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TFA-catalyzed Q-Tube Reactor-Assisted Strategy for the Synthesis of Pyrido[1,2-*b*][1,2,4]triazine and Pyrido[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole Derivatives

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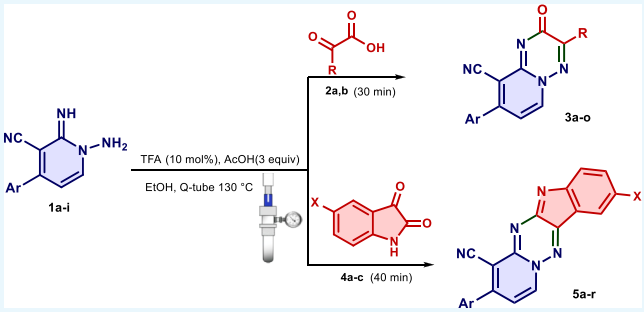
ABSTRACT: An efficient high-pressure-assisted trifluoroacetic acid-catalyzed protocol for synthesizing unreported novel pyrido-[1,2-*b*][1,2,4]triazine and pyrido[1′,2′:2,3][1,2,4]triazino[5,6-*b*]-indole derivatives has been established. This strategy includes the condensation reactions of various 1-amino-2-imino-4-arylpyridine-3-carbonitrile derivatives with indoline-2,3-dione (isatin) derivatives and α-keto acids such as pyruvic acid and phenylglyoxylic acid. This strategy includes utilizing the Q-tube reactor as an efficient and safe tool to conduct these reactions under high-pressure conditions. In addition, trifluoroacetic acid was used to induce this transformation. In this research, conducting the targeted reactions under high pressure using the Q-tube reactor was found to be superb in comparison to that under the traditional refluxing conditions. X-ray single-crystal analysis was utilized in this study to authenticate the structure of the synthesized products.



INTRODUCTION

Fused heterocycles containing nitrogen are distinctive building blocks because they are the primary motifs for many natural products and efficiently incorporated in a broad range of heterocyclic compounds that have a significant pharmaceutical effect.[1−3] As such, these ring systems are often considered as important pillars for the design and development of new pharmaceutically active molecules and drugs.[4,5] Pyrido-triazine derivatives and their analogy are among these significant heterocycles, which have shown distinct and diverse biological activities such as anticancer,[6] anti-avian influenza virus (H5N1),[7] antioxidant,[8] antibacterial,[9,10] antifungal,[11] antimicrobial,[12] and antiviral[13] functions. Moreover, some examples of this class of compounds can act as sirtuin modulators,[14] HIV integrase inhibitors,[15] and antagonists of the histamine H3 receptor.[16] In addition, some pyrido-triazine members showed optical,[17,18] fluorescence,[19] and corrosion inhibition properties.[20] Also, when indole fused or combined with other heterocyclic compounds, it gave them patentable bioactive characteristics and features such as anticancer,[21−23] antituberculosis,[24] anti-HIV,[25] anticonvulsant,[26] antiviral, anti-inflammatory, antibacterial, and antiparasitic properties.[27,28] It is therefore anticipated that the fusion of the indole moiety with the pyrido-triazine system could serve as a privileged nucleus for many biological evaluation. The synthesis of the fused pyrido-triazine derivatives has drawn the interest of chemists around the world. A variety of methods have been developed to synthesize these systems due to the particular properties and applications mentioned above. As shown in Scheme 1, the majority of the reported methods[11,17] used 1,6-diamino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile as a precursor. Following our efforts to synthesize new heterocyclic compounds through eco-friendly green approaches[29−36] and after thorough literature survey, it was noted that the use of 1-amino-2-imino-4-arylpyridine-3-carbonitrile derivatives as precursors to synthesize pyrido[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole and pyrido-[1,2-*b*][1,2,4]triazine derivatives has not been reported to date. The current research involves the reaction of 1-amino-2-imino-4-arylpyridines with indoline-2,3-dione (isatin) and α-keto acids such as pyruvic acid and phenylglyoxylic acid, under high-pressure conditions, using a Q-tube reactor. It is important to note that when the reaction between 1-amino-2-imino-4-arylpyridines and 1,2-dioxo compounds was carried out in AcOH as described in the previous procedures, the desired pyrido-triazine was not produced. The formed product was identified as the corresponding triazolo[1,5-*a*]pyridine derivatives,[34,36] which were generated via the reaction of 1-amino-2-imino-pyridine with AcOH rather than 1,2-dioxo compounds. Even when EtOH/H_3BO_4 is used, the reaction does not work,

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Scheme 1. Previous and Current Work for the Synthesis of Pyrido[1,2-*b*][1,2,4]triazine Derivatives

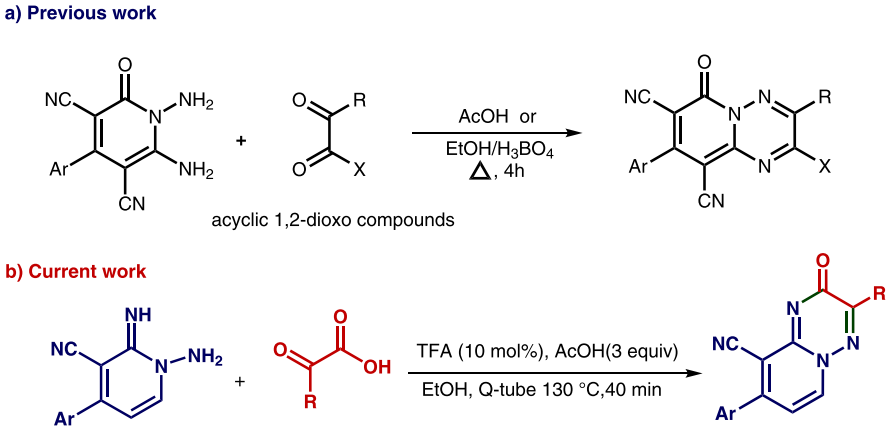
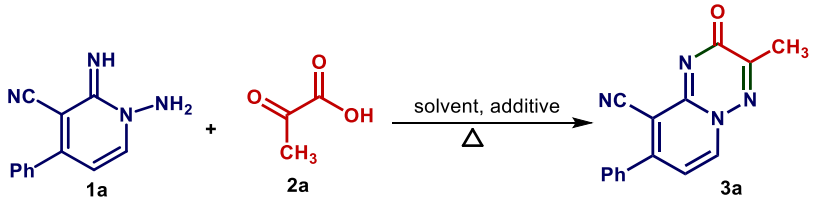


Table 1. Optimization Reaction of 1-Amino-2-imino-pyridine 1a with Pyruvic Acid 2a[a]



entry	solvent	additive (equiv)	temp (°C)	time	yield (%)
1	EtOH	none	120	12 h	0
2	CH_3CN	none	120	12 h	0
3	1,4-dioxane	none	120	12 h	0
4	DMSO	none	140	12 h	0
5	Toluene	none	140	12 h	0
6	EtOH	AcOH (4)	120	12 h	48
7	EtOH	PivOH (4)	120	12 h	33
8	EtOH	PTSA (4)	120	12 h	16
9	EtOH	H_3BO_4 (4)	130	12 h	21
10	EtOH	AcOH (4) + TFA (10 mol %)	130	5 h	72
11	EtOH	AcOH (5) + TFA (10 mol %)	130	5 h	72
12	EtOH	AcOH (3) + TFA (10 mol %)	130	5 h	72
13	EtOH	AcOH (2) + TFA (10 mol %)	130	5 h	64
14[b]	EtOH	AcOH (3) + TFA (10 mol %)	120	40 min	89
15[b]	EtOH	AcOH (3) + TFA (10 mol %)	130	40 min	94
16[b]	EtOH	TFA (10 mol %)	130	40 min	trace

[a]Reaction conditions: independent mixtures of 1-amino-2-imino-pyridine **1a** (5 mmol) and pyruvic acid **2a** (5 mmol) in the solvent (15 mL) containing the additive, by refluxing at the indicated temp (°C), for the reported time. [b]Reaction conditions: independent mixtures of 1-amino-2-imino-pyridine **1a** (5 mmol) and pyruvic acid **2a** (5 mmol) in the solvent (15 mL) containing the additive were charged in the glass tube of the Q-tube reactor and heated in an oil bath at the indicated temp (°C), for 40 min.

and no products are produced. After much effort, we were able to carry out the desired reactions in the current work by employing the conditions stated in Scheme 1 to produce the corresponding pyrido-triazine derivatives in high yield, as shown later. Herein, the Q-tube was used as a high-pressure tool in this study to carry out the current reactions in a low-cost, safe, and eco-sustainable way. The Q-tube is distinguished from conventional heating and MW irradiation by a number of characteristics and features,[37−40] including enhanced yield and performance, a cleaner product profile resulting in lighter color (fewer byproducts and impurities), energy savings, a shorter reaction time, and higher repeatability and being less costly and safer due to the ease of pressing and sealing; as a result, the explosion that may occur when using a typical sealed tube is avoided. Such intriguing and distinguishing features compelled us to employ the Q-tube technique in our research to investigate the effect of high pressure on the reactions proliferating.

RESULTS AND DISCUSSION

On the basis of immense pharmaceutical activities of pyrido-triazine and indole-clubbed systems, it is noteworthy to synthesize pyrido[1,2-*b*][1,2,4]triazine and pyrido[1′,2′:2,3]-[1,2,4]-triazino[5,6-*b*]indole derivatives in a safe and green manner. Initially, a series of 1-amino-2-imino-4-arylpyridine-3-carbonitrile **1a−f** have been synthesized according to the literature;[33] then, compound **1a** was selected to study and estimate the optimal conditions for its reaction with pyruvic acid as an example for α-keto acids. Hence, our investigation began by conducting the reaction between 1-amino-2-imino-pyridine **1a** (5 mmol) and pyruvic acid **2a** (5 mmol) in different solvents

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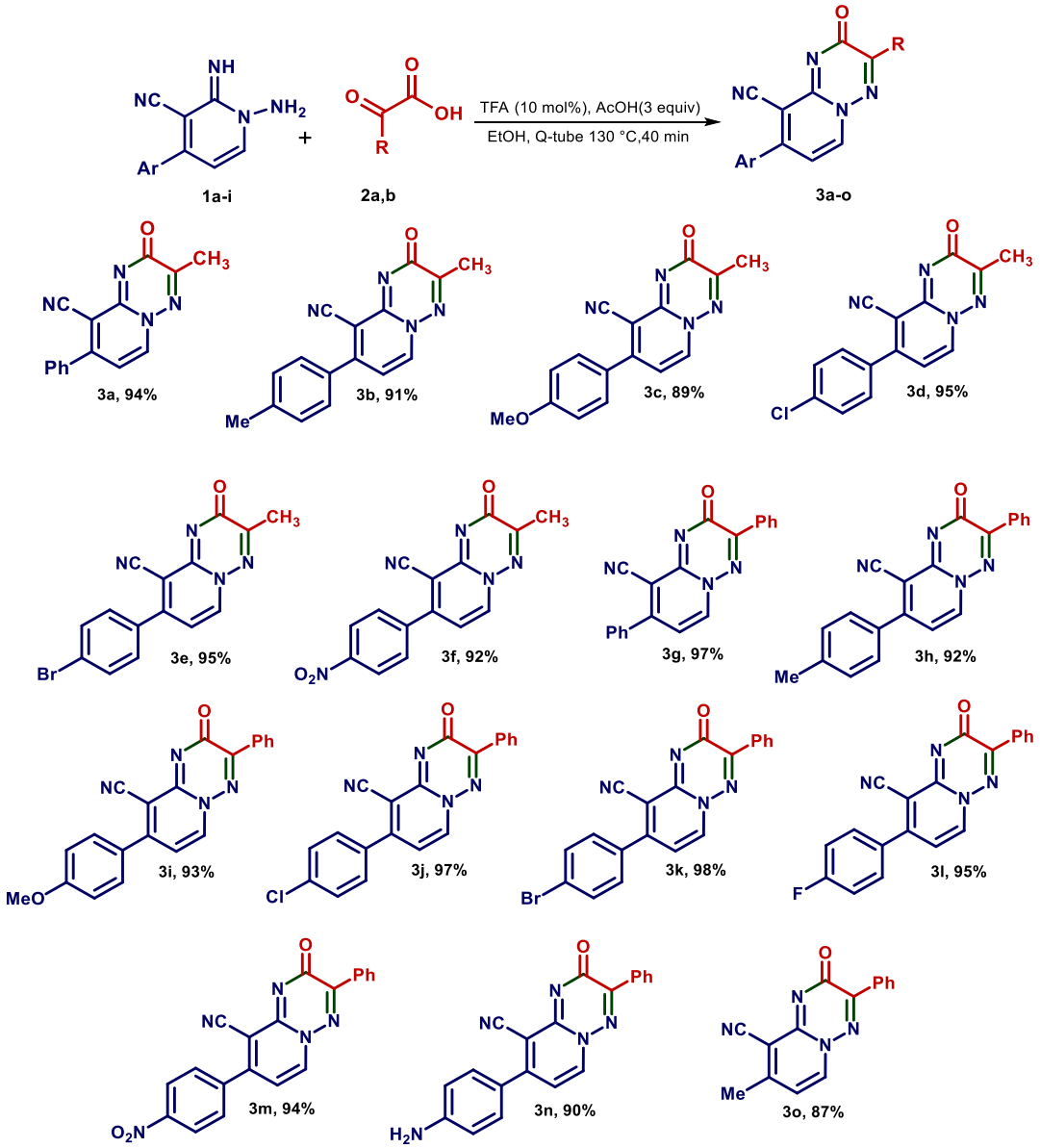
ACS Omega 2021, 6, 16086−16099

Table 2. Cyclocondensation Reactions between *N*-Aminopyridines 1a−i and α-keto Acids 2a,b Using the Q-Tube[a]



[a]Reaction conditions: independent mixtures of 1-amino-2-imino-pyridine **1** (5 mmol) and α-keto acids **2a**,**b** (5 mmol), in EtOH (15 mL), TFA (10 mol %), and AcOH (3 equiv), were charged in the glass tube of the Q-tube reactor and heated in an oil bath at 130 °C for 40 min.

under the ordinary conventional heating conditions to investigate the solvent effect on this reaction profile. Various solvents such as EtOH, acetonitrile, dioxane, dimethyl sulfoxide (DMSO), and toluene (15 mL) have been applied to conduct the abovementioned reaction at refluxing temperature and normal pressure for 12 h. It was found that using these types of solvents did not configure any products. On the other hand, using AcOH or dimethylformamide (DMF) led to the formation of triazolo[1,5-*a*]pyridine derivatives through its reaction with 1-amino-2-imino-pyridine **1a**.[34,36] Interestingly, when the reaction was carried out in EtOH as a solvent containing glacial AcOH (4 equiv) as an additive at reflux for 12 h at 130 °C, the reaction performed well to provide the corresponding 3-methyl-2-oxo-8-phenyl-2*H*-pyrido[1,2-*b*][1,2,4]-triazine-9-carbonitrile (**3a**) in 48% yield (Table 1, entry 6); the assigned structure for **3a** was verified on the basis of the various spectroscopic data, such as MS, HRMS, ^{1}H NMR, and ^{13}C{^{1}H} NMR spectra; furthermore, the X-ray crystallographic technique was used to successfully assign and confirm the structure of an example from this series, 3c, as shown later. Subsequently, we ran the above-modeled reaction under a variety of conditions, in order to boost the reaction yield, as shown in Table 1; the best reaction medium was found to be EtOH/AcOH since acids other than AcOH such as PivOH, PTSA, and H_3BO_4 did not work well, Table 1, entries 6−9. Surprisingly, it was found that addition of 10 mol % from TFA to the reaction mixture enhances the reaction rate and yield (72%), as shown in Table 1, entry 10. After that, the AcOH loading has been monitored (Table 1, entries 10−13) to study its effect on the reaction yield, and it was found that using 3 equiv from AcOH is optimal for the best reaction yield, Table 1, entry 12. Finally, in order to compare carrying out the model reaction under the traditional refluxing conditions with heating under sealed conditions, the Q-tube reactor was used for this purpose to conduct the reaction under

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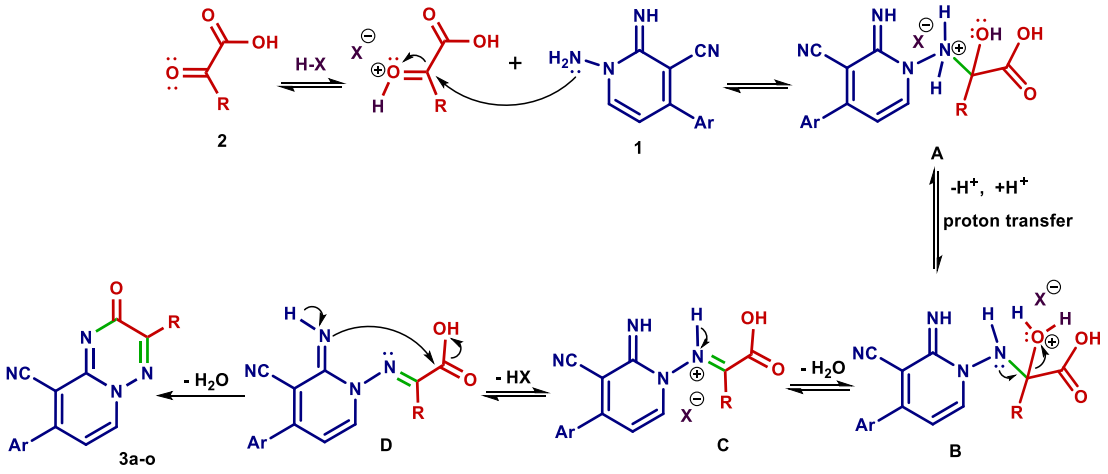
Scheme 2. Plausible Mechanistic Route for the Formation of Pyrido[1,2-*b*][1,2,4]triazine Derivatives 3a−o



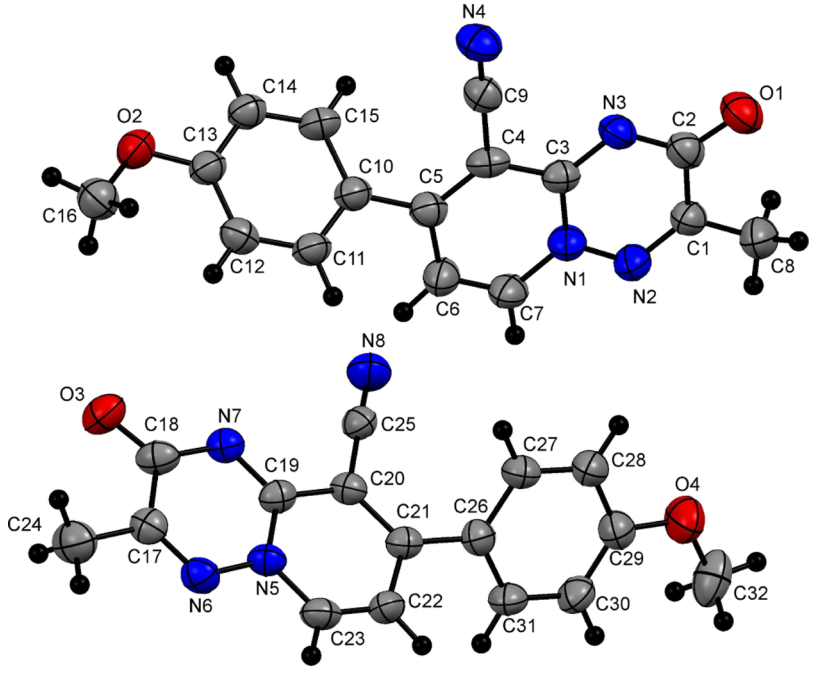


Figure 1. X-ray crystallographic analysis determined for **3c**.

high-pressurized conditions in a safe manner to avoid the accidental explosion that may happen when an ordinary sealed tube was used. Hence, when the model reaction [1-amino-2-imino-pyridine **1a** (5 mmol) and pyruvic acid **2a** (5 mmol) in EtOH (15 mL), TFA (10 mol %), and AcOH (2 equiv)] was carried out using the Q-tube reactor and by heating in an oil bath at 130 °C for 40 min, it yielded **3a** in 94% (Table 1, entry 15), so using the Q-tube reactor was preferred rather than using traditional reflux for this reaction. It is important to note that the presence of AcOH acid is needed for the completion of the abovementioned reaction (entry 16) because it serves two functions: it acts as a co-solvent to make the reaction mixture soluble and it works with TFA to activate the carbonyl carbons to make them more electrophilic, facilitating the nucleophilic addition of the $N-NH_2$ moiety to the α-carbonyl carbon.

Additional research was conducted to investigate the generalization and limits of the aforementioned TFA-induced di-condensation reaction (Table 2) under the optimized conditions achieved from the explorative model reaction (entry 15, Table 1). For this purpose, a variety of *N*-amino-2-iminopyridines **1b−i** were synthesized in order to ascertain their condensation reactions with pyruvic acid and phenylglyoxylic acid as examples for α-keto acids under the defined optimum conditions. It is noted that, preferably, the first stage of these reactions proceeds through a condensation reaction between the amino group attached to the pyridine ring ($N-NH_2$) and the keto moiety at the 2 position rather than the 1-keto function of the α-keto acid to enable the non-isolable hydrazone intermediate to endure a further condensation reaction between the hydroxyl moiety of the carboxylic group and the imino group at C2 (C═NH) to afford the desired pyrido[1,2-*b*][1,2,4]-triazine derivatives **3a−o** in an excellent yield (Table 2, Scheme 2). As noted during this investigation, the aryl moiety of 1-aminopyridine at C-4 is either phenyl or phenyl substituted with electron-donating/withdrawing substituents that did not have a major effect on the reaction yield; however, in general, the yield in the case of phenylglyoxylic acid is marginally better than in the case of pyruvic acid, as shown in Table 2. After several trials, we

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were able to obtain a suitable crystal for the X-ray single-crystallographic measurements in the case of compound **3c** to support the abovementioned finding without any doubt (Figure 1, Table 3).

Table 3. Some Selected Bond Lengths and Angles for Compound 3c

bond	bond length (Å)	bond	bond angle (deg)
C5−C10	1.480(9)	C3−C4−C6	123.4(5)
C5−C6	1.406(9)	C5−C6−C7	120.6(6)
C4−C9	1.451(8)	C4−C5−C10	123.1(5)
C1−C8	1.478(9)	C2−C1−C8	119.5(6)
N1−C3	1.389(7)	C2−N3−C3	118.5(5)
N1−C7	1.368(8)	N1−N2−C1	116.2(5)
N1−N2	1.377(7)	N1−C3−N3	122.9(5)
C2−O1	1.225(8)	N4−C9−C4	176.3(6)
Cl3−O2	1.375(8)	C13−O2−C16	117.1(5)

A possible mechanistic route for the formation of pyrido[1,2-*b*][1,2,4]triazine derivatives **3a−o** is depicted in Scheme 2. The presence of acid makes carbonyl carbons more electrophilic because the proton from acid attaches to the carbonyl oxygen and enfeebles the C═O bond. The nucleophilic addition of the amino group attached to the pyridine ring (N−NH_2) to the carbonyl carbon is now easier, resulting in the adduct **A**, which is converted to the intermediate **B** during a proton transfer process. The intermediate **C** was then formed by separating one water molecule through the good leaving group (OH_2^+) to allow the formation of imine-intermediate **D** via the loss of a HX molecule. Further nucleophilic addition of the imino group at C-2 (C═NH) to the imide-keto moiety enables the formation of final targeted products **3a−o**, through the loss of another water molecule.

Continuing the evaluation of the existing methodological technique, the findings of additional research have also shown that this Q-tube-assisted TFA-induced di-condensation reaction was successfully conducted when indoline-2,3-dione (isatin) derivatives (**4a−c**) were used as cyclic 1,2-dioxo substrates. Hence, reacting 1-amino-2-iminopyridines **1** (5 mmol) with isatin, 5-bromoisatin, and 5-nitroisatin (**4a−c**) (5 mmol) utilizing the defined optimized conditions [EtOH (15 mL), TFA (10 mol %), AcOH (3 equiv), and the Q-tube reactor at 130 °C for 30 min] provided the corresponding pyrido-[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole derivatives **5a−r** in excellent yields (Table 4). It is noted that during this reaction, the 5-bromoisatin and 5-nitroisatin provided better yield than isatin itself. Owing to the crystalline behavior exhibited by this class of compounds, the structure of certain compounds such as **5a**, **d**, **g**, **j**, **m**, and **5o** has been verified by the use of single-crystal X-ray crystallography, as shown in Figures 2−7, Table 5.

A rational mechanistic pathway was postulated for the formation of pyrido[1′,2′:2,3][1,2,4]-triazino[5,6-*b*]indole derivatives **5a−r** (Scheme 3), which was preferably initiated by the nucleophilic addition of the amino group attached to the pyridine ring (N−NH_2) to the keto moiety of the isatin derivatives pendent at position 3 rather than the imide-keto moiety to enable the formed imine-intermediate B (through losing one water molecule) to undergo further nucleophilic addition of the imino group at C2 (C═NH) to the imide-keto moiety to form the adduct C, which further loses one water molecule to furnish finally the targeted products pyrido-[1′,2′:2,3]-[1,2,4]triazino[5,6-*b*]indole derivatives **5a−r**.

CONCLUSIONS

In summary, the abovementioned research led to the development of an effective and straightforward Q-tube-assisted TFA-catalyzed reaction of 1-amino-2-imino-4-arylpyridine-3-carbonitrile derivatives with indoline-2,3-dione (isatin) derivatives and α-keto acids such as pyruvic acid and phenylglyoxylic acid, via utilizing the Q-tube reactor as an efficient and safe tool to conduct these reactions under high-pressurized conditions, to design an unprecedented class from the pyrido[1,2-*b*][1,2,4]-triazine and pyrido[1′,2′:2,3][1,2,4]-triazino[5,6-*b*]indole derivatives in superb yields. This strategy includes a variety of features and characteristics including quick, safe procedures, easy operation and purification, the ability to apply to a wide range of substrates, and high atom economy. We assume that this protocol may provide a basis for potential applications of these heterocycles, particularly in the field of medicinal and industrial chemistry.

EXPERIMENTAL SECTION

General. Melting points were recorded on a Griffin melting point apparatus and were uncorrected. IR spectra were recorded using KBr disks and a Jasco FT-IR-6300 spectrophotometer. ^{1}H NMR (600 MHz) and ^{13}C{^{1}H} NMR (150 MHz) spectra were recorded at 25 °C using DMSO-d_6 or TFA-*d* as solvents with tetramethylsilane as an internal standard on a Bruker DPX 600 super-conducting NMR spectrometer. Chemical shifts (δ) were reported in ppm. Low-resolution electron impact mass spectra [MS (EI)] and high-resolution electron impact mass spectra [HRMS (EI)] were characterized using a high-resolution GC−MS (DFS) thermo-spectrometer at 70.1 eV and a magnetic sector mass analyzer. Following the courses of reactions, checking the homogeneity of products was performed using thin-layer chromatography (TLC). The reactions were conducted using a Q Labtech Q-tube (distributed by Sigma-Aldrich), equipped with a stainless-steel adapter attached with a pressure gauge (300 psi), a needle adapter, a borosilicate glass pressure tube (35 mL), a Teflon sleeve, a PTFE-faced silicone septa, and a catch bottle. The X-ray crystallographic data were collected using a Bruker X8 Prospector at room temperature using Cu Kα radiation. The structures were solved using direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The structures were solved and refined using the Bruker SHELXTL software package (Structure solution program, SHELXS-97, and refinement program, SHELXL-97).[41] Data were corrected for the absorption effects using the multi-scan method (SADABS). The crystal images were created using Mercury software (version 3.8).[42]

General Procedure for the Preparation of Compounds 3a−o and 5a−r. A mixture of 1-amino-2-imino-pyridine **1a−i** (5 mmol) and α-keto acids **2a**,**b** (5 mmol) or isatin derivatives **4a−c** (5 mmol), in EtOH (15 mL) containing TFA (10 mol %) and AcOH (3 equiv), was charged in the Q-tube pressure reactor tube (35 mL, borosilicate glass); then, the PTFE-faced silicon septa were placed on the top of the tubes, and the proper cap and pressure adapter were firmly fitted to prevent any leak of vapor pressure. The mixtures were heated in an oil bath at 130 °C for 40 min in the case of α-keto acids and for 30 min in the case of isatin derivatives. All the reactions were monitored by the use of GC/MS and TLC. After completion, the reaction mixtures were cooled and the pressure was released; the formed solids were collected by filtration, washed with water and then EtOH, and

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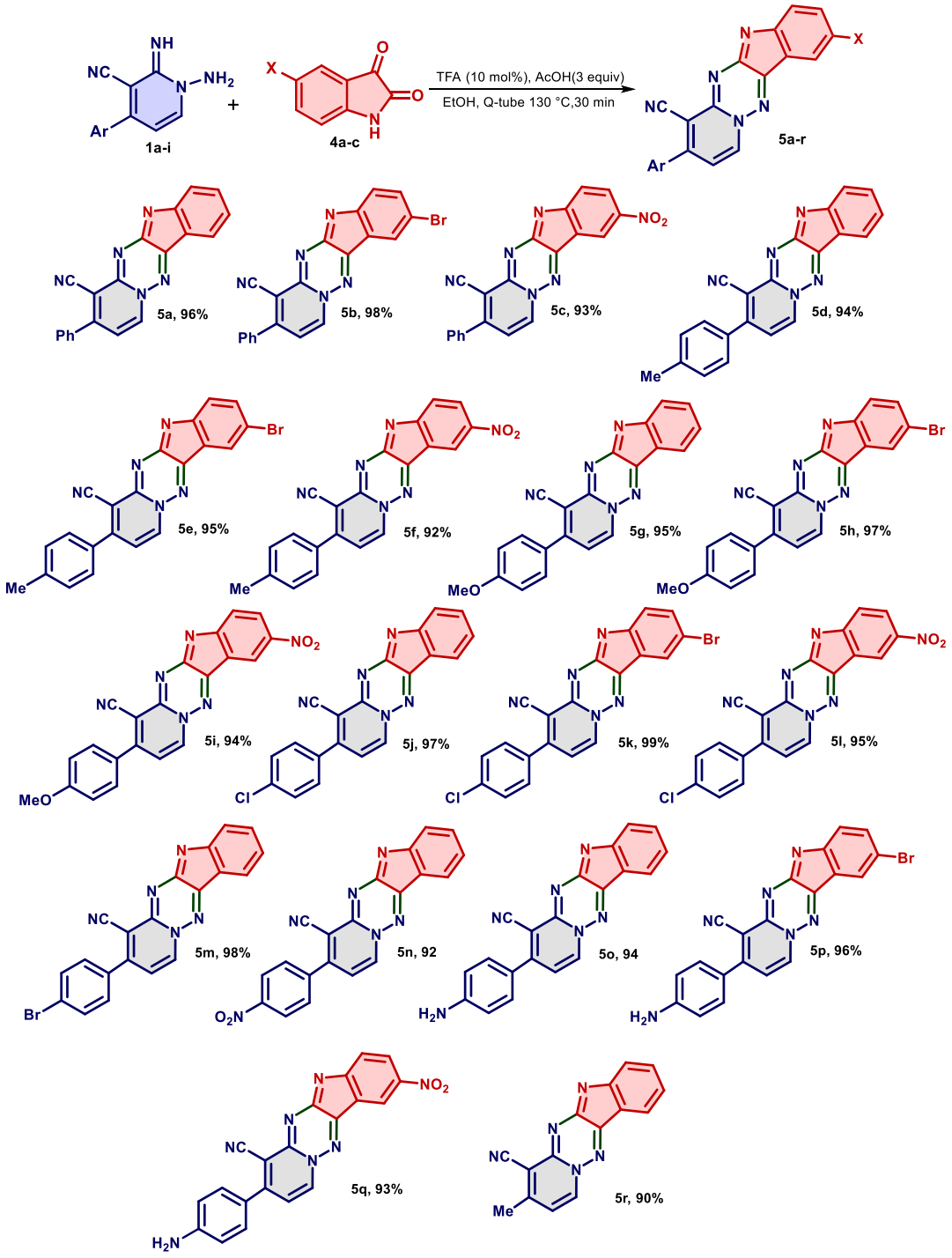
Table 4. Cyclocondensation Reactions between *N*-Aminopyridine 1 and Isatin Derivatives 4 Using the Q-Tube[a]



[a]Reaction conditions: independent mixtures of 1-amino-2-imino-pyridine **1** (5 mmol) and isatin derivatives **4a−c** (5 mmol), in EtOH (15 mL), TFA (10 mol %), and AcOH (3 equiv), were charged in the glass tube of the Q-tube reactor and heated in an oil bath at 130 °C for 30 min.

left to dry. The formed solids were recrystallized from the proper solvents or a mixture of solvents (see below), to give pyrido[1,2-*b*]-[1,2,4]triazines **3a−o** and pyrido[1′,2′:2,3][1,2,4]-triazino-[5,6-*b*]indoles **5a−r** as pure products.

*3-Methyl-2-oxo-8-phenyl-2H-pyrido[1,2-b][1,2,4]triazine-9-carbonitrile (**3a**).* Recrystallized from the EtOH/dioxane mixture (4:1), as a yellowish white crystal, yield: 1.21 g (94%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2234 (C≡N), 1647 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.37 (s, 3H, C*H*$_3$), 7.29 (d, J = 7.2 Hz, 1H, C−*H6*), 7.64−7.65 (m, 3H, Ar−H), 7.78−7.79 (m, 2H, Ar−H), 8.72 (d, J = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 17.66 (CH_3), 103.11, 113.82, 114.28, 128.67, 129.09, 131.20, 134.48, 140.35, 151.84, 156.56, 157.90, 159.63; MS (EI): m/z (%) 263 (M^+ + 1, 30.01), 262 (M^+, 49.21). HRMS (EI): m/z calcd for $C_{15}H_{10}N_4O$ (M^+), 262.0849; found, 262.0848.

*3-Methyl-2-oxo-8-p-tolyl-2H-pyrido[1,2-b][1,2,4]triazine-9-carbonitrile (**3b**).* Recrystallized from the EtOH/dioxane

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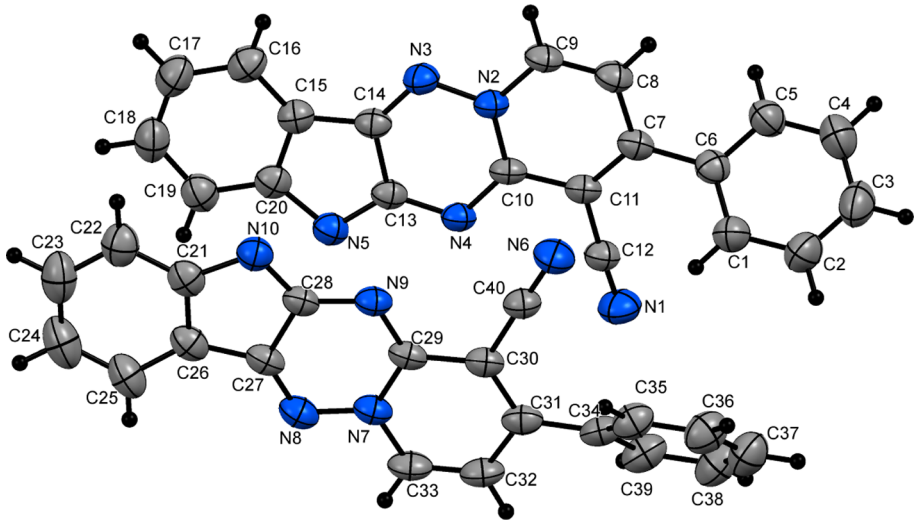

Figure 2. X-ray crystallographic analysis determined for **5a**.

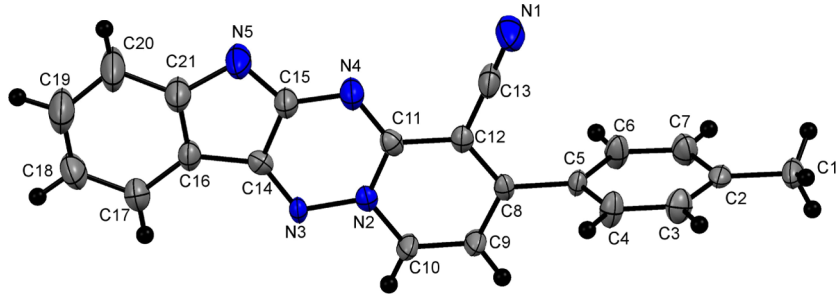

Figure 3. X-ray crystallographic analysis determined for **5d**.

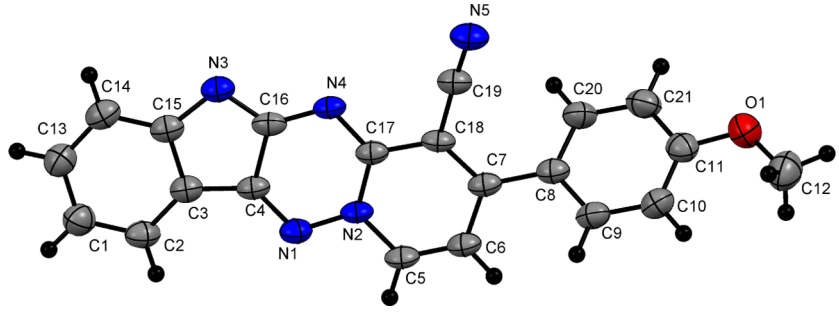

Figure 4. X-ray crystallographic analysis determined for **5g**.

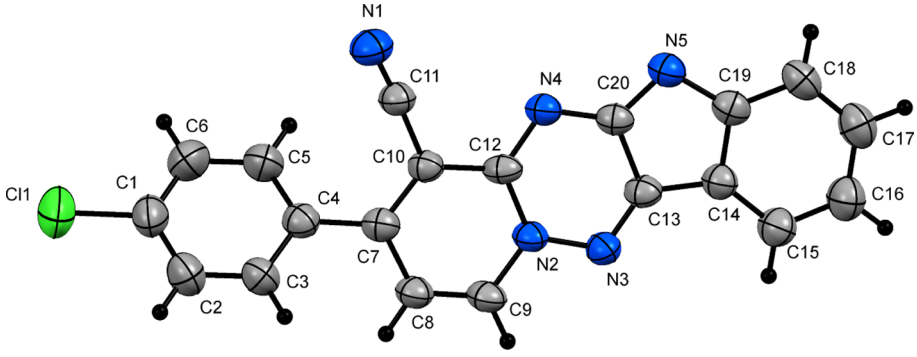

Figure 5. X-ray crystallographic analysis determined for **5j**.

mixture (4:1), as a yellowish white crystal, yield: 125 g (91%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2235 (C≡N), 1647 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.27 (d, J = 7.2 Hz, 1H, C−*H6*), 7.45 (d, J = 7.8

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ACS Omega 2021, 6, 16086−16099

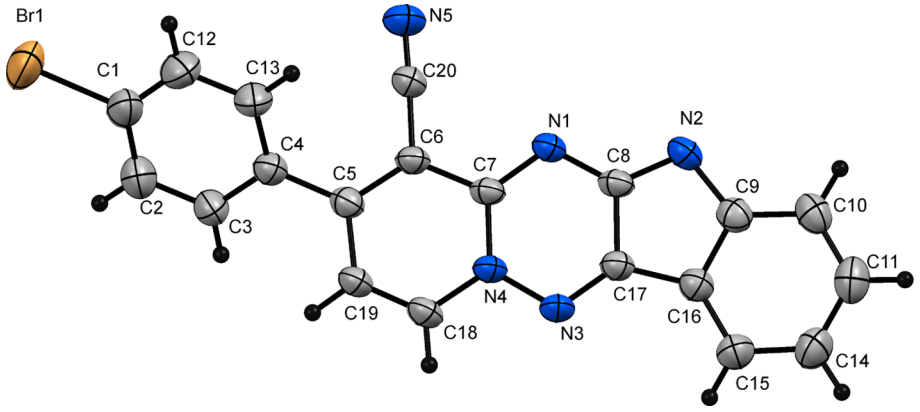

Figure 6. X-ray crystallographic analysis determined for **5m**.

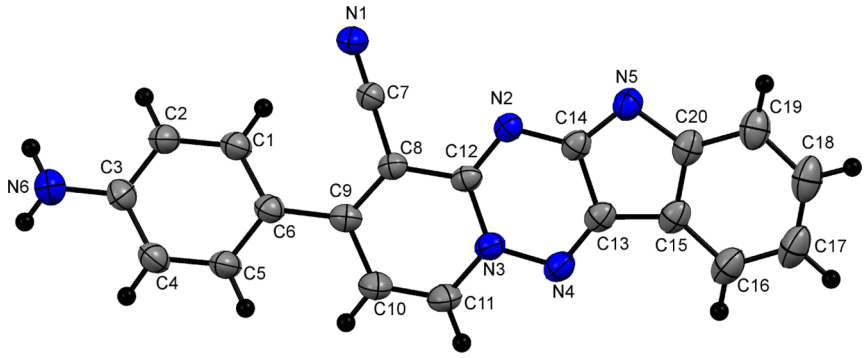

Figure 7. X-ray crystallographic analysis determined for **5o**.

Table 5. Some Selected Bond Lengths and Angles for Compound 5g

bond	bond length (Å)	bond	bond angle (deg)
C3−C15	1.415(6)	C1−C2−C3	118.3(5)
C3−C4	1.415(7)	C3−C4−C16	105.9(4)
C4−C16	1.484(6)	C5−C6−C7	120.8(5)
C6−C7	1.415(6)	C4−C3−C15	103.9(4)
N1−C4	1.303(6)	C15−N3−C16	104.8(4)
N3−C16	1.321(6)	C16−N4−C17	114.7(4)
N1−N2	1.370(5)	C4−N1−N2	114.0(4)
N5−C19	1.147(6)	N5−C19−C18	175.7(5)
O1−C11	1.372(6)	C11−O1−C12	117.6(5)

Hz, 2H, Ar−H), 7.69 (d, J = 7.8 Hz, 2H, Ar−H), 8.68 (d, J = 7.2 Hz, 1H, C*H*-7); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 17.69, 21.00 (2CH_3), 102.61, 113.81, 114.47, 128.71, 129.72, 131.60, 140.24, 141.58, 151.94, 156.53, 157.83, 159.72; MS (EI): m/z (%) 277 (M^+ + 1, 28.64), 276 (M^+, 54.91). HRMS (EI): m/z calcd for $C_{16}H_{12}N_4O$ (M^+), 276.1006; found, 276.1006.

*8-(4-Methoxyphenyl)-3-methyl-2-oxo-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3c**).* Recrystallized from the EtOH/dioxane mixture (4:1), as a yellowish white crystal, yield: 1.30 g (89%), mp 286−287 °C; IR (KBr): ν/cm^{-1} 2233 (C≡N), 1659 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 2.87 (s, 3H, OCH_3), 7.19 (d, J = 8.4 Hz, 2H, Ar−H), 7.28 (d, J = 7.2 Hz, 1H, C−*H6*), 7.80 (d, J = 8.4 Hz, 2H, Ar−H), 8.66 (d, J = 7.2 Hz, 1H, C*H*-7); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 17.58 (CH_3), 55.53 (OCH_3), 101.74, 113.61, 114.59, 114.64, 126.30, 130.65, 139.91, 151.98, 155.92, 157.59, 159.63, 161.78; MS (EI): m/z (%) 293 (M^+ + 1, 2.85), 292 (M^+, 7.32). HRMS (EI): m/z calcd for $C_{16}H_{12}N_4O_2$ (M^+), 292.0955; found, 292.0953. Crystal Data, moiety formula: $C_{16}H_{12}N_4O_2$, M = 292.30, triclinic, a = 7.867(2) Å, b = 10.818(2) Å, c = 16.305(3) Å, V = 1371.8(4) Å^3, α = 94.407(7)°, β = 91.928(7)°, γ = 97.087(7)°, space group: $P\bar{1}$ (#2), Z = 4, D_{calc} = 1.415 g·cm^{-3}, no. of reflection measured: 10,889, unique: 4829, $2\theta_{max}$ = 50.1°, R_1 = 0.0830 (CCDC 2068868).[43]

*8-(4-Chlorophenyl)-3-methyl-2-oxo-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3d**).* Recrystallized from the EtOH/dioxane mixture (4:1), as a yellowish white crystal, yield: 1.40 g (95%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2230 (C≡N), 1658 (C═O); ^{1}H NMR (600 MHz, TFA-d): δ 2.83 (s, 3H, CH_3), 7.75 (d, J = 8.4 Hz, 2H, Ar−H), 7.87 (d, J = 8.4 Hz, 2H, Ar−H), 8.02 (d, J = 7.2 Hz, 1H, C−*H6*), 9.02 (d, J = 7.2 Hz, 1H, C*H*-7); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-d): δ 18.43 (CH_3), 101.89, 112.04, 123.41, 132.43, 132.57, 132.80, 144.41, 144.69, 150.11, 155.49, 164.16, 164.87; MS (EI): m/z (%) 297 (M^+ + 1, 1.69), 296 (M^+, 4.53). HRMS (EI): m/z calcd for $C_{15}H_9ClN_4O$ (M^+), 296.0459; found, 296.0460.

*8-(4-Bromophenyl)-3-methyl-2-oxo-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3e**).* Recrystallized from the EtOH/dioxane mixture (4:1), as a yellowish white crystal, yield: 1.60 g (95%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2229 (C≡N), 1656 (C═O); ^{1}H NMR (600 MHz, TFA-d): δ 2.37 (s, 3H, CH_3), 7.29 (d, J = 7.2 Hz, 1H, C−*H6*), 7.73 (d, J = 8.4 Hz, 2H, Ar−H), 7.86 (d, J = 8.4 Hz, 2H, Ar−H), 8.74 (d, J = 7.2 Hz, 1H, C*H*-7); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-d): δ 17.70 (CH_3), 103.30, 113.62, 114.17, 125.09, 130.78, 132.15, 133.66, 140.53, 151.78, 155.48, 158.04, 159.63; MS (EI): m/z (%) 342 (M^+ + 2, 54.97), 341 (M^+ + 1, 22.63), 340 (M^+, 52.04). HRMS (EI): m/z calcd for $C_{15}H_9BrN_4O$ (M^+), 339.9954; found, 339.9963.

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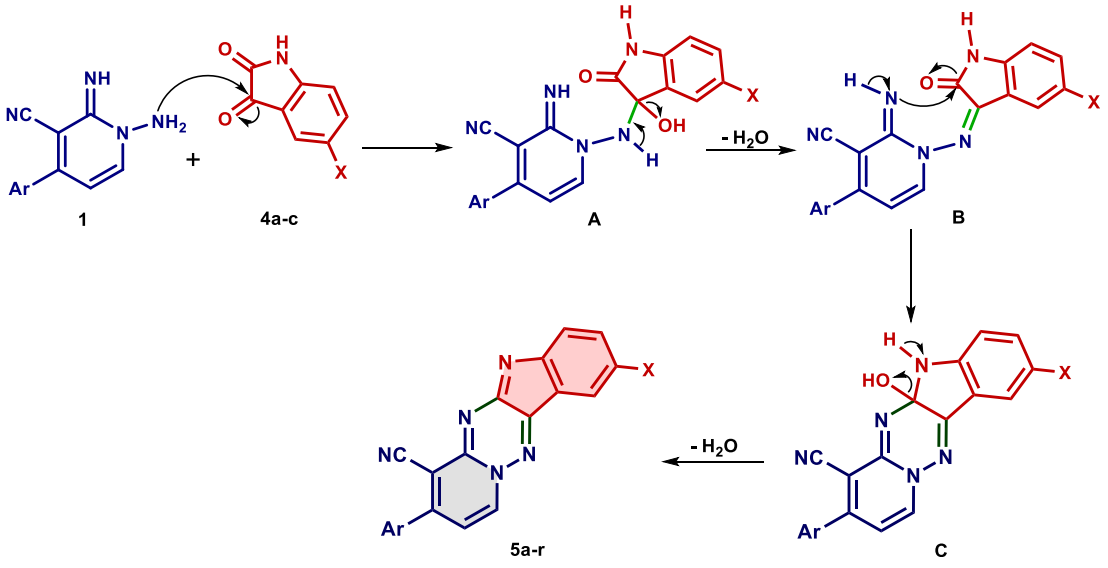
ACS Omega 2021, 6, 16086−16099

Scheme 3. Plausible Mechanistic Route for the Formation of Pyrido[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole Derivatives 5a−r



*3-Methyl-8-(4-nitrophenyl)-2-oxo-2H-pyrido[1,2-b][1,2,4]-triazine-9-carbonitrile (**3f**).* Recrystallized from the EtOH/dioxane mixture (3:1), as a pale white crystal, yield: 1.40 g (92%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2237 (C≡N), 1650 (C═O); ^{1}H NMR (600 MHz, TFA-*d*): δ 2.39 (s, 3H, C*H*$_3$), 7.36 (d, *J* = 7.2 Hz, 1H, C−*H6*), 8.05 (d, *J* = 8.4 Hz, 2H, Ar−H), 8.47 (d, *J* = 8.4 Hz, 2H, Ar−H), 8.82 (d, *J* = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, TFA-*d*): δ 17.71 (*C*H$_3$), 104.23, 113.55, 113.83, 124.07, 130.34, 140.56, 140.82, 148.81, 151.61, 154.61, 158.31, 159.56; MS (EI): *m*/*z* (%) 308 (M$^+$ + 1, 10.98), 307 (M$^+$, 51.13). HRMS (EI): *m*/*z* calcd for $C_{15}H_9N_5O_3$ (M$^+$), 307.0700; found, 307.0704.

*2-Oxo-3,8-diphenyl-2H-pyrido[1,2-b][1,2,4]triazine-9-carbonitrile (**3g**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a white crystal, yield: 1.55 g (97%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2226 (C≡N), 1656 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.37 (d, *J* = 7.2 Hz, 1H, C−*H6*), 7.58 (t, *J* = 7.8 Hz, 2H, Ar−H), 7.63 (t, *J* = 7.8 Hz, 1H, Ar−H), 7.67−7.68 (m, 3H, Ar−H), 7.82−7.84 (m, 2H, Ar−H), 8.24 (d, *J* = 7.2 Hz, 2H, Ar−H), 8.52 (d, *J* = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 102.83, 114.19, 114.29, 128.25, 128.72, 129.16, 129.52, 131.32, 131.53, 134.46, 140.69, 151.16, 152.51, 156.61, 158.75; MS (EI): *m*/*z* (%) 325 (M$^+$ + 1, 5.96), 324 (M$^+$, 8.05). HRMS (EI): *m*/*z* calcd for $C_{20}H_{12}N_4O$ (M$^+$) 324.1006; found, 324.1007.

*2-Oxo-3-phenyl-8-p-tolyl-2H-pyrido[1,2-b][1,2,4]triazine-9-carbonitrile (**3h**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a white crystal, yield: 1.55 g (92%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2225 (C≡N), 1656 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.45 (s, 3H, C*H*$_3$), 7.35 (d, *J* = 7.2 Hz, 1H, C−*H6*), 7.48 (d, *J* = 7.8 Hz, 2H, Ar−H), 7.57 (t, *J* = 7.8 Hz, 2H, Ar−H), 7.62 (t, *J* = 7.8 Hz, 1H, Ar−H), 7.74 (d, *J* = 7.8 Hz, 2H, Ar−H), 8.23 (d, *J* = 7.8 Hz, 2H, Ar−H), 8.81 (d, *J* = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 21.00, 102.29, 114.12, 114.45, 128.25, 129.73, 129.52, 129.74, 131.50, 131.56, 140.54, 141.68, 151.23, 152.42, 156.52, 158.78; MS (EI): *m*/*z* (%) 339 (M$^+$ + 1, 5.02), 338 (M$^+$, 10.03). HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}N_4O$ (M$^+$), 338.1162; found, 338.1163.

*8-(4-Methoxyphenyl)-2-oxo-3-phenyl-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3i**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a white crystal, yield: 1.65 g (93%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2229 (C≡N), 1648 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.90 (s, 3H, OC*H*$_3$), 7.23 (d, *J* = 7.8 Hz, 2H, Ar−H), 7.36 (d, *J* = 7.2 Hz, 1H, C−*H6*), 7.57 (t, *J* = 7.8 Hz, 2H, Ar−H), 7.62 (t, *J* = 7.8 Hz, 1H, Ar−H), 7.85 (d, *J* = 7.8 Hz, 2H, Ar−H), 8.22 (d, *J* = 7.8 Hz, 2H, Ar−H), 8.78 (d, *J* = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 55.60, 101.42, 114.02, 114.69, 114.71, 126.30, 128.24, 129.50, 130.76, 131.45, 131.59, 140.29, 151.34, 152.29, 155.98, 158.79, 161.91; MS (EI): *m*/*z* (%) 355 (M$^+$ + 1, 4.83), 354 (M$^+$, 6.12). HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}N_4O_2$ (M$^+$), 354.1111; found, 354.1111.

*8-(4-Chlorophenyl)-2-oxo-3-phenyl-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3j**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a white crystal, yield: 1.72 g (97%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2232 (C≡N), 1649 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.38 (d, *J* = 7.2 Hz, 1H, C−*H6*), 7.58 (t, *J* = 7.8 Hz, 2H, Ar−H), 7.63 (t, *J* = 7.8 Hz, 1H, Ar−H), 7.76 (d, *J* = 8.4 Hz, 2H, Ar−H), 7.85 (d, *J* = 8.4 Hz, 2H, Ar−H), 8.23 (d, *J* = 7.8 Hz, 2H, Ar−H), 8.87 (d, *J* = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 103.08, 114.00, 114.15, 128.26, 129.24, 129.52, 130.65, 131.50, 131.58, 133.27, 140.80, 151.05, 151.12, 152.58, 155.49, 158.73; MS (EI): *m*/*z* (%) 359 (M$^+$ + 1, 19.98), 358 (M$^+$, 46.13). HRMS (EI): *m*/*z* calcd for $C_{20}H_{11}ClN_4O$ (M$^+$), 358.0616; found, 358.0614.

*8-(4-Bromophenyl)-2-oxo-3-phenyl-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3k**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a white crystal, yield: 1.95 g (98%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2231 (C≡N), 1648 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.37 (d, *J* = 7.2 Hz, 1H, C−*H6*), 7.58 (t, *J* = 7.8 Hz, 2H, Ar−H), 7.63 (t, *J* = 7.8 Hz, 1H, Ar−H), 7.78 (d, *J* = 8.4 Hz, 2H, Ar−H), 7.89 (d, *J* = 8.4 Hz, 2H, Ar−H), 8.23 (d, *J* = 7.8 Hz, 2H, Ar−H), 8.87 (d, *J* = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 102.99, 113.95, 114.16, 125.19, 128.27, 129.53, 130.80, 131.48, 131.57, 132.19, 133.61, 140.83, 151.07, 152.58, 155.49, 158.71; MS (EI): *m*/*z* (%) 404 (M$^+$ + 2, 8.01), 403 (M$^+$ + 1, 3.49), 402 (M$^+$, 6.72). HRMS (EI): *m*/*z* calcd for $C_{20}H_{11}BrN_4O$ (M$^+$), 402.0111; found, 402.0115.

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*8-4-(Fluorophenyl)-2-oxo-3-phenyl-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrileitrile (**3l**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a white crystal, yield: 1.60 g (95%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2230 (C≡N), 1647 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.31 (d, J = 7.2 Hz, 1H, C−*H6*), 7.47−7.50 (m, 2H, Ar−H), 7.57 (t, J = 7.8 Hz, 2H, Ar−H), 7.63 (t, J = 7.8 Hz, 1H, Ar−H), 7.88−7.91 (m, 2H, Ar−H), 8.27 (d, J = 7.8 Hz, 2H, Ar−H), 8.74 (d, J = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 103.76, 113.45, 113.55, 115.64, 115.78, 124.04, 127.69, 129.03, 130.75, 130.81, 130.95, 139.88, 149.06, 150.60, 152.24, 155.21; MS (EI): m/z (%) 343 (M$^+$ + 1, 8.91), 342 (M$^+$, 21.19). HRMS (EI): m/z calcd for $C_{20}H_{11}FN_4O$ (M$^+$), 342.0911; found, 342.0913.

*8-(4-Nitrophenyl)-2-oxo-3-phenyl-2H-pyrido[1,2-b][1,2,4]-triazine-9-carbonitrile (**3m**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a canary-yellow crystal, yield: 1.70 g (94%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2235 (C≡N), 1650 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.39 (d, J = 7.2 Hz, 1H, C−*H6*), 7.58 (t, J = 7.8 Hz, 2H, Ar−H), 7.64 (t, J = 7.8 Hz, 1H, Ar−H), 8.08 (d, J = 8.4 Hz, 2H, Ar−H), 8.27 (d, J = 7.8 Hz, 2H, Ar−H), 8.48 (d, J = 8.4 Hz, 2H, Ar−H), 8.88 (d, J = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 103.88, 113.40, 113.56, 123.79, 127.99, 129.29, 130.03, 131.22, 131.35, 140.37, 140.73, 148.73, 150.62, 152.59, 154.42, 158.30; MS (EI): m/z (%) 370 (M$^+$ + 1, 2.01), 369 (M$^+$, 5.42). HRMS (EI): m/z calcd for $C_{20}H_{11}N_5O_3$ (M$^+$), 369.0856; found, 369.0857.

*8-(4-Aminophenyl)-2-oxo-3-phenyl-2H-pyrido[1,2-b]-[1,2,4]triazine-9-carbonitrile (**3n**).* Recrystallized from the EtOH/dioxane mixture (2:1), as an orange crystal, yield: 1.50 g (90%), mp above 300 °C; IR (KBr): ν/cm^{-1} 3479, 3360 (NH_2), 2214 (C≡N), 1650 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.22 (s, 2H, N*H*$_2$), 6.75 (d, J = 8.4 Hz, 2H, Ar−H), 7.29 (d, J = 7.2 Hz, 1H, C−*H6*), 7.55 (t, J = 7.8 Hz, 2H, Ar−H), 7.60 (t, J = 7.8 Hz, 1H, Ar−H), 7.68 (d, J = 8.4 Hz, 2H, Ar−H), 8.20 (d, J = 7.8 Hz, 2H, Ar−H), 8.61 (d, J = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 97.94, 113.43, 113.52, 115.53, 119.78, 128.17, 129.43, 130.88, 131.24, 131.75, 139.34, 151.72, 151.78, 152.87, 155.82, 158.88; MS (EI): m/z (%) 340 (M$^+$ + 1, 1.02), 339 (M$^+$, 3.12). HRMS (EI): m/z calcd for $C_{20}H_{13}N_5O$ (M$^+$), 339.1115; found, 339.1115.

*8-Methyl-2-oxo-3-phenyl-2H-pyrido[1,2-b][1,2,4]triazine-9-carbonitrile (**3o**).* Recrystallized from the EtOH/dioxane mixture (2:1), as a pale-yellow crystal, yield: 1.15 g (87%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2227 (C≡N), 1651 (C═O); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.65 (s, 3H, C*H*$_3$), 7.20 (d, J = 7.2 Hz, 1H, C−*H6*), 7.56 (t, J = 7.8 Hz, 2H, Ar−H), 7.61 (t, J = 7.8 Hz, 1H, Ar−H), 8.18 (d, J = 7.8 Hz, 2H, Ar−H), 8.70 (d, J = 7.2 Hz, 1H, C*H*-7); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 20.99 (*C*H$_3$), 104.56, 113.66, 115.37, 128.19, 129.44, 131.36, 131.59, 139.97, 150.45, 152.46, 158.32, 158.75; MS (EI): m/z (%) 263 (M$^+$ + 1, 3.85), 262 (M$^+$, 13.02). HRMS (EI): m/z calcd for $C_{15}H_{10}N_4O$ (M$^+$), 262.0849; found, 262.0847.

*9-Phenylpyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]indole-10-carbonitrile (**5a**).* Recrystallized from the EtOH/DMF mixture (1:4), as orange crystals, yield: 1.55 g (96%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2227 (C≡N), 1640, 1603 (C═N); ^{1}H NMR (600 MHz, TFA-*d*): δ 7.66−7.72 (m, 4H, Ar−H), 7.79 (d, J = 7.8 Hz, 1H, C*H*-7), 7.87 (d, J = 7.2 Hz, 2H, Ar−H), 8.03 (t, J = 7.2 Hz, 1H, Ar−H), 8.08 (d, J = 7.2 Hz, 1H, Ar−H), 8.51 (d, J = 7.8 Hz, 1H, C*H*-8), 9.33 (d, J = 7.2 Hz, 1H, Ar−H); ^{13}C{^{1}H} NMR (150 MHz, TFA-*d*): δ 108.03, 112.35, 115.52, 116.25, 122.75, 126.66, 127.59, 129.98, 130.99, 133.91, 134.49, 139.11, 142.69, 145.57, 146.60, 147.34, 148.99, 162.24; MS (EI): m/z (%) 322 (M$^+$ + 1, 23.05), 321 (M$^+$, 100.00). HRMS (EI): m/z calcd for $C_{20}H_{11}N_5$ (M$^+$), 321.1009; found, 321.1008. Crystal data, moiety formula: $C_{20}H_{11}N_5$, M = 321.34, sum formula: $C_{40}H_{22}N_{10}$, M = 642.68, triclinic, a = 7.0765(5) Å, b = 14.1844(9) Å, c = 15.9271(10) Å, V = 1515.44(17) Å^3, α = 76.326(4)°, β = 77.458(5)°, γ = 88.903(5)°, space group: $P\bar{1}$, Z = 2, D_{calc} = 1.408 g·cm^{-3}, no. of reflection measured: 21,148, unique: 5231, θ_{max} = 66.69°, R_1 = 0.049 (CCDC 2070152).[43]

*3-Bromo-9-phenylpyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5b**).* Recrystallized from DMF, as reddish pink crystals, yield: 1.95 g (98%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2228 (C≡N), 1640, 1600 (C═N); ^{1}H NMR (600 MHz, TFA-*d*): δ 7.72−7.78 (m, 4H, 3Ar−H and C*H*-7), 7.93 (d, J = 7.8 Hz, 2H, Ar−H), 8.16−8.19 (m, 2H, Ar−H), 8.67 (d, J = 1.8 Hz, 1H, Ar−H), 9.39 (d, J = 7.2 Hz, 1H, C*H*-8); ^{13}C{^{1}H} NMR (150 MHz, TFA-*d*): δ 109.35, 113.47, 118.09, 119.08, 122.14, 124.34, 130.49, 131.32, 132.30, 135.08, 135.90, 143.15, 144.04, 145.88, 146.57, 148.52, 150.36, 163.76; MS (EI): m/z (%) 401 (M$^+$ + 2, 100.00), 400 (M$^+$ + 1, 49.23), 399 (M$^+$, 96.14). HRMS (EI): m/z calcd for $C_{20}H_{10}BrN_5$ (M$^+$), 399.0114; found, 399.0113.

*3-Nitro-9-phenylpyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5c**).* Recrystallized from DMF, as reddish brown crystals, yield: 1.70 g (93%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2233 (C≡N), 1644, 1603 (C═N); ^{1}H NMR (600 MHz, TFA-*d*): δ 7.72 (t, J = 7.8 Hz, 2H, Ar−H), 7.77 (t, J = 7.8 Hz, 1H, Ar−H), 7.93 (d, J = 7.8 Hz, 2H, Ar−H), 8.02 (d, J = 9.0 Hz, 1H, Ar−H), 8.25 (d, J = 7.2 Hz, 1H, C*H*-7), 8.92 (dd, J = 9.0, 2.4 Hz, 1H, Ar−H), 9.43 (d, J = 1.8 Hz, 1H, Ar−H), 9.46 (d, J = 7.2 Hz, 1H, C*H*-8); ^{13}C{^{1}H} NMR (150 MHz, TFA-*d*): δ 109.48, 113.00, 118.07, 123.74, 125.05, 131.18, 132.11, 134.35, 134.66, 135.89, 144.00, 146.11, 147.49, 150.00, 150.48, 151.56, 164.14; MS (EI): m/z (%) 367 (M$^+$ + 1, 25.68), 366 (M$^+$, 100.00). HRMS (EI): m/z calcd for $C_{20}H_{10}N_6O_2$ (M$^+$), 366.0860; found, 366.0862.

*9-(p-Tolyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]indole-10-carbonitrile (**5d**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.55 g (94%), mp 295−296 °C; IR (KBr): ν/cm^{-1} 2235 (C≡N), 1641, 1602 (C═N); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.46 (s, 3H, C*H*$_3$), 7.40 (t, J = 7.2 Hz, 1H, Ar−H), 7.49 (d, J = 7.8 Hz, 2H, Ar−H), 7.56 (d, J = 7.2 Hz, 1H, C*H*-7), 7.76 (d, J = 7.2 Hz, 1H, Ar−H), 7.79−8.82 (m, 3H, Ar−H), 8.28 (d, J = 7.2 Hz, 1H, Ar−H), 9.22 (d, J = 7.2 Hz, 1H, C*H*-8); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 21.01 (*C*H$_3$), 105.04, 114.65, 114.92, 118.72, 119.50, 121.88, 123.69, 128.95, 129.80, 131.76, 134.57, 141.10, 141.46, 146.00, 147.63, 150.54, 154.44, 161.46; MS (EI): m/z (%) 336 (M$^+$ + 1, 34.08), 335 (M$^+$, 100.00). HRMS (EI): m/z calcd for $C_{21}H_{13}N_5$ (M$^+$), 335.1165; found, 335.1167. Crystal data, moiety formula: $C_{21}H_{13}N_5$, M = 335.36, orthorhombic, a = 18.444(2) Å, b = 12.6807(12) Å, c = 6.8046(7) Å, V = 1591.5(3) Å^3, α = β = γ = 90.0, space group: $Pna2_1$, Z = 4, D_{calc} = 1.400 g·cm^{-3}, no. of reflection measured: 13,184, unique: 2379, θ_{max} = 66.62°, R_1 = 0.0687 (CCDC 2070156).[43]

*3-Bromo-9-(p-tolyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5e**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.95 g (95%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2227 (C≡N), 1640, 1599 (C═N); ^{1}H NMR (600 MHz, TFA-*d*): δ 2.50 (s, 3H, C*H*$_3$), 7.53 (d, J = 7.8 Hz, 2H, Ar−H), 7.70 (d, J = 9.0 Hz, 1H, Ar−H), 7.82 (d, J = 7.8 Hz, 2H, Ar−H), 8.11−8.15 (m, 2H, C*H*-7 and 1

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Ar−H), 8.63 (d, J = 1.8 Hz, 1H, Ar−H), 9.30 (d, J = 7.2 Hz, 1H, C*H*-8); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-*d*): δ 22.28 (CH_3), 108.37, 113.63, 117.94, 119.02, 122.00, 124.14, 130.35, 131.39, 132.02, 132.99, 142.97, 143.66, 145.66, 146.44, 148.42, 148.46, 150.40, 163.56; MS (EI): m/z (%) 415 (M^+ + 2, 100.00), 414 (M^+ + 1, 40.11), 413 (M^+, 99.18). HRMS (EI): m/z calcd for $C_{21}H_{12}N_5Br$ (M^+), 413.0271; found, 413.0277.

*3-Nitro-9-(p-tolyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5f**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.75 g (92%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2228 (C≡N), 1642, 1602 (C═N); ^1H NMR (600 MHz, TFA-*d*): δ 2.52 (s, 3H, CH_3), 7.56 (d, J = 7.8 Hz, 2H, Ar−H), 7.88 (d, J = 7.8 Hz, 2H, Ar−H), 8.03 (d, J = 9.0 Hz, 1H, Ar−H), 8.25 (d, J = 7.8 Hz, 1H, C*H*-7), 8.91 (dd, J = 9.0, 1.8 Hz, 1H, Ar−H), 9.41−9.43 (m, 2H, C*H*-8 and 1Ar−H); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-*d*): δ 22.46 (CH_3), 108.87, 113.61, 117.80, 118.41, 123.94, 125.23, 131.67, 132.04, 133.17, 134.50, 144.03, 146.23, 147.69, 148.76, 150.31, 150.88, 151.884, 164.24; MS (EI): m/z (%) 381 (M^+ + 1, 24.36), 380 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{21}H_{12}N_6O_2$ (M^+), 380.1016; found, 380.1020.

*9-(4-Methoxyphenyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]indole-10-carbonitrile (**5g**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.65 g (95%), mp 292−293 °C; IR (KBr): ν/cm^{-1} 2226 (C≡N), 1641, 1607 (C═N); ^1H NMR (600 MHz, DMSO-d_6): δ 3.93 (s, 3H, OCH_3), 7.23 (d, J = 8.4 Hz, 2H, Ar−H), 7.40 (t, J = 7.2 Hz, 1H, Ar−H), 7.52 (d, J = 7.2 Hz, 1H, C*H*-7), 7.76 (d, J = 7.2 Hz, 1H, Ar−H), 7.82 (t, J = 7.2 Hz, 1H, Ar−H), 7.90 (d, J = 8.4 Hz, 2H, Ar−H), 8.26 (d, J = 7.2 Hz, 1H, Ar−H), 9.09 (d, J = 7.2 Hz, 1H, C*H*-8); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 55.16 (OCH_3), 104.07, 113.99, 114.22, 114.36, 118.31, 119.01, 121.28, 122.98, 126.28, 130.22, 133.91, 139.95, 145.51, 147.29, 149.92, 153.54, 161.21, 161.47; MS (EI): m/z (%) 352 (M^+ + 1, 31.14), 351 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{21}H_{13}N_5O$ (M^+), 351.1115; found, 351.1115. Crystal data, moiety formula: $C_{21}H_{13}N_5O$, M = 351.36, monoclinic, a = 16.3529(14) Å, b = 14.2319(13) Å, c = 7.2576(8) Å, V = 1675.6(3) Å^3, $\alpha = \gamma = 90.0°$, β = 97.256(8)°, space group: $P12_1/c1$, Z = 4, D_{calc} = 1.393 g·cm^{-3}, no. of reflection measured: 14,541, unique: 2896, θ_{max} = 66.77°, R_1 = 0.0712 (CCDC 2070154).[43]

*3-Bromo-9-(4-methoxyphenyl)pyrido[1′,2′:2,3][1,2,4]-triazino[5,6-b]indole-10-carbonitrile (**5h**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 2.00 g (97%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2227 (C≡N), 1642, 1602 (C═N); ^1H NMR (600 MHz, TFA-*d*): δ 4.25 (s, 3H, OCH_3), 7.51 (d, J = 8.4 Hz, 2H, Ar−H), 7.93 (d, J = 7.2 Hz, 1H, C*H*-7), 8.21 (d, J = 7.8 Hz, 2H, Ar−H), 8.34 (d, J = 8.4 Hz, 2H, Ar−H), 8.84 (s, 1H, Ar−H), 9.51 (d, J = 7.2 Hz, 1H, C*H*-8); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-*d*): δ 57.78 (OCH_3), 107.74, 114.23, 118.24, 119.32, 122.06, 124.09, 128.02, 130.52, 134.10, 143.03, 143.77, 145.78, 146.67, 148.73, 150.75, 162.56, 166.48; MS (EI): m/z (%) 431 (M^+ + 2, 100.00), 430 (M^+ + 1, 32.98), 429 (M^+, 99.10). HRMS (EI): m/z calcd for $C_{21}H_{12}BrN_5O$ (M^+), 429.0220; found, 429.0223.

*9-(4-Methoxyphenyl)-3-nitropyrido[1′,2′:2,3][1,2,4]-triazino[5,6-b]indole-10-carbonitrile (**5i**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.85 g (94%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2226 (C≡N), 1643, 1598 (C═N); ^1H NMR (600 MHz, TFA-*d*): δ 4.03 (s, 3H, OCH_3), 7.30 (d, J = 9.0 Hz, 2H, Ar−H), 8.00−8.02 (m, 3H, Ar−H), 8.22 (d, J = 7.2 Hz, 1H, C*H*-7), 8.91 (dd, J = 9.0, 2.4 Hz, 1H, Ar−H), 9.36 (d, J = 7.2 Hz, 1H, C*H*-8), 9.41 (d, J = 1.8 Hz, 1H, Ar−H); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-*d*): δ 57.39 (OCH_3), 107.59, 113.56, 117.49, 118.00, 118.18, 123.66, 124.61, 127.37, 133.91, 134.25, 143.51, 145.86, 147.46, 150.11, 150.81, 151.56, 162.82, 166.55; MS (EI): m/z (%) 397 (M^+ + 1, 29.13), 396 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{21}H_{12}N_6O_3$ (M^+), 396.0965; found, 396.0961.

*9-(4-Chlorophenyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5j**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.70 g (97%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2228 (C≡N), 1640, 1597 (C═N); ^1H NMR (600 MHz, DMSO-d_6): δ 7.41 (t, J = 7.2 Hz, 1H, Ar−H), 7.58 (d, J = 7.2 Hz, 1H, C*H*-7), 7.76−7.78 (m, 3H, Ar−H), 7.83 (t, J = 7.2 Hz, 1H, Ar−H), 7.91 (d, J = 8.4 Hz, 2H, Ar−H), 8.29 (d, J = 7.2 Hz, 1H, Ar−H), 9.28 (d, J = 7.2 Hz, 1H, C*H*-8); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 105.69, 113.88, 114.01, 118.35, 119.20, 121.56, 123.21, 128.80, 130.27, 133.21, 134.20, 135.82, 140.63, 145.33, 147.56, 149.90, 152.97, 161.26; MS (EI): m/z (%) 357 (M^+ + 2, 28.05), 356 (M^+ + 1, 24.89), 355 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{20}H_{10}ClN_5$ (M^+), 355.0619; found, 355.0618. Crystal data, moiety formula: $C_{20}H_{10}ClN_5$, M = 355.78, monoclinic, a = 16.5160(13) Å, b = 14.1547(11) Å, c = 7.1025(7) Å, V = 1660.1(2) Å^3, $\alpha = \gamma = 90.0°$, β = 91.122(6)°, space group: $P12_1/c1$, Z = 4, D_{calc} = 1.423 g·cm^{-3}, no. of reflection measured: 14,441, unique: 2891, θ_{max} = 66.61°, R_1 = 0.0628 (CCDC 2070153).[43]

*3-Bromo-9-(4-chlorophenyl)pyrido[1′,2′:2,3][1,2,4]-triazino[5,6-b]indole-10-carbonitrile (**5k**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 2.15 g (99%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2227 (C≡N), 1640, 1595 (C═N); ^1H NMR (600 MHz, TFA-*d*): δ 7.49 (d, J = 7.2 Hz, 2H, Ar−H), 7.54 (d, J = 7.2 Hz, 1H, C*H*-7), 7.69 (d, J = 7.2 Hz, 2H, Ar−H), 7.95 (d, J = 7.8 Hz, 2H, Ar−H), 8.46 (s, 1H, Ar−H), 9.22 (d, J = 7.2 Hz, 1H, C*H*-8); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-*d*): δ 110.09, 114.12, 118.85, 119.74, 122.64, 124.66, 131.11, 133.28, 133.35, 134.15, 143.66, 143.73, 144.94, 146.50, 147.24, 149.09, 150.92, 162.66; MS (EI): m/z (%) 435 (M^+ + 2, 100.00), 434 (M^+ + 1, 34.02), 433 (M^+, 77.10). HRMS (EI): m/z calcd for $C_{20}H_9BrClN_5$ (M^+), 432.9724; found, 432.9722.

*9-(4-Chlorophenyl)-3-nitropyrido[1′,2′:2,3][1,2,4]triazino-[5,6-b]indole-10-carbonitrile (**5l**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.90 g (95%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2230 (C≡N), 1643, 1593 (C═N); ^1H NMR (600 MHz, TFA-*d*): δ 7.65 (d, J = 8.4 Hz, 2H, Ar−H), 7.85 (d, J = 8.4 Hz, 2H, Ar−H), 7.99 (d, J = 9.0 Hz, 1H, Ar−H), 8.19 (d, J = 7.2 Hz, 1H, C*H*-7), 8.87 (dd, J = 9.0, 1.8 Hz, 1H, Ar−H), 9.37 (d, J = 2.4 Hz, 1H, Ar−H), 9.43 (d, J = 7.2 Hz, 1H, C*H*-8); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-*d*): δ 110.09, 113.47, 118.61, 124.29, 125.29, 133.05, 133.07, 133.53, 134.90, 143.93, 144.78, 146.70, 148.02, 150.53, 151.01, 152.11, 163.12; MS (EI): m/z (%) 401 (M^+ + 1, 24.05), 400 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{20}H_9ClNO_2$ (M^+), 400.0470; found, 400.0469.

*9-(4-Bromophenyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5m**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.95 g (98%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2227 (C≡N), 1639, 1590 (C═N); ^1H NMR (600 MHz, DMSO-d_6): δ 7.42 (t, J = 7.2 Hz, 1H, Ar−H), 7.58 (d, J = 7.2 Hz, 1H, C*H*-7), 7.78 (d, J = 7.2 Hz, 1H, Ar−H), 7.82−7.84 (m, 3H, Ar−H), 7.91 (d, J = 8.4 Hz, 2H, Ar−H), 8.30 (d, J = 7.2 Hz, 1H, Ar−H), 9.28 (d, J = 7.2 Hz, 1H,

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CH-8); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 105.75, 114.45, 114.64, 118.69, 119.56, 122.00, 123.76, 125.06, 131.03, 132.24, 133.82, 134.68, 141.38, 145.82, 147.75, 150.43, 153.39, 161.44; MS (EI): m/z (%) 401 (M^+ + 2, 100.00), 400 (M^+ + 1, 37.04), 399 (M^+, 98.23). HRMS (EI): m/z calcd for $C_{20}H_{10}BrN_5$ (M^+) 399.0114; found, 399.0115. Crystal data, moiety formula: $C_{20}H_{10}BrN_5$, M = 400.24, monoclinic, a = 16.8422(8) Å, b = 14.1742(8) Å, c = 7.0948(4) Å, V = 1693.45(16) Å^3, $\alpha = \gamma = 90.0°$, β = 90.995(4)°, space group: $P12_1/c1$, Z = 4, D_{calc} = 1.570 g·cm^{-3}, no. of reflection measured: 16,759, unique: 2893, θ_{max} = 66.75°, R_1 = 0.0551 (CCDC 2070155).[43]

*9-(4-Nitrophenyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5n**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.65 g (92%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2230 (C≡N), 1641, 1598 (C═N); ^1H NMR (600 MHz, TFA-d): δ 7.76 (t, J = 7.8 Hz, 1H, Ar−H), 7.84 (d, J = 7.8 Hz, 1H, Ar−H), 8.06−8.13 (m, 4H, CH-7 and 3 Ar−H), 8.55−8.58 (m, 3H, Ar−H), 9.48 (d, J = 7.2 Hz, 1H, CH-8); $^{13}C\{^1H\}$ NMR (150 MHz, TFA-d): δ 105.74, 112.71, 116.75, 117.25, 123.23, 127.07, 127.92, 128.84, 132.54, 140.48, 141.60, 144.72, 146.93, 147.76, 148.25, 149.80, 152.15, 160.03; MS (EI): m/z (%) 367 (M^+ + 1, 23.41), 366 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{20}H_{10}N_6O_2$ (M^+), 366.0860; found, 366.0862.

*9-(4-Aminophenyl)pyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]-indole-10-carbonitrile (**5o**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.55 g (94%), mp above 300 °C; IR (KBr): ν/cm^{-1} 3431, 3302 (NH_2), 2228 (C≡N), 1637, 1589 (C═N); ^1H NMR (600 MHz, DMSO-d_6): δ 6.18 (s, 2H, NH_2), 6.77 (d, J = 8.4 Hz, 2H, Ar−H), 7.34 (t, J = 7.2 Hz, 1H, Ar−H), 7.49 (d, J = 7.2 Hz, 1H, CH-7), 7.69−7.73 (m, 3H, Ar−H), 7.77 (t, J = 7.2 Hz, 1H, Ar−H), 8.21 (d, J = 7.2 Hz, 1H, Ar−H), 9.01 (d, J = 7.2 Hz, 1H, CH-8); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 101.42, 114.12, 114.63, 116.37, 119.32, 119.78, 120.61, 122.05, 123.92, 131.42, 134.73, 140.40, 147.12, 147.70, 151.31, 153.09, 154.52, 161.96; MS (EI): m/z (%) 337 (M^+ + 1, 28.07), 336 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{20}H_{12}N_6$ (M^+), 336.1118; found, 336.1117. Crystal data, moiety formula: $C_{20}H_{12}N_6$, M = 336.36, monoclinic, a = 7.4315(3) Å, b = 15.4721(7) Å, c = 13.5859(6) Å, V = 1561.55(12) Å^3, $\alpha = \gamma = 90.0°$, β = 91.551(2)°, space group: $P12_1/c1$, Z = 4, D_{calc} = 1.431 g·cm^{-3}, no. of reflection measured: 14,333, unique: 2641, θ_{max} = 66.49°, R_1 = 0.0441 (CCDC 2070157).[43]

*9-(4-Aminophenyl)-3-bromopyrido[1′,2′:2,3][1,2,4]-triazino[5,6-b]indole-10-carbonitrile (**5p**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 2.00 g (96%), mp above 300 °C; IR (KBr): ν/cm^{-1} 3438, 3320 (NH_2), 2230 (C≡N), 1639, 1589 (C═N); ^1H NMR (600 MHz, TFA-d): δ 7.66 (d, J = 7.2 Hz, 1H, CH-7), 7.84 (d, J = 8.4 Hz, 2H, Ar−H), 8.02−8.09 (m, 4H, Ar−H), 8.59 (s, 1H, Ar−H), 9.38 (d, J = 7.2 Hz, 1H, CH-8), the deuterium from the TFA-d has been exchanged with the exchangeable protons of NH_2 in our sample effectively deuterating them and making them invisible in the proton spectrum; $^{13}C\{^1H\}$ NMR (150 MHz, TFA-d): δ 110.80, 118.20, 118.97, 122.25, 123.83, 127.25, 130.56, 133.50, 134.79, 137.72, 143.30, 144.81, 146.08, 146.60, 148.33, 150.07, 160.70; MS (EI): m/z (%) 416 (M^+ + 2, 100.00), 415 (M^+ + 1, 37.89), 414 (M^+, 95.83). HRMS (EI): m/z calcd for $C_{20}H_{11}BrN_6$ (M^+), 414.0219; found, 414.0223.

*9-(4-Aminophenyl)-3-nitropyrido[1′,2′:2,3][1,2,4]triazino-[5,6-b]indole-10-carbonitrile (**5q**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.75 g (93%), mp above 300 °C; IR (KBr): ν/cm^{-1} 3432, 3358 (NH_2), 2224 (C≡N), 1640, 1590 (C═N); ^1H NMR (600 MHz, TFA-d): δ 7.91 (d, J = 7.2 Hz, 2H, Ar−H), 8.03 (d, J = 8.4 Hz, 1H, Ar−H), 8.11 (d, J = 7.2 Hz, 2H, Ar−H), 8.23 (d, J = 6.6 Hz, 1H, CH-7), 8.89 (d, J = 8.4 Hz, 1H, Ar−H), 9.39 (s, 1H, Ar−H), 9.53 (d, J = 6.6 Hz, 1H, CH-8) The deuterium from the TFA-d has been exchanged with the exchangeable protons of NH_2 in our sample effectively deuterating them and making them invisible in the proton spectrum; $^{13}C\{^1H\}$ NMR (150 MHz, TFA-d): δ 111.53, 113.11, 118.62, 124.43, 125.25, 127.71, 133.99, 135.06, 135.34, 137.92, 145.45, 147.00, 148.06, 150.52, 150.84, 152.24, 161.79; MS (EI): m/z (%) 382 (M^+ + 1, 27.08), 381 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{20}H_{11}N_7O_2$ (M^+), 381.1095; found, 381.1098.

*9-Methylpyrido[1′,2′:2,3][1,2,4]triazino[5,6-b]indole-10-carbonitrile (**5r**).* Recrystallized from the EtOH/DMF mixture (1:4), as deep-orange crystals, yield: 1.15 g (90%), mp above 300 °C; IR (KBr): ν/cm^{-1} 2226 (C≡N), 1643, 1595 (C═N); ^1H NMR (600 MHz, DMSO-d_6): δ 2.74 (s, 3H, CH_3), 7.39 (t, J = 7.8 Hz, 1H, Ar−H), 7.73−7.79 (m, 2H, Ar−H), 7.94 (d, J = 7.2 Hz, 1H, CH-7), 8.24 (d, J = 7.8 Hz, 1H, Ar−H), 9.11 (d, J = 7.2 Hz, 1H, CH-8); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 20.98 (CH_3), 107.21, 114.12, 116.03, 118.64, 119.33, 121.80, 123.60, 134.47, 138.40, 140.54, 145.35, 147.63, 150.46, 156.04; MS (EI): m/z (%) 260 (M^+ + 1, 21.36), 259 (M^+, 100.00). HRMS (EI): m/z calcd for $C_{15}H_9N_5$ (M^+), 259.0852; found, 259.0852.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01980.

MS, HRMS, ^1H NMR, and ^{13}C NMR spectra for the reported compounds (PDF)

Crystallographic data for compound **3c** (CIF)

Crystallographic data for compound **5a** (CIF)

Crystallographic data for compound **5d** (CIF)

Crystallographic data for compound **5g** (CIF)

Crystallographic data for compound **5j** (CIF)

Crystallographic data for compound **5m** (CIF)

Crystallographic data for compound **5o** (CIF)

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Notes

The authors declare no competing financial interest.

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