JOC The Journal of Organic Chemistry

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Synthesis of Azacarbolines via $PhIO_2$-Promoted Intramolecular Oxidative Cyclization of α-Indolylhydrazones

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Cite This: J. Org. Chem. 2021, 86, 17918−17929 Read Online

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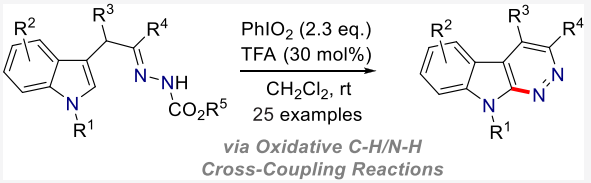
ABSTRACT: An unprecedented synthesis of polysubstituted indole-fused pyridazines (azacarbolines) from α-indolylhydrazones under oxidative conditions using a combination of iodylbenzene ($PhIO_2$) and trifluoroacetic acid (TFA) has been developed. This transformation is conducted without the need for transition metals, harsh conditions, or an inert atmosphere.



INTRODUCTION

Selective carbon−nitrogen (C−N) bond formation is one of the most important processes in organic chemistry since it enables key steps in the synthesis of complex nitrogen-containing compounds from simple precursors.[1] Traditionally, methods for C−N bond construction were routinely focused on copper-catalyzed Ullmann−Goldberg,[2] Chan−Lam,[3] and Pd-catalyzed Buchwald−Hartwig[4] aminations using (pseudo)-halocarbon or organometallic reagents. The recent maturation of methodologies (photochemical included) operating via transition-metal [Pd, Rh, Ru, Cu, etc.] catalyzed direct C−H bond amination[5] without prefunctionalization of simple starting materials offers a valuable alternative. However, these reactions generally suffer from high reaction temperature, narrow substrate scope, and high loading of the catalyst and/or metal oxidant. In addition, the contamination of heavy metals in the final product has limited their potential application in drug synthesis in the later stages. Hence, the development of alternative, effective, and safe metal-free methods for the formation of C−N bonds that can be performed at milder conditions starting from nonprefunctionalized simple precursor bonds is highly desirable. In this context, hypervalent iodine reagents[6] (HIRs) have captured our attention because of their inherent low toxicity, ready accessibility, low cost, high chemoselectivity, and mild conditions. Despite substantial advances in the oxidative C−H amination/amidation aiming at a greener goal,[7,8] to the best of our knowledge, the application of HIRs in the C(sp^2)−H/N−H dehydrogenative coupling annulation reactions of hydrazone systems[9] to assemble N-heterocycles, especially those fused, still remains limited. Specifically, Tanimori's[9a] and Zhu's[9b] groups independently reported the synthesis of structurally diversified pyrazole/1*H*-indazole derivatives through metal-free oxidative C(sp^2)−H cycloamination of both vinyl and aryl hydrazones (Figure 1a). Almost simultaneously, Chen, Xiao, and coauthors[9c] disclosed a $PhI(OAc)_2$-promoted radical cyclization of allyl hydrazones

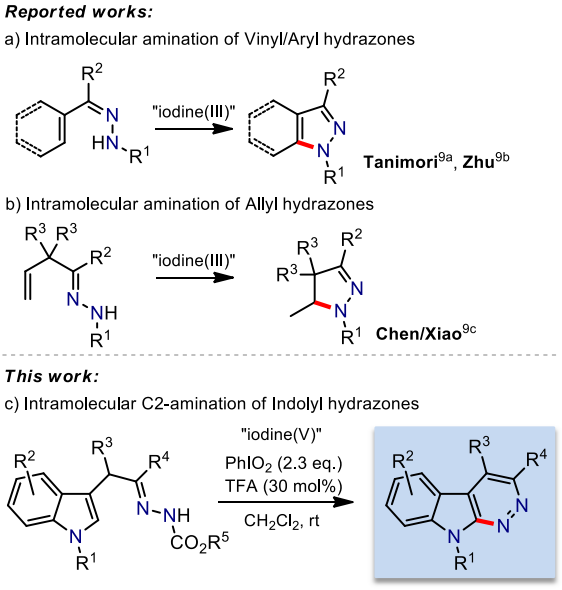
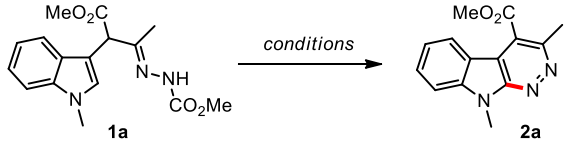


Figure 1. Hypervalent iodine-promoted C(sp^2)−H cycloamination of hydrazones.

for the assembly of a wide range of five-membered dihydropyrazoles (Figure 1b). Although an excellent example describing a copper-catalyzed intramolecular C−N bond formation to afford cinnolines has been reported by Xiao, Xu, and co-workers,[10] a metal-free approach to access a fused

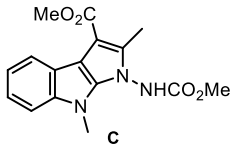
Received: September 10, 2021
Published: December 6, 2021

Table 1. Optimization Studies[a]



entry	oxidant (equiv)	additive (equiv)	solvent (2 mL)	time (h)[b]	yield (%)[c]
1	PIDA (2.3)	TFA (0.3)	CH_2Cl_2	0.5	56
2[d]	PIDA (2.3)	TFA (0.3)	CH_2Cl_2	4	43
3	PIDA (2.3)	DPP (0.3)	CH_2Cl_2	3	44
4	PIDA (2.3)	I_2 (1.5)	CH_2Cl_2	1	<5
5	PIDA (2.3)	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	>24	17
6	PIDA (2.3)	DBU (1.2)	CH_2Cl_2	12	25
7	PIDA (2.3)	K_2CO_3 (1.2)	CH_2Cl_2	12	35[e]
8[f]	PIDA (2.3)	TFA (0.3)	CH_2Cl_2	0.5	51
9	PIDA (2.3)	TFA (1.0)	CH_2Cl_2	0.2	41
10	PIDA (2.3)	TFA (0.3)	$CHCl_3$	0.5	55
11	PIDA (2.3)	TFA (0.3)	CH_3OH	0.5	35
12	PIDA (2.3)	TFA (0.3)	CH_3CN	0.5	40
13	PIDA (2.3)	TFA (0.3)	THF	1	43
14	PIFA (2.3)	TFA (0.3)	CH_2Cl_2	0.3	46
15	HTIB (2.3)	TFA (0.3)	CH_2Cl_2	5	<5
16	PhIO (2.3)	TFA (0.3)	CH_2Cl_2	3	37
17	IBX (2.3)	TFA (0.3)	CH_2Cl_2	4	79
18	DMP (2.3)	TFA (0.3)	CH_2Cl_2	12	64
19	$PhIO_2$ (2.3)	TFA (0.3)	CH_2Cl_2	5	82
20[g]	$PhIO_2$ (2.3)	TFA (0.3)	DCE	2.5	70
21	$PhIO_2$ (2.3)	TFA (0.3)	THF	6	68
22	$PhIO_2$ (2.3)	TFA (0.3)	CH_3CN	6	65 (16)[h]
23	$PhIO_2$ (2.3)	TFA (0.3)	HFIP	3	38
24	$PhIO_2$ (2.3)	–	AcOH	1	47
25	$PhIO_2$ (1.5)	TFA (0.3)	CH_2Cl_2	12	73 (9)[h]
26	–	TFA (0.3→1)	CH_2Cl_2	24[i]	0
27	$PhIO_2$ (2.3)	–	CH_2Cl_2	24[i]	0 (5)[h]

[a]All reactions were performed on a 0.2 mmol scale. [b]Denotes complete consumption of **1a** unless otherwise noted. [c]Isolated yields. [d]Performed at 0 °C. [e]1-Methyl-1*H*-indole-2,3-dione[17] (12% yield) byproduct was also recovered. [f]$Cu(OTf)_2$ (5 mol %) was added. [g]Performed at 50 °C. [h]Five-membered cross-coupled product **C** was also observed. [i]Denotes unreacted starting material. Abbreviations used: PIDA = phenyliodine diacetate, PIFA = phenyliodine bis(trifluoroacetate), HTIB = hydroxy(tosyloxy)iodobenzene, IBX = *o*-iodoxybenzoic acid [1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide], DMP = Dess–Martin periodinate, DPP = diphenyl phosphoric acid, TFA = trifluoroacetic acid, AcOH = acetic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, THF = tetrahydrofuran, HFIP = hexafluoroisopropanol.



six-membered pyridazine skeleton from hydrazone substrates is yet to be realized.

Following our interest in the construction of polycyclic N-heterocycles[11] and aware of the privileged role of the indole nucleus in natural products and medicinal science,[12,13] we envisaged that the NH moiety in α-(indol-3-yl)hydrazones can be used as a N donor in coupling with the indole C2–H[7a,i,14] bond in the presence of the hypervalent iodine reagents (HIRs) to construct fused indole pyridazines (Figure 1c).

Herein, we report an unprecedented example of $PhIO_2$-promoted dehydrogenative cyclization of α-indolylhydrazones **1**, whereby a sequential C–N bond formation, aromatization, N–C bond cleavage of a carbamate residue, ring expansion, and oxidative process are involved. Notably, this approach has resulted in a convenient assemblage of two biologically important heterocycles such as indole and pyridazine frameworks. The fusion of these two privileged heterocycles in one molecule[15] may create rigid entities endowed with either enhanced (synergistic effect) or new biological activities, which may feature promising bioactivity for screening. Furthermore, compared with Xiao and Xu's protocol,[10] this method offers the clear advantage of not requiring the use of transition metal catalysts and harsh reaction conditions.

RESULTS AND DISCUSSION

Generation of the required substrates **1** is readily achieved in 23–95% yields by $ZnCl_2$-catalyzed reaction of the indoles with azoalkenes in CH_2Cl_2[16] (see Supporting Information). The intramolecular cyclization of α-indolylhydrazone **1a** was initially investigated by applying Reddy's conditions.[7e] To our satisfaction, the combination of PIDA with TFA (30 mol %) in CH_2Cl_2 at room temperature for 0.5 h afforded the

https://doi.org/10.1021/acs.joc.1c02217
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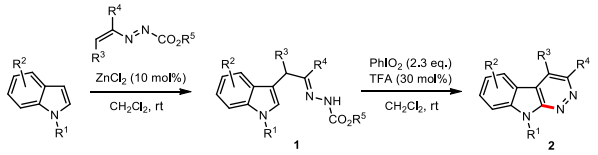
Table 2. Synthesis of Azacarbolines via Intramolecular Oxidative Indole C−H Amination Mediated by $PhIO_2$[a]



entry	substrate	product	yield[b] (%)	entry	substrate	product	yield[b] (%)
1	**1a**	**2a**	82 (79)[c]	14	**1n**	**2n**	78
2	**1b**	**2b**	75	15	**1o**	**2o**	76
3	**1c**	**2c**	67	16	**1p**	**2p**	21
4	**1d**	**2d**	56	17	**1q**	**2q**	79
5	**1e**	**2e**	71	18	**1r**	**2r**	81
6	**1f**	**2f**	59	19	**1s**	**2s**	80
7	**1g**	**2g**	46	20	**1t**	**2t**	79
8	**1h**	**2h**	77	21	**1u**	**2u**	65
9	**1i**	**2i**	46	22	**1v**	**2v**	80
10	**1j**	**2j**	67	23	**1w**	**2w**	80
11	**1k**	**2k**	80	24	**1x**[d]	**2x**	73
12	**1l**	**2l**	76	25	**1y**	**2y**	67
13	**1m**[d]	**2m**	60				

[a]Reactions were conducted on a 0.2 mmol scale in 2.0 mL of solvent. [b]Isolated yields. [c]3.0 mmol scale reaction (0.605 g). [d]Hydrazine tautomeric form.

product **2a** in 56% yield (Table 1, entry 1). Conducting the reaction at 0 °C instead of ambient temperature resulted in a slower and lower conversion (entry 2). The replacement of TFA by diphenyl phosphoric acid (DPP) under identical reaction conditions also decreased the yield of **2a** (entry 3). Additional variations of the initial conditions, including the use

https://doi.org/10.1021/acs.joc.1c02217
J. Org. Chem. 2021, 86, 17918−17929

of I_2 or $Cu(OTf)_2$ as a promoter, led to poorer results (entries 4 and 5). It was also found that basic additives such as DBU and K_2CO_3 had a detrimental effect, as lower yields were achieved (entries 6 and 7). Whereas $Cu(OTf)_2$ was crucial as an additive in previously reported iodine(III)-promoted oxidative C(sp^2)−H cycloamination,[18] here it showed lower efficiency (entry 8). Though a more rapid consumption of α-indolylhydrazone **1a** was observed with the use of a stoichiometric amount of TFA, the reaction only furnished 41% yield of the desired product **2a** (entry 9). Solvents like $CHCl_3$, CH_3OH, CH_3CN, and THF (entries 10−13) were substantially less efficient in terms of the product yield. While replacing PIDA with PIFA, HTIB (Koser's reagent), or PhIO failed to furnish better results (entries 14−16), at the switching of PIDA to other hypervalent iodine(V) oxidants[19] such as IBX, DMP, and iodylbenzene ($PhIO_2$), we were pleased to witness higher yields of **1a** into **2a** (entries 17−19). In particular, when $PhIO_2$ as an uncommon iodine(V) reagent (λ^5-iodane) was applied, the yield was improved to 82% (entry 19). A brief re-examination of the solvents still identified CH_2Cl_2 as optimal (entries 19−24). No improvement in yield was attained when the reaction was performed at 50 °C in DCE (entry 20) or when reducing the amount of $PhIO_2$ to 1.5 equiv (entry 25).

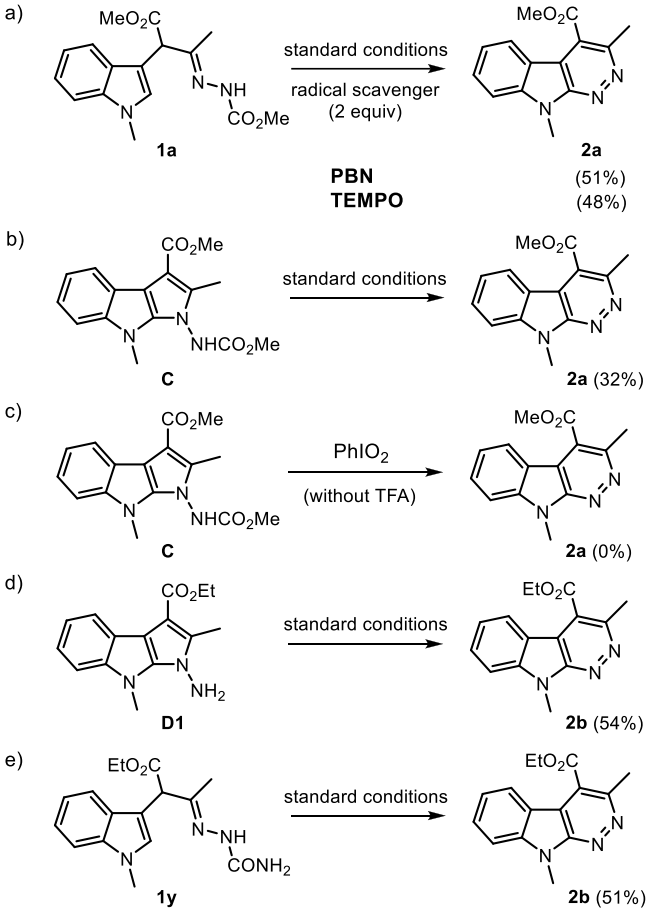
Control experiments also revealed that no product formation **2a** was detected in the absence of $PhIO_2$ (entry 26) or TFA (entry 27). This indicated that both $PhIO_2$ and TFA were essential for the reaction to proceed smoothly. Therefore, the optimal reaction conditions can be summarized as follows: 0.2 mmol of substrate in CH_2Cl_2 (2 mL) with $PhIO_2$ oxidant (2.3 equiv) and TFA additive (30 mol %) at room temperature for 5 h (Table 1).

With the optimal conditions in hand, the substrate scope and the limitations of the oxidative intramolecular C−H amination with $PhIO_2$ were investigated (Table 2). An array of α-indolylhydrazones **1a−y** were explored, resulting in the expected azacarbolines **2a−y** in good to excellent yields. As shown in Table 2, various substituents on the azacarboline skeleton were accommodated. Although the ester (R^3 = CO_2Me, CO_2Et, CO_2i-Pr, CO_2t-But, and CO_2Allyl) or phosphonate (R^3 = $PO(OMe)_2$) groups in substrates **1** were well supported, the tolerance of amide (R^3 = $CON(Me)_2$) as well as the phenyl (R^3 = Ph) group was lower. It was pleasing to find that incorporation of a bisindole moiety into the substrate proved a success, furnishing intriguing polyazaheterocyclic architecture **2j**. The reaction conditions were also suitable for substrates bearing R^4 alkyl groups, such as methyl, ethyl, and an *n*-propyl or ethyl acetate appendage. Various functional groups at the 4-, 5-, 6-, or 7-positions of the indole ring, regardless of electron-donating (Me, MeO, BnO) (**2q−2s**) and electron-withdrawing (Cl, Br, F, CO_2Me) ones (**2t−2x**), were compatible with the optimized conditions. Furthermore, indole substrates with *N*-methyl, *N*-propyl, and *N*-benzyl (R^1 = Me, *n*-Pr, Bn) substituents gave good yields of cyclized products. In contrast, the NH-free indole **1p** proceeded with poor conversion (21% yield), probably due to its attenuate intrinsic reactivity. Pleasantly, azacarboline **2y** incorporating a ring system between the N and C7 atoms of the indole ring was also prepared in good yield. It is important to note that this transformation allowed the installation of plural functionalities that are potentially well suited for future synthetic manipulations (for example, metal-catalyzed cross-coupling reactions, etc.). Interestingly, azacarboline with phosphorus substitution (**2h**) could serve as novel pharmaceuticals and agrochemicals.[20]

The cycloamination reaction of **1a** was also conducted on a 3 mmol scale, thus demonstrating the scalability of the present method (79% yield).

To gain insight into the reaction mechanism, we carried out further control experiments (Scheme 1).

Scheme 1. Control Experiments[a]



[a]PBN = *N*-*tert*-butyl-α-phenylnitrone; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl).

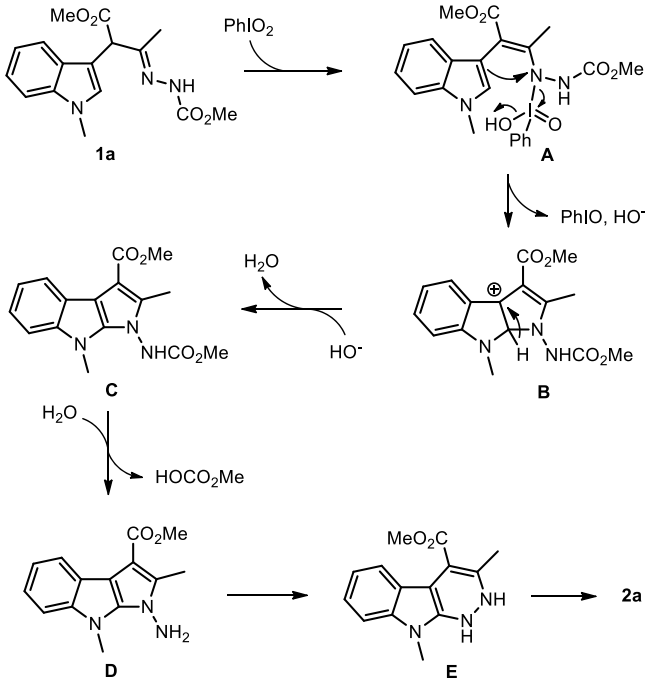
First, the application of *N*-*tert*-butyl-α-phenylnitrone (PBN)[21] or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)[9a] as a radical scavenger evidenced that the transformation of **1a** to **2a** was not suppressed (51% and 48% yield, respectively, Scheme 1a). This fact suggests that radical intermediates were not involved in this process. Second, the treatment of isolated five-membered cross-coupled product **C** (entries 22, 25, and 27, Table 1) under the reaction conditions was found to give product **2a** (Scheme 1b), the result of which indicated its effective involvement in the reaction mechanism. The preliminary formation of a less polar spot which gradually disappeared in favor of the final product **2a** (TLC monitoring) also confirmed that **C** was the productive intermediate for this transformation. On the other hand, the same intermediate **C** did not work when subjected with $PhIO_2$ alone (Scheme 1c). Third, when the prepared hydrolyzed pyrrolo[2,3-*b*]indole **D1** was subjected under standard conditions, the expected **2b** was successfully obtained (Scheme 1d). Lastly, substrate **1z** with an

https://doi.org/10.1021/acs.joc.1c02217
J. Org. Chem. 2021, 86, 17918−17929

amide N-protective group ($CONH_2$) also furnished the corresponding azacarboline **2b** in good yields (Scheme 1e).

Based on these results and in agreement with the previous references, a tentative mechanism for the oxidative C−H amination of α-indolylhydrazones is presented in Scheme 2.

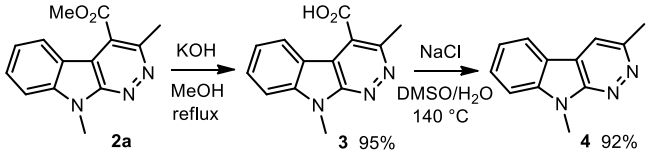
Scheme 2. Tentative Mechanism for the Oxidative C−H Amination



Initially, $PhIO_2$ reacts with **1a** to give an *N*-iodo intermediate **A** after a CH/NH tautomerization (1,3-H shift). The subsequent electrophilic cyclization (oxidative C−N bond formation) step takes place between C-2 of the indole and nitrogen activated by the electrophilic iodine species generating intermediate **B** with simultaneous loss of PhIO and HO^-. This was then followed by the formation of key pyrrolo[2,3-*b*]indole intermediate **C** through successive deprotonation and aromatization. Finally, the hydrolysis of a carbamic residue (intermediate **D**), ring expansion reaction,[22] and oxidative aromatization from **E** afford the desired azacarboline **2a**. The explanation for the role of TFA is not immediately intuited, but its beneficial effect is clearly demonstrated in these latter steps (see Scheme 1b, 1c, and 1d).[22] However, considering that the transformation of intermediate **C** into **2a** under standard conditions is not straightforward (32% yield, Scheme 1b), an alternative reaction pathway resulting from six-membered electrophilic cyclization may also be operative. In this case, the oxidative C−N bond formation would occur at the other nitrogen atom of the hydrazone residue, which could afford the final product **2a** after undergoing the hydrolysis and oxidative aromatization steps.[23]

To further demonstrate the potential and synthetic usefulness of this method, the generated azacarbolines were transformed as shown in Scheme 3. The ester group at the 4-position of **2a** could be easily hydrolyzed by treatment with KOH in methanol at reflux.[24] Decarboxylation was possible from **3** by heating at 140 °C in the presence of NaCl in $DMSO/H_2O$.[25]

Scheme 3. Transformation of Generated Azacarbolines



CONCLUSION

In conclusion, we have developed a practical, environmentally friendly, and metal-free methodology for intramolecular oxidative cyclization of α-indolylhydrazones at room temperature. Complementary with existing methods, this approach allows direct access to scarcely represented azacarbolines[14] via dehydrogenative $C(sp^2)$−N bond formation using the less emblazoned $PhIO_2$[26,27] hypervalent iodine(V) reagent. We believe that obtaining of such fused N-heterocyclic scaffolds that incorporate both the privileged indole and pyridazine core with the aid of a "forgotten" $PhIO_2$ through the not easy oxidative C−H/N−H cross coupling could open the way for further interesting novel applications.

EXPERIMENTAL SECTION

General Experimental Details. All the commercially available reagents and solvents were used without further purification. The following compounds were synthesized according to literature procedures: HTIB,[28] PhIO,[29] $PhIO_2$,[30] IBX,[31] and DMP.[32] *CAUTION!* PhIO, $PhIO_2$, and IBX are explosive under impact or heating to >200 °C, and appropriate precautions should be taken while handling these products. However, we have not experienced any explosions while working with these compounds at room temperature.

α-(Indol-3-yl)hydrazones **1a−i,k−z** were prepared according to our previously reported methods[16a,b] with a slight modification. Bis(indolyl)methane hydrazone **1j** was prepared following literature procedure.[16c] Chromatographic purification of compounds was carried out on silica gel (60−200 μm). TLC analysis was performed on preloaded (0.25 mm) glass-supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$ and 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using DMSO-d_6 or $CDCl_3$ as solvent on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA). Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, t = triplet, q = quartet, sex = sextet, sept = septet, m = multiplet, and br = broad signal. All coupling constants (*J* value) are given in Hertz [Hz]. High-resolution mass spectroscopy was performed on a Micromass Q-TOF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected.

General Procedure for the Preparation of α-(Indol-3-yl)hydrazones 1a−i,k−z.[16a,b] To a stirred mixture of indole (1.0 mmol) and azoalkene (1.5 mmol, 1.5 equiv) in dichloromethane (4 mL), zinc dichloride (13.6 mg, 0.1 mmol, 10 mol %) was added. (In order to obtain compound **1p**, the addition of DIPEA (174 μL, 1 mmol, 1 equiv) was required.) After the disappearance of indole (TLC check), the solvent was removed, and the crude mixture was purified by column chromatography on silica gel to afford, after crystallization, the α-(indol-3-yl)hydrazones **1**.

Procedure for the Preparation of Bis(indolyl)Methane Hydrazone 1j.[16c] 1-Methylindole (0.75 mL, 6 mmol, 4 equiv) was added to a previously stirred solution of Na_2CO_3 (1.59 g, 15 mmol, 10 equiv) in water (5 mL). The dichloroacetone hydrazone (298.5

https://doi.org/10.1021/acs.joc.1c02217
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mg, 1.5 mmol) in dichloromethane (5 mL) was added, and the reaction mixture was stirred at room temperature. Upon completion of the reaction (1 h, TLC check), the mixture was diluted with water (10 mL) and extracted with dichloromethane (3 × 20 mL), and the collected organic phases were dried over anhydrous Na_2SO_4. After filtration, the reaction was concentrated *in vacuo*, and the obtained crude was purified by flash chromatography to afford the bis(indolyl)-methane hydrazone **1j**.

The NMR spectra in DMSO-d_6 showed that compounds **1** exist predominantly in the hydrazone structure; however, signals related to the hydrazine tautomeric form can be also observed.

Methyl 2-(4-Methoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-lidene)hydrazinecarboxylate. Compound **1a** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 68% yield (216.8 mg) for 1 h; white solid; mp 122−124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.47−7.43 (m, 1H), 7.43−7.39 (m, 1H), 7.32 (s, 1H), 7.19−7.13 (m, 1H), 7.04−7.00 (m, 1H), 4.87 (s, 1H), 3.80 (s, 3H), 3.68 (s, 6H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.1, 154.5, 151.0, 136.5, 128.5, 126.8, 121.3, 119.0, 118.7, 109.8, 107.5, 51.9, 51.7, 51.3, 32.4, 14.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{20}N_3O_4$ 318.1448; Found 318.1445.

Methyl 2-(4-Ethoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1b** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 89% yield (294.0 mg) for 0.5 h; white solid; mp 119−121 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.47−7.45 (m, 1H), 7.42−7.40 (m, 1H), 7.32 (s, 1H), 7.18−7.14 (m, 1H), 7.04−7.00 (m, 1H), 4.84 (s, 1H), 4.20−4.12 (m, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.6, 154.6, 151.1, 136.5, 128.4, 126.8, 121.3, 119.0, 118.7, 109.8, 107.6, 60.6, 51.8, 51.4, 32.4, 14.4, 14.0; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1611.

***tert*-Butyl 2-(4-Isopropoxy-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate.** Compound **1c** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 84% yield (325.7 mg) for 1 h; white solid; mp 108−110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.43−7.39 (m, 1H), 7.30 (s, 1H), 7.17−7.12 (m, 1H), 7.05−7.00 (m, 1H), 4.98 (sept, J = 6.4 Hz, 1H), 4.76 (d, J = 0.4 Hz, 1H), 3.77 (s, 3H), 1.76 (s, 3H), 1.45 (s, 9H), 1.21 (t, J = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.1, 153.1, 150.3, 136.5, 128.3, 126.9, 121.3, 118.9, 118.8, 109.8, 107.8, 73.1, 68.0, 51.6, 32.4, 28.1, 21.5, 14.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{21}H_{30}N_3O_4$ 388.2231; Found 388.2226.

***tert*-Butyl 2-(4-(*tert*-Butoxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate.** Compound **1d** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 95% yield (380.1 mg) for 7 h; orange solid; mp 91−93 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.17−7.12 (m, 1H), 7.04−7.00 (m, 1H), 4.68 (s, 1H), 3.77 (s, 3H), 1.76 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.3, 153.6, 151.1, 137.0, 128.6, 127.4, 121.8, 119.4, 119.3, 110.2, 108.6, 81.2, 79.6, 52.9, 32.9, 28.6, 28.2, 14.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{32}N_3O_4$ 402.2387; Found 402.2400.

Methyl 2-(4-(Allyloxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1e** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 59% yield (203.9 mg) for 3 h; orange solid; mp 178−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.46 (dt, J = 8.0, 0.8 Hz, 1H), 7.41 (dt, J = 8.0, 0.8 Hz, 1H), 7.33 (s, 1H), 7.16 (td, J = 8.0, 0.8 Hz, 1H), 7.02 (td, J = 8.0, 0.8 Hz, 1H), 5.99−5.89 (m, 1H), 5.32−5.27 (m, 1H), 5.21−5.18 (m, 1H), 4.90 (s, 1H), 4.65−4.62 (m, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.8, 155.1, 151.4, 137.0, 133.0, 129.0, 127.3, 121.8, 119.5, 119.3, 118.4, 110.3, 107.9, 65.5, 52.3, 51.8, 32.9, 15.0; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{22}N_3O_4$ 344.1605; Found 344.1621.

***tert*-Butyl 2-(4-(Benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate.** Compound **1f** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 75% yield (325.6 mg) for 3 h; white solid; mp 118−120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.41−7.30 (m, 7H), 7.17−7.11 (m, 1H), 7.00 (t, J = 7.4 Hz, 1H), 5.21 (d, J = 12.4 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 4.91 (s, 1H), 3.75 (s, 3H), 1.78 (s, 3H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.6, 163.6, 153.0, 136.5, 136.0, 128.6, 128.3, 128.1, 128.0, 127.9, 126.9, 121.3, 118.9, 109.7, 107.6, 79.1, 66.0, 51.4, 32.4, 28.1, 14.6; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{25}H_{30}N_3O_4$ 436.2231; Found 436.2234.

***tert*-Butyl 2-(4-(Dimethylamino)-3-(1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate.** Compound **1g** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 82% yield (303.8 mg) for 24 h; white solid; mp 108−110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.17−7.13 (m, 1H), 7.03−7.00 (m, 1H), 5.02 (s, 1H), 3.76 (s, 3H), 2.88 (s, 3H), 2.87 (s, 3H), 1.73 (s, 3H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.4, 153.1, 136.6, 128.4, 126.8, 121.3, 118.9, 118.5, 109.8, 108.2, 79.0, 48.9, 37.0, 35.1, 32.4, 28.1, 14.9; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{20}H_{29}N_4O_3$ 373.2234; Found 373.2238.

Methyl 2-(1-(Dimethoxyphosphoryl)-1-(1-methyl-1*H*-indol-3-yl)propan-2-ylidene)hydrazinecarboxylate. Compound **1h** was isolated by column chromatography (ethyl acetate/methanol 95:5) in 69% yield (261.9 mg) for 18 h; orange solid; mp 159−161 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (br, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.18−7.14 (m, 1H), 7.06−7.02 (m, 1H), 4.55 (d, $^2J_{HP}$ = 24.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.67 (d, $^3J_{HP}$ = 10.4 Hz, 3H), 3.60 (d, $^3J_{HP}$ = 10.4 Hz, 3H), 1.85 (d, $^4J_{HP}$ = 1.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 154.7, 150.0, 136.3, 129.0 (d, $^3J_{CP}$ = 5.6 Hz), 127.3 (d, $^2J_{CP}$ = 10.5 Hz), 121.5, 119.0, 118.7, 109.8, 105.0 (d, $^3J_{CP}$ = 6.5 Hz), 53.0 (d, $^2J_{CP}$ = 6.8 Hz), 52.9 (d, $^2J_{CP}$ = 6.8 Hz), 51.9, 43.7 (d, $^1J_{CP}$ = 138.0 Hz), 32.5, 15.0 (d, $^3J_{CP}$ = 3.0 Hz); HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{23}N_3O_5P$ 368.1370; Found 368.1368.

Methyl 2-(1-(1-Methyl-1*H*-indol-3-yl)-1-phenylpropan-2-ylidene)hydrazinecarboxylate. Compound **1i** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 73% yield (244.2 mg) for 1 h; white solid; mp 179−181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.42−7.38 (m, 1H), 7.35−7.20 (m, 6H), 7.16−7.11 (m, 2H), 6.95 (t, J = 7.4 Hz, 1H), 5.19 (s, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 1.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.2, 141.5, 137.2, 128.9, 128.9, 128.7, 128.6, 127.5, 127.0, 121.7, 119.4, 119.1, 113.6, 110.1, 52.2, 51.4, 32.8, 15.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{20}H_{22}N_3O_2$ 336.1707; Found 336.1717.

Methyl 2-(1,1-Bis(1-methyl-1*H*-indol-3-yl)propan-2-ylidene)hydrazinecarboxylate. Compound **1j** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 24% yield (142.0 mg) for 1 h; white solid; mp 188−190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.16 (s, 2H), 7.16−7.12 (m, 2H), 7.00−6.96 (m, 2H), 5.40 (s, 1H), 3.74 (s, 6H), 3.67 (s, 3H), 1.83 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.6, 154.7, 136.7, 127.9, 127.1, 121.1, 119.0, 118.5, 113.1, 109.6, 51.7, 42.8, 32.3, 14.3; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{25}N_4O_2$ 389.1972; Found 389.1979.

Methyl 2-(1-Methoxy-2-(1-methyl-1*H*-indol-3-yl)-1-oxopentan-3-ylidene)hydrazinecarboxylate. Compound **1k** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 80% yield (264.1 mg) for 1 h; white solid; mp 124−126 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 7.51−7.49 (m, 1H), 7.41−7.39 (m, 1H), 7.33 (s, 1H), 7.17−7.13 (m, 1H), 7.03−7.00 (m, 1H), 4.88 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.45−2.35 (m, 1H), 2.21−2.12 (m, 1H), 0.74 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 154.5, 154.5, 136.5, 128.8, 127.0, 121.3, 119.0, 119.0, 109.7, 107.6, 51.8, 51.8, 49.9, 32.4, 21.0, 9.7; HRMS

https://doi.org/10.1021/acs.joc.1c02217
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(ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1598.

Methyl 2-(1-Methoxy-2-(1-methyl-1*H*-indol-3-yl)-1-oxohexan-3-ylidene)hydrazinecarboxylate. Compound **1l** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 73% yield (251.8 mg) for 2 h; white solid; mp 124−126 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.51−7.49 (m, 1H), 7.41−7.39 (m, 1H), 7.33 (s, 1H), 7.16−7.12 (m, 1H), 7.03−6.99 (m, 1H), 4.86 (s, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.42−2.35 (m, 1H), 2.13−2.06 (m, 1H), 1.31−1.07 (m, 2H), 0.74 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.1, 154.4, 153.4, 136.5, 128.8, 127.0, 121.2, 119.0, 118.8, 109.6, 107.6, 51.7, 51.7, 50.0, 32.3, 29.7, 18.2, 13.7. HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{24}N_3O_4$ 346.1761; Found 346.1752.

Diethyl 3-(2-(*tert*-Butoxycarbonyl)hydrazono)-2-(1-methyl-1*H*-indol-3-yl)pentanedioate. Compound **1m** was isolated as a hydrazine tautomeric form by column chromatography (ethyl acetate/cyclohexane 40:60) in 75% yield (333.1 mg) for 3 h; white solid; mp 150−152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.08 (br, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.03 (s, 1H), 6.98 (t, J = 7.2 Hz, 1H), 4.00−3.92 (m, 4H), 3.75 (s, 3H), 3.12 (s, 2H), 1.41 (s, 9H), 1.11 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.1, 168.7, 159.0, 156.9, 136.7, 130.1, 129.0, 121.3, 119.7, 119.0, 110.2, 110.0, 80.2, 60.8, 59.2, 35.9, 32.8, 28.5, 28.4, 14.8, 14.3; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{32}N_3O_6$ 446.2286; Found 446.2298.

Methyl 2-(4-Methoxy-4-*oxo*-3-(1-propyl-1*H*-indol-3-yl)-butan-2-ylidene)hydrazinecarboxylate. Compound **1n** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 70% yield (242.8 mg) for 1 h; white solid; mp 116−118 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.15−7.11 (m, 1H), 7.02−6.99 (m, 1H), 4.86 (s, 1H), 4.14−4.10 (m, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 1.76 (s, 3H), 1.75 (sex, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.1, 154.6, 151.0, 135.8, 127.6, 126.9, 121.3, 118.9, 118.8, 110.0, 107.5, 51.9, 51.8, 51.3, 47.0, 23.1, 14.3, 11.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{24}N_3O_4$ 346.1761; Found 346.1767.

Methyl 2-(3-(1-Benzyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1o** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 44% yield (147.1 mg) for 3 h; white solid; mp 128−130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.53 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.32−7.28 (m, 2H), 7.25−7.23 (m, 1H), 7.21−7.17 (m, 2H), 7.12−7.08 (m, 1H), 7.03−6.99 (m, 1H), 5.42 (s, 2H), 4.91 (s, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.1, 154.6, 150.9, 138.1, 135.9, 128.5, 128.1, 127.3, 127.1, 126.9, 121.5, 119.2, 118.9, 110.3, 108.2, 52.0, 51.8, 51.3, 49.0, 14.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{24}N_3O_4$ 394.1761; Found 394.1768.

Methyl 2-(3-(1*H*-Indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1p** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 23% yield (69.0 mg) for 6 h; whitish solid; mp 112−114 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.90 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.10−7.06 (m, 1H), 7.00−6.96 (m, 1H), 4.86 (s, 1H), 3.67 (s, 6H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.3, 154.6, 151.2, 136.1, 126.5, 124.3, 121.3, 118.9, 118.5, 111.6, 108.3, 51.9, 51.8, 51.4, 14.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{15}H_{18}N_3O_4$ 304.1292; Found 318.1297.

Methyl 2-(3-(1,5-Dimethyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1q** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (252.5 mg) for 0.25 h; white solid; mp 120−122 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 7.24−7.23 (m, 1H), 6.97 (dd, J = 8.4, 1.6 Hz, 1H), 4.82 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 2.36 (s, 3H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 154.6, 151.2, 135.0, 128.5, 127.5, 127.0, 123.0, 118.2, 109.6, 106.9, 52.0, 51.8, 51.2, 32.4, 21.3, 14.5; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1593.

Methyl 2-(4-Methoxy-3-(5-methoxy-1-methyl-1*H*-indol-3-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1r** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 62% yield (215.1 mg) for 0.5 h; white solid; mp 108−110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.30 (d, J = 9.2 Hz, 1H), 7.28 (s, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 9.2, 2.4 Hz, 1H), 4.84 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 117.2, 154.6, 153.4, 151.1, 131.8, 128.9, 127.2, 111.3, 110.6, 106.9, 100.8, 55.2, 52.0, 51.8, 51.3, 32.6, 14.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{22}N_3O_5$ 348.1554; Found 348.1543.

Methyl 2-(3-(4-(Benzyloxy)-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1s** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 32% yield (133.6 mg) for 1 h; white solid; mp 129−130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.50−7.48 (m, 2H), 7.40−7.37 (m, 2H), 7.33−7.29 (m, 1H), 7.05−6.98 (m, 3H), 6.59 (d, J = 7.2 Hz, 1H), 5.22 (s, 1H), 5.19 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.48 (s, 3H), 1.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.4, 154.5, 152.7, 151.1, 138.0, 137.2, 128.3, 127.5, 127.4, 126.9, 122.2, 116.9, 108.2, 103.2, 100.8, 69.1, 51.9, 51.7, 51.6, 32.6, 15.5; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{26}N_3O_5$ 424.1867; Found 424.1872.

Methyl 2-(3-(7-Chloro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1t** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 50% yield (174.6 mg) for 3 h; white solid; mp 130−132 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.00−6.96 (m, 1H), 4.88 (s, 1H), 4.08 (s, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 1.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.9, 154.6, 150.6, 131.7, 131.4, 130.2, 122.8, 120.1, 118.2, 116.0, 108.0, 52.1, 51.8, 51.0, 36.2, 14.5; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{19}ClN_3O_4$ 352.1059; Found 352.1054.

Methyl 2-(3-(4-Chloro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1u** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 32% yield (113.6 mg) for 2 h; white solid; mp 148−150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.42 (dd, J = 8.0, 0.8 Hz, 1H), 7.22 (s, 1H), 7.16−7.12 (m, 1H), 7.05 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 5.31 (s, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 3.64 (s, 3H), 1.92 (s, 3H). Interconversion to the hydrazine tautomeric form occurred during the carbon spectrum acquisition, and as a result, two distinct sets of signals of both hydrazone and hydrazine tautomers (ca. 50:50) were observed in DMSO-d_6 solution at 20 °C. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.3, 170.0, 162.2, 156.9, 154.5, 138.0, 137.7, 131.2, 130.1, 125.1, 124.7, 124.3, 123.4, 122.1, 121.6, 119.9, 119.4, 110.0, 109.4, 108.9, 108.1, 88.8, 52.2, 52.0, 51.8, 51.5, 50.4, 32.8, 32.6, 15.9, 15.9; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{19}ClN_3O_4$ 352.1059; Found 352.1051.

Methyl 2-(3-(5-Bromo-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1v** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 39% yield (156.3 mg) for 1 h; white solid; mp 155−157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.42−7.40 (m, 2H), 7.26 (dd, J = 8.8, 2.0 Hz, 1H), 4.89 (s, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.67 (s, 3H), 1.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.9, 154.6, 150.8, 130.3, 130.2, 128.6, 123.8, 121.3, 112.0, 111.7, 107.3, 52.0, 51.8, 51.0, 32.6, 14.7; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{19}BrN_3O_4$ 396.0553; Found 396.0545.

Methyl 2-(3-(6-Fluoro-1-methyl-1*H*-indol-3-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1w** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 56% yield (187.2 mg) for 1 h; white solid; mp 140−142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.42 (dd, J = 8.8 Hz,

https://doi.org/10.1021/acs.joc.1c02217
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$^4J_{HF}$ = 5.6 Hz, 1H), 7.33 (s, 1H), 7.29 (dd, $^3J_{HF}$ = 10.4 Hz, J = 2.4 Hz, 1H), 6.91−6.86 (m, 1H), 4.86 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.34 (s, 3H), 1.77 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 171.0, 159.0 (d, $^1J_{CF}$ = 233.6 Hz), 154.5, 150.9, 136.6 (d, $^3J_{CF}$ = 12.3 Hz), 129.1 (d, $^4J_{CF}$ = 3.3 Hz), 123.5, 120.0 (d, $^3J_{CF}$ = 10.2 Hz), 107.9, 107.4 (d, $^2J_{CF}$ = 24.4 Hz), 96.2 (d, $^2J_{CF}$ = 25.9 Hz), 52.0, 51.8, 51.2, 32.6, 14.5; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{19}FN_3O_4$ 336.1354; Found 336.1358.

Methyl 3-(1-Methoxy-3-(2-(methoxycarbonyl)hydrazono)-1-oxobutan-2-yl)-1-methyl-1*H*-indole-4-carboxylate. Compound **1x** was isolated as the hydrazine tautomeric form by column chromatography (ethyl acetate/cyclohexane 50:50) in 64% yield (200.3 mg) for 1 h; white solid; mp 162−164 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.45 (br, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 6.4 Hz, 1H), 7.21−7.17 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.36 (s, 3H), 1.67 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.3, 169.2, 161.3, 157.4, 137.7, 133.0, 125.7, 124.8, 121.3, 120.3, 113.8, 110.8, 91.2, 52.6, 52.5, 50.6, 32.9, 16.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{18}H_{22}N_3O_6$ 376.1503; Found 376.1499.

Methyl 2-(3-(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate. Compound **1y** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 44% yield (152.5 mg) for 1 h; white solid; mp 138−140 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.31 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 4.85 (s, 1H), 4.13 (t, J = 5.6 Hz, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 2.90 (t, J = 6.0 Hz, 2H), 2.14−2.08 (m, 2H), 1.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 171.3, 154.6, 151.3, 133.8, 125.8, 124.4, 121.9, 119.4, 118.3, 116.3, 107.5, 51.9, 51.8, 51.6, 43.4, 24.0, 22.3, 14.5; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{18}H_{22}N_3O_4$ 344.1605; Found 344.1604.

Ethyl 3-(2-Carbamoylhydrazono)-2-(1-methyl-1*H*-indol-3-yl)butanoate. The chemical−physical data of compound **1z** are in agreement with those previously reported.[16b]

General Procedure for the Synthesis of Azacarbolines 2 via $PhIO_2$-Mediated Intramolecular Oxidative Cyclization of α-Indolylhydrazones 1. To a stirred mixture of α-indolylhydrazone **1** (0.2 mmol) in dichloromethane (2 mL) were added $PhIO_2$ (108.6 mg, 0.46 mmol, 2.3 equiv) and TFA (5 μL, 0.06 mmol, 30 mol %). After that, the solution was stirred overnight at room temperature. The crude product was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate) to give the corresponding product **2**.

Methyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 82% yield (41.7 mg); yellow solid; mp 112−114 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 8.0 Hz, 1H), 7.81−7.77 (m, 2H), 7.38−7.34 (m, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 2.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.6, 152.8, 146.8, 142.7, 131.2, 124.9, 121.7, 120.9, 115.9, 114.9, 110.5, 53.2, 28.1, 20.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{14}N_3O_2$ 256.1081; Found 256.1078.

Ethyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 75% yield (40.2 mg); yellow solid; mp 127−129 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.79−7.77 (m, 2H), 7.38−7.33 (m, 1H), 4.61 (q, J = 7.2 Hz, 2H), 4.04 (s, 3H), 2.82 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.1, 152.8, 146.7, 142.6, 131.1, 124.9, 122.1, 120.8, 115.9, 114.8, 110.5, 62.4, 28.1, 20.2, 13.9; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_2$: 270.1237; Found 270.1240.

Isopropyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 67% yield (38.1 mg); yellow solid; mp 105−107 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.82−7.76 (m, 2H), 7.41−7.33 (m, 1H), 5.47 (sept, J = 6.4 Hz, 1 H), 4.04 (s, 3H), 2.82 (s, 3H), 1.44 (d, J = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.6, 152.8, 146.4, 142.6, 131.1, 124.7, 122.5, 120.8, 115.9, 114.6, 110.6, 70.5, 28.1, 21.4, 20.0; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_2$ 284.1394; Found 284.1390.

***tert*-Butyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate.** Compound **2d** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 56% yield (33.4 mg); yellow solid; mp 160−162 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 1H), 7.80−7.76 (m, 2H), 7.41−7.35 (m, 1H), 4.04 (s, 3H), 2.81 (s, 3H), 1.69 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.4, 152.9, 146.2, 142.5, 131.0, 124.4, 123.4, 120.9, 115.9, 114.2, 110.6, 84.1, 28.1, 27.7, 19.9; HRMS (ESI/Q-TOF) m/z $[M + H]^+$Calcd for $C_{17}H_{20}N_3O_2$ 298.1550; Found 298.1561.

Allyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 71% yield (39.8 mg); yellow solid; mp 102−104 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.15 (dt, J = 8.0, 0.8 Hz, 1H), 7.80−7.78 (m, 2H), 7.37−7.33 (m, 1H), 6.20−6.10 (m, 1H), 5.53−5.48 (m, 1H), 5.40−5.36 (m, 1H), 5.10 (dt, J = 6.0, 1.2 Hz, 2H), 4.05 (s, 3H), 2.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.8, 152.8, 146.7, 142.7, 131.6, 131.1, 124.9, 121.7, 120.7, 119.7, 115.9, 114.8, 110.5, 66.6, 28.1, 20.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_2$ 282.1237; Found 282.1245.

Benzyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2f** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 59% yield (39.0 mg); yellow solid; mp 132−134 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.0 Hz, 1H), 7.78−7.41 (m, 2H), 7.47−7.38 (m, 3H), 7.58−7.54 (m, 2H), 7.24−7.19 (m, 1H), 5.64 (s, 2H), 4.03 (s, 3H), 2.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.9, 152.8, 146.6, 142.6, 134.9, 131.1, 129.1, 128.7, 128.6, 124.9, 121.9, 120.7, 115.8, 114.8, 110.5, 67.9, 28.1, 20.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{18}N_3O_2$ 332.1394; Found 332.1387.

***N*,*N*,3,9-Tetramethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxamide.** Compound **2g** was isolated by column chromatography (ethyl acetate/cyclohexane 100:0) in 46% yield (24.7 mg); yellow solid; mp 154−156 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.82−7.72 (m, 3H), 7.38−7.32 (m, 1H), 4.04 (s, 3H), 3.24 (s, 3H), 2.77 (s, 3H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.6, 152.5, 145.9, 142.1, 130.6, 126.2, 123.3, 120.9, 116.3, 113.9, 110.4, 36.7, 33.9, 28.0, 18.9; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{17}N_4O$ 269.1397; Found 269.1404.

Dimethyl (3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indol-4-yl)-phosphonate. Compound **2h** was isolated by column chromatography (ethyl acetate/cyclohexane 100:0) in 77% yield (46.8 mg); yellow solid; mp 137−139 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 8.0 Hz, 1H), 7.82−7.75 (m, 2H), 7.39−7.33 (m, 1H), 4.05 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.03 (d, J = 1.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 152.2 (d, $^2J_{CP}$ = 11.0 Hz), 151.2 (d, $^2J_{CP}$ = 10.2 Hz), 143.1, 131.3, 127.9, 120.6, 120.1 (d, $^3J_{CP}$ = 8.8 Hz), 116.8, 116.7, 116.3 (d, $^1J_{CP}$ = 178.0 Hz), 110.1, 52.7 (d, $^2J_{CP}$ = 5.2 Hz), 28.1, 22.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{17}N_3O_3P$ 306.1002; Found 306.1006.

3,9-Dimethyl-4-phenyl-9*H*-pyridazino[3,4-*b*]indole. Compound **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 46% yield (24.9 mg); yellow solid; mp 166−168 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.73−7.59 (m, 5H), 7.56−7.49 (m, 2H), 7.11−7.03 (m, 2H), 4.03 (s, 3H), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 152.9, 149.0, 142.1, 135.2, 132.7, 129.9, 129.2, 128.9, 128.3, 123.5, 120.1, 117.5, 116.6, 110.2, 28.0, 20.0; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{18}H_{16}N_3$ 274.1339; Found 274.1332.

3,9-Dimethyl-4-(1-methyl-1*H*-indol-3-yl)-9*H*-pyridazino[3,4-*b*]indole. Compound **2j** was isolated by column chromatography (ethyl acetate/cyclohexane 90:10) in 67% yield (43.7 mg); orange solid; mp 106−108 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60−7.56 (m, 1H), 7.30−7.26 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02−7.00 (m, 2H), 6.98−6.94 (m, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 2.66 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 152.8, 150.8, 142.0, 136.7,

https://doi.org/10.1021/acs.joc.1c02217
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129.6, 129.5, 126.6, 125.8, 124.2, 121.9, 119.8, 119.7, 119.4, 118.0, 117.6, 110.7, 109.8, 107.5, 32.9, 28.0, 20.5; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{21}H_{19}N_4$ 327.1604; Found 327.1593.

Methyl 3-Ethyl-9-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2k** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 80% yield (43.3 mg); yellow solid; mp 148−150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 8.0 Hz, 1H), 7.79−7.75 (m, 2H), 7.38−7.32 (m, 1H), 4.14 (s, 3H), 4.05 (s, 3H), 3.14 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.6, 152.6, 151.2, 142.6, 131.0, 124.5, 121.5, 120.9, 115.9, 114.7, 110.5, 53.2, 28.1, 26.8, 14.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_2$ 270.1237; Found 270.1254.

Methyl 9-Methyl-3-propyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (43.1 mg); yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.0 Hz, 1 H), 7.81−7.74 (m, 2 H), 7.38−7.32 (m, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 1.76 (sex, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.7, 152.6, 150.1, 142.5, 131.1, 124.5, 121.9, 120.9, 115.9, 114.7, 110.6, 53.3, 35.2, 28.1, 23.2, 13.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_2$ 284.1394; Found 284.1408.

Ethyl 3-(2-Ethoxy-2-oxoethyl)-9-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 60% yield (41.3 mg); yellow solid; mp 102−104 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (dt, J = 8.0, 0.8 Hz, 1H), 7.81−7.77 (m, 2H), 7.39−7.33 (m, 1H), 4.54 (q, J = 7.2 Hz, 2H), 4.38 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 4.05 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.3, 165.5, 153.3, 145.1, 142.9, 131.4, 126.0, 122.2, 120.9, 116.2, 115.7, 110.5, 62.4, 60.7, 28.2, 14.0, 13.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{18}H_{20}N_3O_4$ 342.1448; Found 342.1439.

Methyl 3-Methyl-9-propyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2n** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 78% yield (44.2 mg); yellow solid; mp 144−146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.76 (dt, J = 7.2, 1.2 Hz, 1H), 7.35 (dt, J = 7.2, 1.2 Hz, 1H), 4.58 (t, J = 7.6 Hz, 2H), 4.13 (s, 3H), 2.82 (s, 3H), 1.86 (sex, J = 7.6 Hz, 2H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.5, 152.6, 146.7, 142.1, 131.1, 124.9, 121.8, 120.8, 115.9, 114.7, 110.7, 53.1, 43.0, 21.4, 20.1, 11.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_2$ 284.1394; Found 284.1399.

Methyl 9-Benzyl-3-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 76% yield (50.5 mg); yellow solid; mp 132−134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.73 (dt, J = 8.0, 1.2 Hz, 1H), 7.35 (dt, J = 8.0, 1.2 Hz, 1H), 7.31−7.21 (m, 5H), 5.87 (s, 2H), 4.13 (s, 3H), 2.83 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.4, 152.7, 147.4, 141.9, 136.9, 131.3, 128.6, 127.5, 127.1, 125.1, 121.9, 121.2, 116.2, 115.1, 110.9, 53.3, 44.7, 20.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{18}N_3O_2$ 332.1394; Found 332.1387.

Methyl 3-Methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2p** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 21% yield (10.0 mg); yellow solid; mp 200−202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (br, 1H), 8.09 (dt, J = 8.4, 0.8 Hz, 1H), 7.72−7.68 (m, 1H), 7.62−7.60 (m, 1H), 7.33−7.29 (m, 1H), 4.13 (s, 3H), 2.81 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.7, 154.0, 146.6, 142.0, 131.1, 124.9, 121.7, 120.6, 116.4, 114.9, 112.2, 53.1, 20.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{12}N_3O_2$ 242.0924; Found 242.0932.

Methyl 3,6,9-Trimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2q** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 79% yield (42.7 mg); yellow solid; mp 118−120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 8.4, 1.2 Hz, 1H), 4.13 (s, 3H), 4.01 (s, 3H), 2.80 (s, 3H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.7, 152.9, 146.6, 141.0, 132.6, 129.9, 124.4, 121.7, 115.9, 114.7, 110.4, 53.3, 28.2, 21.0, 20.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_2$ 270.1237; Found 270.1255.

Methyl 6-Methoxy-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]-indole-4-carboxylate. Compound **2r** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 81% yield (46.1 mg); yellow solid; mp 117−119 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 9.2 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 9.2, 2.4 Hz, 1H), 4.13 (s, 3H), 4.00 (s, 3H), 3.85 (s, 3H), 2.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.5, 153.9, 153.0, 146.5, 137.7, 121.4, 120.8, 116.1, 114.6, 111.5, 106.7, 55.5, 53.1, 28.2, 20.3; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_3$ 286.1186; Found 286.1183.

Methyl 5-(Benzyloxy)-9-methyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2s** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 80% yield (57.9 mg); yellow solid; mp 176−178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (t, J = 8.4 Hz, 1H), 7.48−7.44 (m, 2H), 7.37−7.33 (m, 2H), 7.30−7.26 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.46 (s, 2H), 3.99 (s, 3H), 3.79 (s, 3H), 2.69 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.8, 155.9, 152.0, 145.8, 143.9, 136.5, 132.4, 128.5, 127.8, 127.4, 124.0, 112.6, 106.0, 103.7, 102.7, 69.5, 52.4, 28.3, 19.4; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{21}H_{20}N_3O_3$ 362.1499; Found 362.1505.

Methyl 8-Chloro-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2t** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 79% yield (45.8 mg); orange solid; mp 140−142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 4.35 (s, 3H), 4.12 (s, 3H), 2.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.2, 153.2, 147.5, 137.8, 132.5, 123.9, 122.0, 121.8, 119.1, 116.3, 114.2, 53.4, 31.2, 20.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{13}ClN_3O_2$ 290.0691; Found 290.0697.

Methyl 5-Chloro-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2u** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 65% yield (37.4 mg); orange solid; mp 144−146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77−7.72 (m, 2H), 7.39 (dd, J = 7.2, 1.6 Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 2.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.1, 151.7, 146.2, 143.9, 131.7, 129.8, 124.3, 121.9, 114.1, 111.7, 109.6, 52.9, 28.6, 19.6; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{13}ClN_3O_2$ 290.0691; Found 290.0705.

Methyl 6-Bromo-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2v** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 80% yield (53.7 mg); yellow solid; mp 131−133 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.8, 2.0 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 4.13 (s, 3H), 4.04 (s, 3H), 2.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.3, 152.9, 147.7, 141.6, 133.7, 127.5, 121.8, 117.7, 114.2, 112.8, 112.5, 53.3, 28.3, 20.6; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{13}BrN_3O_2$ 334.0186; Found 334.0182.

Methyl 7-Fluoro-3,9-dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylate. Compound **2w** was isolated by column chromatograpy (ethyl acetate/cyclohexane 30:70) in 80% yield (43.5 mg); yellow solid; mp 188−190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.2 Hz, 1H), 7.66 (dd, $^3J_{HF}$ = 10.4 Hz, J = 2.4 Hz, 1H), 7.17−7.12 (m, 1H), 4.11 (s, 3H), 3.98 (s, 3H), 2.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.2, 164.9 (d, $^1J_{CF}$ = 249.4 Hz), 154.1, 148.7, 144.7 (d, $^3J_{CF}$ = 12.5 Hz), 128.0 (d, $^3J_{CF}$ = 10.9 Hz), 121.8, 116.5, 113.6, 109.6 (d, $^2J_{CF}$ = 24.1 Hz), 96.6 (d, $^2J_{CF}$ = 26.8 Hz), 53.0, 28.5, 21.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{13}FN_3O_2$ 274.0986; Found 274.0993.

Dimethyl 3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4,5-dicarboxylate. Compound **2x** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 73% yield (45.8 mg); brown solid; mp 136−138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (dd, J = 8.4, 0.8 Hz, 1H), 7.87 (dd, J = 8.4, 7.6 Hz, 1H), 7.79 (dd, J = 7.6,

https://doi.org/10.1021/acs.joc.1c02217
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0.8 Hz, 1H), 4.12 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 167.6, 166.4, 152.5, 147.3, 143.1, 130.4, 129.6, 123.4, 122.4, 114.6, 113.7, 113.5, 52.5, 52.5, 28.4, 20.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_4$ 314.1135; Found 314.1146.

Methyl 10-Methyl-5,6-dihydro-4*H*-pyridazino[4′,3′:4,5]-pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate. Compound **2y** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 67% yield (37.5 mg); yellow solid; mp 130−132 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 7.2, 0.8 Hz, 1H), 7.23 (dd, J = 8.0, 7.2 Hz, 1H), 4.46 (t, J = 6.0 Hz, 2H), 4.12 (s, 3H), 3.08 (t, J = 6.0 Hz, 2H), 2.83 (s, 3H), 2.24 (quint, J = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.6, 152.0, 146.8, 139.5, 128.6, 122.6, 122.6, 121.8, 120.7, 115.5, 114.1, 53.1, 40.2, 24.2, 21.2, 20.4; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O_2$ 282.1237; Found 282.1239.

Methyl 1-((Methoxycarbonyl)amino)-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carboxylate. Intermediate **C** (entries 22, 25, and 27, Table 1) was isolated as a byproduct by column chromatography (ethyl acetate/cyclohexane 40:60); mp 164−166 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (br, 1H), 7.93 (dd, J = 8.0, 0.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.19−7.14 (m, 1H), 7.12−7.08 (m, 1H), 3.89 (s, 3H), 3.79 (s, 6H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.1, 156.2, 139.7, 136.5, 136.3, 120.6, 120.1, 119.7, 119.2, 109.5, 102.7, 102.1, 53.3, 50.9, 29.1, 10.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{18}N_3O_4$ 316.1292; Found 316.1288.

Ethyl 1-Amino-2,8-dimethyl-1,8-dihydropyrrolo[2,3-*b*]-indole-3-carboxylate. Compound **D1** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 30% yield (22.5 mg); red solid; mp 168−170 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.93−7.91 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.12−7.08 (m, 1H), 7.06−7.02 (m, 1H), 6.02 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 2.62 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.0, 139.9, 137.5, 137.4, 120.4, 119.8, 119.5, 118.6, 109.1, 102.1, 100.2, 58.9, 29.7, 14.7, 10.7; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{18}N_3O_2$ 272.1394; Found 272.1388.

Hydrolysis of 2a. To a solution of **2a** (127.6 mg, 0.5 mmol) in MeOH (5 mL) was added KOH (280.0 mg, 5 mmol, 10 equiv). The mixture was refluxed (heating mantle) until the disappearance of **2a** (1.5 h, TLC check). The reaction mixture was cooled to r.t. and the solvent evaporated *in vacuo*. The residue was dissolved in water (2 mL) and acidified to pH 2 via the addition of 4 N aq HCl under stirring at 0 °C. The precipitate was filtered off, washed with diethyl ether, and dried to afford compound **3** as a yellow solid.

3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole-4-carboxylic Acid. compound **3** was isolated in 95% yield (114.2 mg); yellow solid; mp 248−250 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 14.57 (br, 1H), 8.22 (dt, J = 8.0, 0.8 Hz, 1H), 7.80−7.77 (m, 2H), 7.39−7.35 (m, 1H), 4.04 (s, 3H), 2.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 167.2, 152.8, 146.4, 143.2, 131.6, 125.1, 124.5, 121.1, 116.1, 116.0, 110.7, 28.3, 19.5; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{12}N_3O_2$ 242.0924; Found 242.0916.

Decarboxylation of 3. To a solution of compound **3** (48.2 mg, 0.2 mmol) in DMSO/water (10:1, 2 mL) was added NaCl (81.8 mg, 1.4 mmol, 7 equiv). The solution was stirred at 140 °C (oil bath) until the disappearance of the starting material (24 h, TLC check). After cooling to room temperature, the mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL), washed with brine (10 mL), and dried over anhydrous sodium sulfate. The residue was purified by column chromatography on silica gel to give the product **4**.

3,9-Dimethyl-9*H*-pyridazino[3,4-*b*]indole. Compound **4** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 92% yield (36.2 mg); light brown solid; mp 142−144 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.31−8.30 (m, 1H), 8.28 (s, 1H), 7.74−7.69 (m, 2H), 7.36−7.32 (m, 1H), 3.98 (s, 3H), 2.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 152.4, 150.7, 142.2, 130.4, 123.7, 120.4, 119.5, 118.0, 117.6, 110.2, 28.0, 21.5; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{12}N_3$ 198.1026; Found 198.1031.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02217.

Copies of NMR spectra for all products (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a−z**, **2a−y**, **C**, **D1**, **3**, and **4** (ZIP)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the University of Urbino "Carlo Bo" for the financial support. The authors also thank Dr. P. Caputo for his precious collaboration and Dr. Anna Maria Gioacchini who competently performed the mass spectra.

■ DEDICATION

This work is dedicated to Prof. Paolino Filippone, colleague, coauthor, and friend, who passed away on September 17, 2020.

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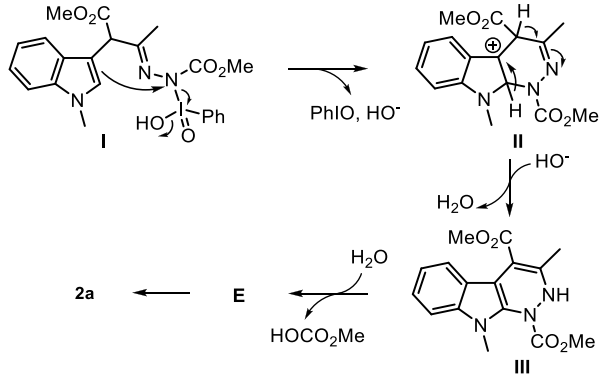

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