = 8.4 Hz, 2H), 4.07 (q, *J* = 8.9 Hz, 1H), 3.22 (d, *J* = 12.4 Hz, 1H), 3.02 (d, *J* = 13.7 Hz, 1H), 2.92 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.64 (t, *J* = 12.0 Hz, 1H), 2.48−2.42 (m, 1H), 2.36−2.24 (m, 1H), 2.17 (q, *J* = 7.7 Hz, 1H), 2.09−1.90 (m, 2H), 1.84 (t, *J* = 8.7 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.8 (d, *J* = 241.7 Hz), 139.5 (d, *J* = 2.8 Hz), 128.5 (d, *J* = 7.9 Hz), 114.9 (d, *J* = 20.9 Hz), 42.1, 40.6, 38.4, 37.6, 31.7, 25.8, 24.4 ppm. LCMS (*m/z*): 206 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{17}FN$, 206.1345; found, 206.1350.

*8-Phenyl-3-azabicyclo[4.2.0]octane Hydrochloride (**39**).* Scale: 0.01 mol. Yield 1.9 g, 86%, white solid, mp 215−216 °C. ^1H NMR (400 MHz, D_2O): δ 7.43−7.27 (m, 5H), 3.66 (q, *J* = 9.0 Hz, 1H), 3.45−3.37 (m, 1H), 3.25 (d, *J* = 13.8 Hz, 1H), 3.12 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.85 (td, *J* = 13.0, 2.7 Hz, 1H), 2.74−2.65 (m, 1H), 2.55−2.40 (m, 1H), 2.32−2.18 (m, 2H), 2.03−1.85 (m, 2H) ppm. ^{13}C $\{^1H\}$ NMR (126 MHz, D2O): δ 143.2, 128.8, 126.79, 126.78, 43.4, 41.8, 39.7, 36.7, 31.7, 25.9, 24.6 ppm. LCMS (*m/z*): 188 (M + H^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{18}N$, 188.1439; found, 188.1432.

*8-(Furan-2-yl)-3-azabicyclo[4.2.0]octane Hydrochloride (**40**).* A solution of **35a** (1.46 g, 5.2 mmol, 1 equiv) in THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.2 g, 5.2 mmol, 1 equiv) in THF (50 mL) at 0−10 °C. Then, the reaction mixture was warmed to rt and left stirring overnight. The mixture was quenched with water and a sat. solution of NaOH. The mixture was filtered through a thick pad of Na_2SO_4. The solid residue was washed with hot THF. The filtrated was concentrated. The residue was dissolved in CH_2Cl_2 (50 mL), and 1-chloroethyl chloroformate (1.49 g, 10.4 mmol, 2 equiv) was added. The reaction was heated under reflux overnight. The solvent was removed in *vacuo*. The residue was dissolved in CH_3OH (30 mL) and heated under reflux for 2 h. The solvent was removed in *vacuo* and Et_2O (80 mL) was added. The precipitate was filtered and dried. Yield: 0.62 g, 56%, white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 9.23 (br s, 2H), 7.54 (s, 1H), 6.36 (s, 1H), 6.16 (d, *J* = 2.6 Hz, 1H), 3.96 (q, *J* = 8.9 Hz, 1H), 3.19 (d, *J* = 12.1 Hz, 1H), 2.98 (br s, 2H), 2.68−2.61 (m, 2H), 2.37−2.30 (m, 1H), 2.17−2.11 (m, 1H), 2.07−2.01 (m, 1H), 1.91−1.83 (m, 2H) ppm. ^{13}C $\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 156.5, 141.6, 110.4, 104.9, 42.2, 40.5, 35.4, 33.1, 30.9, 26.0, 24.1 ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{16}NO$, 178.1232; found, 178.1237.

*3-Benzoyl-3-azabicyclo[4.2.0]octane-8-carboxylic Acid (**41**).* A solution of **40** (150 mg, 0.7 mmol, 1.0 equiv) and NEt(*i*Pr)2 (271 mg, 2.1 mmol, 3 equiv) in CH_2Cl_2 (20 mL) was cooled to −20 °C under Ar. Benzoyl chloride (119 mg, 0.84 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred overnight. The reaction mixture was washed with a solution of 10% citric acid (20 mL) and saturated $NaHCO_3$ (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the protected amide. The crude product was dissolved in CH_3CN (1.5 mL) and added under Ar to a vigorously stirred mixture of $NaIO_4$ (910 mg, 4.27 mmol, 6.1 equiv) and $RuCl_3 \cdot H_2O$ (8 mg, 0.04 mmol, 0.05 equiv) in a mixture of H_2O (6 mL), CCl_4 (4 mL), and CH_3CN (6 mL). The reaction mixture was stirred for 1 h. The color of the solution changed from yellowish to black. Then, $NaIO_4$ was added to restore the yellowish color. The reaction mixture was stirred for 1 h, then diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with a 20% solution of $NaHSO_3$ until colorless and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified *via* column chromatography to give the desired product. Yield: 56 mg, 31% yield, yellow oil. ^1H NMR (500 MHz, DMSO-d_6): δ 9.75 (br s, 1H), 8.03−7.89 (m, 5H), 4.84−4.69 (m, 1H), 4.18−3.83 (m, 2H), 3.77−3.45 (m, 3H), 2.96 (br s, 1H), 2.80 (br s, 1H), 2.57 (br s, 1H), 2.37 (br s, 1H), 2.31−2.13 (m, 1H) ppm. ^{13}C $\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 214.4, 176.1, 168.5, 167.6, 166.0, 156.5, 86.5, 84.2, 81.5, 79.2, 77.3, 76.8, 75.9, 75.6, 67.2, 66.6, 65.6 ppm.

https://dx.doi.org/10.1021/acs.joc.0c02355
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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02355.

Photos of experimental setup, experimental procedures, copies of NMR spectra, and X-ray crystallography data (PDF)

Crystallography data of **30a** (CIF)

Crystallography data of **32a** (CIF)

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Notes

The authors declare the following competing financial interest(s): P.M. is also an employee of a chemical supplier - Enamine.

■ ACKNOWLEDGMENTS

Authors are grateful to Enamine Ltd for financial support. P.M. is grateful to I. Sadkova for the help with the preparation of the manuscript. A.S.K. acknowledges financial support by Tomsk polytechnic university competitiveness enhancement program (project CEP-SAMT-208/2020). We are grateful to Dr. E. Rusanov (IOC, Kyiv) for performing X-ray crystallographic analysis, and to Dr. A. Kozytskiy (Enamine) for the help with NMR measurements. PM is also thankful to reviewer 1 for the deep and comprehensive revision of this work that helped to improve significantly the manuscript.

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