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One-Step Synthesis of 2-Amino-5*H*-pyrimido[5,4-*b*]indoles, Substituted 2-(1,3,5-triazin-2-yl)-1*H*-indoles, and 1,3,5-Triazines from Aldehydes[‡]

Subhasish Biswas[a] and Sanjay Batra*[a]

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An efficient one-step synthesis of 2-amino-5*H*-pyrimido[5,4-*b*]-indoles through a copper-catalyzed cascade reaction between 3-haloindole-2-carbaldehydes and guanidine hydrochloride is described. In contrast, the base-mediated reactions of either 3-haloindole-2-carbaldehydes or substituted indole-2-carbaldehydes with substituted amidine hydrochlorides in DMSO result in the formation of 2-(1,3,5-triazin-2-yl)-1*H*-indole derivatives in one step in excellent yields. Studies toward exploring the utility of the method demonstrate that even substituted benzaldehydes undergo a similar reaction to efficiently yield 2,4,6-trisubstituted 1,3,5-triazines. A plausible mechanism for the formation of substituted 1,3,5-triazines identifies the role of DMSO as an oxidant during the reaction.

Introduction

Fused indoles constitute one of the largest family of organic compounds, as they are represented in numerous natural alkaloids, pharmaceuticals, and agrochemicals.[1] Owing to their significant relevance, there is continued interest in the development of newer approaches to the syntheses of fused indoles.[2] Amongst these approaches, transition-metal-catalyzed processes have proved complementary to the conventional protocols and have allowed the reactions to be performed under relatively mild conditions. In an ongoing project in our lab, we have successfully employed substituted indole-2-carbaldehydes and their derivatives to such protocols to synthesize indole-fused pyridine, diazocine, quinoxaline, and benzodiazepine.[3] More recently, we reported a facile and efficient synthesis of pyrazolo[4,3-*d*]-pyrimidines through a copper-catalyzed cascade reaction between 4-iodopyrazole-3-carbaldehydes and substituted amidines.[4] Essentially, to extend the scope of this protocol, we envisage that reacting guanidine or substituted amidines with 3-haloindole-2-carbaldehydes under identical conditions should lead to 2-substituted 5*H*-pyrimido[5,4-*b*]-indoles (Figure 1), which is the core framework of compounds associated with a variety of biological properties such as PDE inhibition, ionotropic and chronotropic activities, and benzodiazepine receptor binding activity.[5–7] The general routes to this core involve either the condensation of formamide with 3-aminoindole-2-carboxylate or the reaction between guanidine and *N*-acetylindole-3-one.[8,9] These routes, however, result in 5*H*-pyrimido[5,4-*b*]indoles which are either substituted at the 4-position or both the 2- and 4-positions simultaneously.

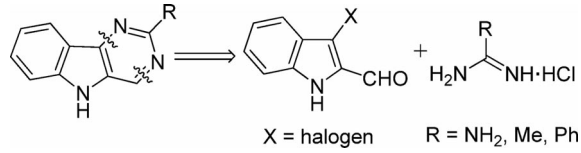

Figure 1. Retrosynthetic analysis for the synthesis of substituted 5*H*-pyrimido[5,4-*b*]indoles.

It is worthwhile to mention that there exists only one report describing the preparation of 2-substituted 5*H*-pyrimido[5,4-*b*]indoles, achieved in 8–10 steps (Figure 2).[7] Despite this, we decided to test our protocol for the synthesis of 2-substituted 5*H*-pyrimido[5,4-*b*]indoles. Although the reaction of 3-haloindole-2-carbaldehydes with guanidine hydrochloride gave the expected 5*H*-pyrimido[5,4-*b*]indol-2-amines, it was surprising to discover that a similar reaction with substituted amidines resulted in substituted 2-(1,3,5-triazin-2-yl)-1*H*-indoles. Furthermore, copper was not essential for both reactions, although the formation of 2-amino-5*H*-pyrimido[5,4-*b*]indoles was facilitated by its presence. As the formation of the 2-(1,3,5-triazin-2-yl)-1*H*-indoles did not involve a halo group at the 3-position of the indole, the methodology was successful with simple substituted indole-2-carbaldehydes, and the application of the method was extended to substituted benzaldehydes. A literature search for a similar precedence revealed that substituted benzaldehydes have been treated with benzamidine hydrochloride under basic conditions to give substituted 1,3,5-dihydrotriazines.[10] Studies into a plausible mechanism for the formation of the 1,3,5-triazines emphasized the

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[a] Medicinal and Process Chemistry Division, CSIR – Central Drug Research Institute,
P. O. Box 173, Lucknow 226001, India
Fax: +91-522-2623405, -2623938
E-mail: batra_san@yahoo.co.uk
s_batra@cdri.res.in

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role of DMSO (dimethyl sulfoxide) as an oxidant, which was confirmed experimentally. These unusual results prompted us to present the results of this study.

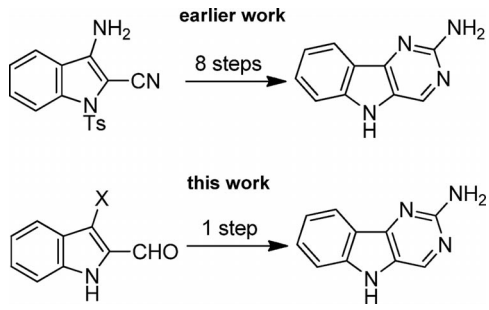
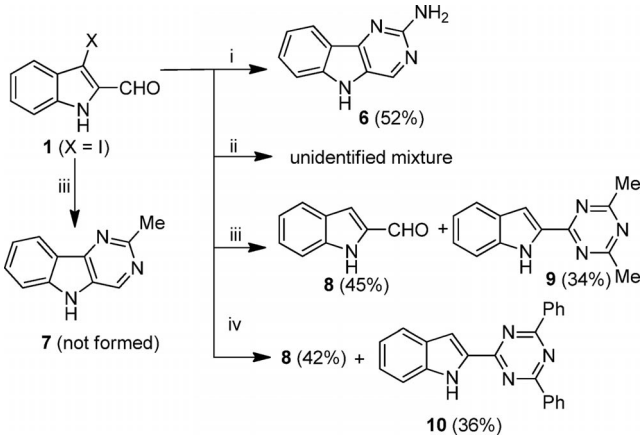


Figure 2. Synthesis of 5*H*-pyrimido[5,4-*b*]indol-2-amine.

Results and Discussion

The sequence began with several substituted 3-haloindole-2-carbaldehydes **1** (X = I), which were prepared as previously reported.[3b] Because we knew the optimized conditions for the anticipated coupling reaction,[4] we simultaneously investigated the reaction of 3-haloindole-2-carbaldehyde **1** with guanidine hydrochloride (**2**), formamidine acetate (**3**), acetamidine hydrochloride (**4**), and benzamidine hydrochloride (**5**). These reactions were performed under the standardized conditions of CuI, L-proline, and Cs_2CO_3 in DMSO at 90 °C (Scheme 1). The reaction between **1** and 1.0 equiv. of guanidine hydrochloride (**2**) resulted in the formation of a single product as evident from the TLC analysis. In contrast, the reaction with 1.0 equiv. of formamidine acetate (**3**) produced a mixture of products. However, the reaction with 1.0 equiv. of either acetamidine hydrochloride (**4**) or benzamidine hydrochloride (**5**) resulted in a mixture of two products. The product obtained from the reaction with guanidine hydrochloride (**2**) was characterized spectroscopically as the expected 2-amino-5*H*-pyrimido[5,4-*b*]indole (**6**). The mixture resulting from the reaction with acetamidine hydrochloride (**4**) was purified, yielding two solid products. The spectroscopic characterization of one of the products, isolated in 45% yield, led us to establish its structure as indole-2-carbaldehyde (**8**). Notably, the spectroscopic data of the second product, obtained in 34% yield, differed from that of the anticipated 2-methyl 5*H*-pyrimido[5,4-*b*]indole (**7**). On the basis of the data, the structure was tentatively assigned as 2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1*H*-indole (**9**). Nevertheless, to secure an unambiguous structure of the product, a single crystal was prepared from its DMSO solution and subjected to X-ray crystallographic analysis. The result proved the structure to be 2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1*H*-indole (**9**) which remains hitherto unreported in the literature (Figure 3).[11] In a similar fashion to the reaction with **4**, benzamidine hydrochloride (**5**) also gave a mixture of **8** (42%) and 2-(4,6-diphenyl-1,3,5-triazin-2-yl)-1*H*-indole (**10**, 36%).



Scheme 1. Reagents and conditions: (i) Guanidine hydrochloride (**2**, 1.0 equiv.), CuI (0.1 equiv.), L-proline (0.2 equiv.), Cs_2CO_3 (2.0 equiv.), DMSO (2 mL), 90 °C, 12 h; (ii) formamidine acetate (**3**, 1.0 equiv.), CuI (0.1 equiv.), L-proline (0.2 equiv.), Cs_2CO_3 (2.0 equiv.), DMSO (2 mL), 90 °C, 12 h; (iii) acetamidine hydrochloride (**4**, 1.0 equiv.), CuI (0.1 equiv.), L-proline (0.2 equiv.), Cs_2CO_3 (2.0 equiv.), DMSO (2 mL), 90 °C, 12 h; (iv) benzamidine hydrochloride (**5**, 1.0 equiv.), CuI (0.1 equiv.), L-proline (0.2 equiv.), Cs_2CO_3 (2.0 equiv.), DMSO (2 mL), 90 °C, 12 h.

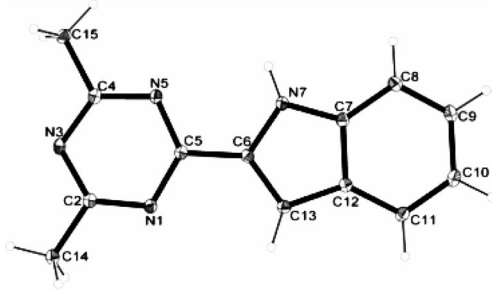


Figure 3. Ortep diagram for **9** at 35% probability level.

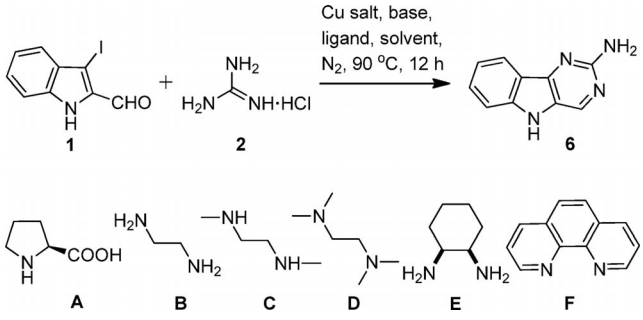
Studies Related to the Synthesis of 2-Amino-5*H*-pyrimido[5,4-*b*]indoles

Encouraged by the success of the copper-catalyzed reaction of guanidine hydrochloride (**2**) with 3-iodoindole-2-carbaldehyde (**1**) to afford a single product, we examined its optimization and scope for the first phase of the study. As a consequence, the reaction was screened for varying copper sources, ligands, bases, and solvents.

As indicated in Table 1, among the different copper sources examined, Cu^{I} salts were found to be better than Cu^{II} salts, and the yields were good with CuI (Table 1, Entries 1–5). In terms of the ligands which were evaluated, that is, L-proline, ethylenediamine, *N*,*N*′-dimethylethylenediamine, *N*,*N*′-tetramethylethylenediamine, cyclohexanediamine (*cis*/*trans* mixture), and 1,10-phenanthroline, 1,10-phenanthroline afforded **6** in 68% yield (Table 1, Entries 1, 6–10). We investigated other bases, namely K_2CO_3 and K_3PO_4, but Cs_2CO_3 gave the best yields (Table 1, Entries 10–12). Additionally, we realized that DMSO was the most suitable solvent for the reaction, giving rise to product **6** (Table 1, Entries 10, 13–15). Inferior results were produced when the reaction was conducted in other solvents

[DMF (dimethylformamide), toluene, dioxane). Although the control experiment in which neither a copper source nor a ligand (Table 1, Entry16) were used was successful, the rate was sluggish, and the reaction required 52 h to reach completion as compared to 12 h in the presence of copper. The other control experiment performed in the presence of CuI but absence of the ligand was also successful, but the yield of the product was relatively low (Table 1, Entry 17).

Table 1. Results of the study for optimization of reaction of 3-iodoindole-2-carbaldehyde (**1**) with guanidine hydrochloride (**2**).[a]

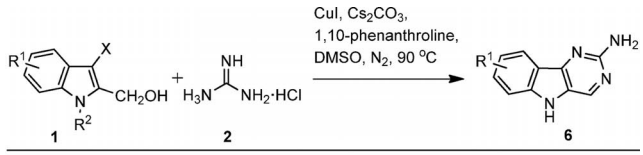


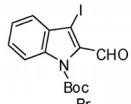
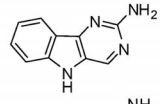
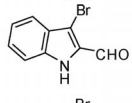
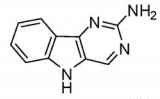
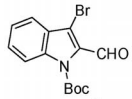
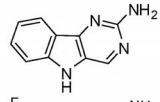
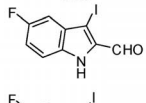
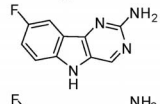
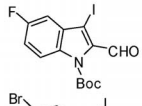
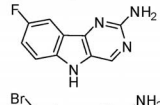
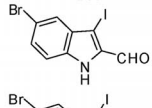
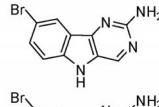
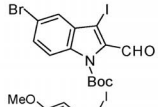
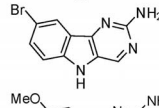
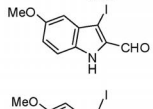
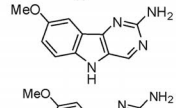
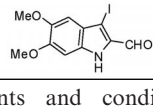
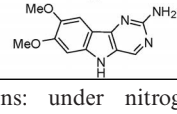
Entry	Cu cat.	Ligand	Base	Solvent	Yield [%][b]
1	CuI	A	Cs_2CO_3	DMSO	52
2	CuBr	A	Cs_2CO_3	DMSO	47
3	Cu_2O	A	Cs_2CO_3	DMSO	43
4	$CuSO_4$	A	Cs_2CO_3	DMSO	11
5	$Cu(OAc)_2$	A	Cs_2CO_3	DMSO	08
6	CuI	B	Cs_2CO_3	DMSO	46
7	CuI	C	Cs_2CO_3	DMSO	54
8	CuI	D	Cs_2CO_3	DMSO	57
9	CuI	E	Cs_2CO_3	DMSO	41
10	CuI	F	Cs_2CO_3	DMSO	68
11	CuI	F	K_2CO_3	DMSO	55
12	CuI	F	K_3PO_4	DMSO	42
13	CuI	F	Cs_2CO_3	DMF	58
14	CuI	F	Cs_2CO_3	toluene	48
15	CuI	F	Cs_2CO_3	dioxane	34
16	–	–	Cs_2CO_3	DMSO	46[c]
17	CuI	–	Cs_2CO_3	DMSO	59

[a] Reagents and conditions: under nitrogen atmosphere, 3-iodoindole-2-carbaldehyde (**1**, 1.1 mmol), guanidine hydrochloride (**2**, 2.2 mmol), Cu salt (0.11 mmol), ligand (0.22 mmol), base (2.2 mmol), solvent (2 mL), temperature (90 °C), time (12 h). [b] Isolated yields. [c] Reaction completed in 52 h.

The scope of the copper-catalyzed cascade synthesis of the 5*H*-pyrimido-[5,4-*b*]-indol-2-amine derivatives from the reactions of substituted 3-haloindole-2-carbaldehydes **1** with guanidine hydrochloride (**2**) was tested under the optimized conditions (10 mol-% CuI, 20 mol-% of 1,10-phenanthroline, and 2.0 equiv. of Cs_2CO_3 in DMSO under nitrogen). As shown in Table 2, most of the substrates afforded products in moderate to good yields. In line with an observation made in our previous studies,[3] here too we found that the reaction with *N*-Boc-protected indoles produced *N*-deprotected products in less time, but the yields were relatively low in comparison to the reaction with the unprotected indoles (compare Table 1, Entry 10 and Table 2, Entries 1–5). In general, the substrates with electron-donating substituents on the phenyl ring of the indole gave better yields than the ones without substituents or with a halo group on the phenyl ring (Table 2, Entries 8 and 9). Changing the iodo to a bromo group at the 3-position of indole resulted in products with relatively low yields (Table 2, Entries 2 and 3). To assess the significance of copper in the protocol, all of the reactions were performed in the absence of copper and the ligand. In each case, though the reaction was successful, the time required for completion increased, and the isolated yields were comparatively less (see Supporting Information).

Table 2. Scope of the copper-catalyzed cascade process for the synthesis of 2-amino-5*H*-pyrimido[5,4-*b*]indoles.[a]



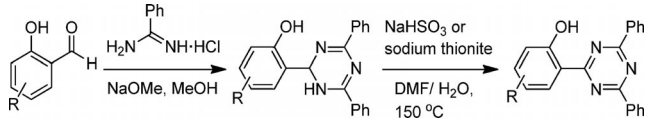
Entry	1	6	Time [h][b]	Yield [%][c]
1			8	64
2			9	54
3			8	52
4			11	63
5			10	60
6			11	64/52[d]
7			10	61
8			12	69
9			12	67

[a] Reagents and conditions: under nitrogen atmosphere, **1** (1.1 mmol), **2** (1.1 mmol), CuI (0.11 mmol), 1,10-phenanthroline (0.22 mmol), Cs_2CO_3 (2.2 mmol), DMSO (2 mL), temperature (90 °C). [b] Time of completion. [c] Isolated yields. [d] Isolated yield obtained in the presence of copper salt and without ligand.

Studies Related to the Synthesis of 2,4,6-Trisubstituted 1,3,5-Triazines

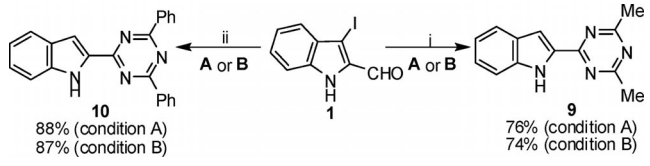
Having studied the transformation of 3-haloindole-2-carbaldehydes to 2-amino-5*H*-pyrimido[5,4-*b*]indoles, we turned our attention to its reactions with substituted amid-

ine hydrochlorides. As mentioned earlier, it was reported that benzamidine hydrochloride (2.0 equiv.) was treated with substituted benzaldehydes to furnish 1,3,5-dihydrotriazines which were oxidized in the presence of sodium sulfite or sodium thionite to obtain substituted 1,3,5-triazines (Scheme 2).[9]



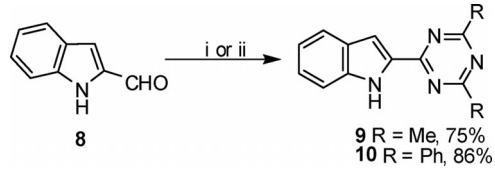
Scheme 2. Reported method[10] for the synthesis of substituted 1,3,5-triazines from substituted benzaldehydes.

From our initial results of the reaction with substituted amidines, it was evident that no cross-coupling reaction involving the iodine at the 3-position of the indole was occurring, and formation of the substituted 1,3,5-triazine would require 2.0 equiv. of the substituted amidine hydrochloride. Henceforth, in a representative study, the reaction between 3-iodoindole-2-carbaldehyde (**1**) and acetamidine hydrochloride (**4**) was investigated systematically. Accordingly, first **1** was treated with 2.0 equiv. of acetamidine hydrochloride under the optimized conditions both with CuI and in the absence of the copper source. It was satisfying to note that under these conditions the reaction gave the identical product in comparable yields, which was identified as expected **9** (Scheme 3). Furthermore, by using 2.0 equiv. of **4**, we did not observe the formation of indole-2-aldehyde (**8**). A similar reaction of 3-iodoindole-2-carbaldehyde with 2.0 equiv. of benzamidine hydrochloride (**5**) also proceeded smoothly affording the corresponding substituted triazine **10** in excellent yields. Nevertheless, formation of **9** and **10** suggested that under the reaction conditions deiodination invariably occurs.



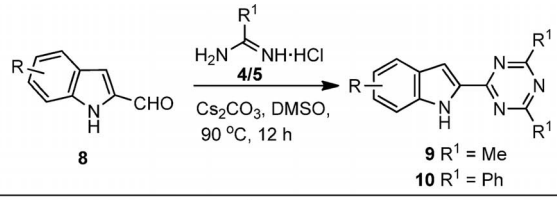
Scheme 3. Reagents and conditions: (i) acetamidine hydrochloride (**4**, 2.0 equiv.), (**A**) CuI (0.1 equiv.), Cs_2CO_3 (2.0 equiv.), 1,10-phenanthroline (0.2 equiv.), DMSO (2 mL), 90 °C, and 12 h or (**B**) Cs_2CO_3 (2.0 equiv.), DMSO (2 mL), 90 °C, and 12 h; (ii) benzamidine hydrochloride (**5**, 2.0 equiv.), **A** or **B** (same as above).

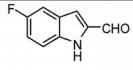
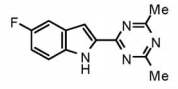
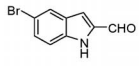
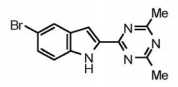
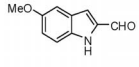
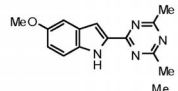
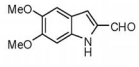
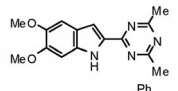
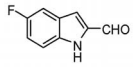
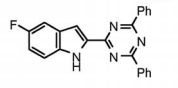
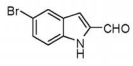
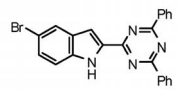
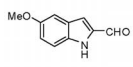
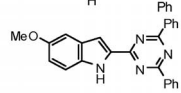
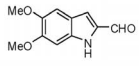
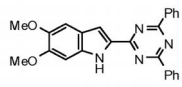
Consequently, as an obvious step, we next investigated the success of the protocol with indole-2-carbaldehyde. Therefore, indole-2-carbaldehyde (**8**) was treated with acetamidine hydrochloride (**4**) or benzamidine hydrochloride (**5**) in the presence of Cs_2CO_3 in DMSO at 90 °C, and as expected, these reactions afforded 1,3,5-triazines **9** and **10** in 75% and 86% yields, respectively (Scheme 4). Next, the generality of the methodology was evaluated by subjecting several indole-2-carbaldehydes to similar reactions. It was satisfying to note that in each case the substituted triazines were isolated in 72–89% yields (Table 3). In contrast to the literature, it is worthwhile to mention that we detected no cases of 1,3,5-dihydrotriazine formation during our studies.



Scheme 4. Reagents and conditions: (i) acetamidine hydrochloride (**4**, 2.0 equiv.), Cs_2CO_3, DMSO, 90 °C, 12 h; (ii) benzamidine hydrochloride (**5**, 2.0 equiv.), Cs_2CO_3, DMSO, 90 °C, 12 h.

Table 3. Scope of base-mediated transformation of indole-2-carbaldehyde to substituted 2-(1,3,5-triazin-2-yl)-1*H*-indoles.[a]



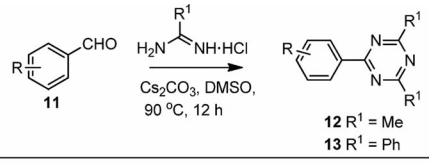
Entry	8	R^1 (4/5)	9 or 10	Yield [%][b]
1		R^1 = Me		72
2		R^1 = Me		74
3		R^1 = Me		79
4		R^1 = Me		74
5		R^1 = Ph		84
6		R^1 = Ph		86
7		R^1 = Ph		89
8		R^1 = Ph		88

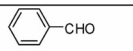
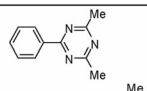
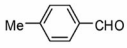
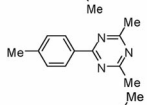
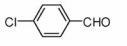
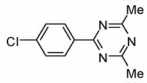
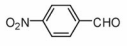
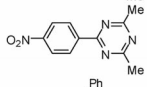
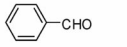
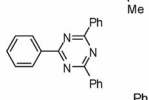
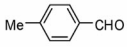
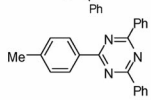
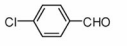
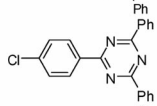
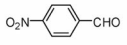
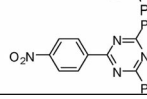
[a] Reagents and conditions: **8** (1.4 mmol), substituted amidine hydrochloride **4/5** (2.8 mmol), Cs_2CO_3 (2.8 mmol), DMSO (2 mL), temperature (90 °C). [b] Isolated yields.

Because 1,3,5-triazines are an important class of compounds having significant antibacterial,[12] pesticidal,[13] and optoelectronic,[14] properties, we considered investigating the extension of our method to simple benzaldehydes. Therefore, different benzaldehydes **11** were treated with acetamidine hydrochloride and benzamidine hydrochloride in the presence of Cs_2CO_3 in DMSO at 90 °C in a parallel

fashion. It was a delight to discover that all of the reactions proceeded smoothly to furnish the respective substituted 1,3,5-triazines **12** and **13** in good to excellent isolated yields (Table 4).

Table 4. Scope of base-mediated transformation of substituted benzaldehyde to 2,4,6-trisubstituted 1,3,5-triazines.[a]

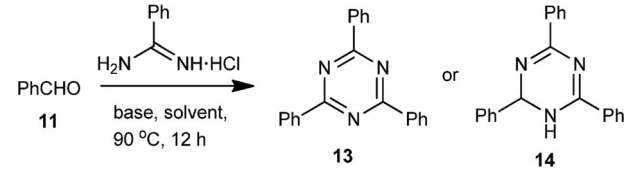


Entry	Benzaldehyde	R^1 H_2N NH·HCl	12 or 13	Yield [%][b]
1		R^1 = Me		78
2		R^1 = Me		81
3		R^1 = Me		76
4		R^1 = Me		73
5		R^1 = Ph		87
6		R^1 = Ph		89
7		R = Ph		85
8		R = Ph		82

[a] Reagents and conditions: **11** (2.8 mmol), substituted amidine hydrochloride (5.6 mmol), Cs_2CO_3 (5.6 mmol), DMSO (2 mL), temperature (90 °C). [b] Isolated yields.

However, mechanistic considerations and a different result from the literature for the reaction of benzaldehyde with benzamidine hydrochloride warranted an investigation into the reaction conditions. Therefore, in a model study, the reaction between benzaldehyde **11** and benzamidine hydrochloride (**5**) was carried out using different bases and solvents (Table 5). In the first set of experiments, DMSO as the solvent was kept constant, and the bases were altered to include both organic and inorganic bases. All of the reactions were performed at 90 °C (Table 5, Entries 1–6). In each case, 2,4,6-triphenyl-1,3,5-triazine (**13**) was isolated in good yields. In the second set of experiments, the base was maintained as Cs_2CO_3, and different solvents including MeCN, DMF, PhMe, and H_2O were examined (Table 5, Entries 7–10,). Notably, in each case, the isolated product was identified to be 2,4,6-triphenyl-1,3,5-dihydrotriazine (**14**) instead of 1,3,5-triazine **13**. From the results of this study, it was evident that the reaction proceeds in the reported fashion, affording the 1,3,5-dihydrotriazine first which then gets converted into the 2,4,6-trisubstituted 1,3,5-triazine, thereby suggesting the role of DMSO as an oxidant during the reaction (Figure 4). Furthermore, to provide chemical evidence to this effect, a representative study of 2,4,6-triphenyl-1,3,5-dihydrotriazine (**14**) was heated at 90 °C in DMSO in either the presence or absence of Cs_2CO_3. Under both conditions, it was observed that the transformation of **14** to 2,4,6-triphenyl-1,3,5-triazine (**13**) occurred, though the reaction was comparatively faster in the presence of the base (Scheme 5).

Table 5. Scope of the base and solvent in the reaction[a] of benzaldehyde and benzamidine hydrochloride.



Entry	Base	Solvent	Yield [%] 13	Yield [%] 14
1	Et_3N	DMSO	68	–
2	DBU[b]	DMSO	64	–
3	DABCO[b]	DMSO	63	–
4	Na_2CO_3	DMSO	72	–
5	K_2CO_3	DMSO	70	–
6	K_3PO_4	DMSO	65	–
7	Cs_2CO_3	toluene	–	81
8	Cs_2CO_3	MeCN	–	82
9	Cs_2CO_3	DMF	–	85
10	Cs_2CO_3	water	–	76[c]

[a] Reagents and conditions: benzaldehyde (**11**, 1.0 mmol), benzamidine hydrochloride (**5**, 2.0 mmol), base (2.2 mmol), solvent (2 mL), temperature (90 °C). [b] DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane. [c] Reaction completed in 36 h.

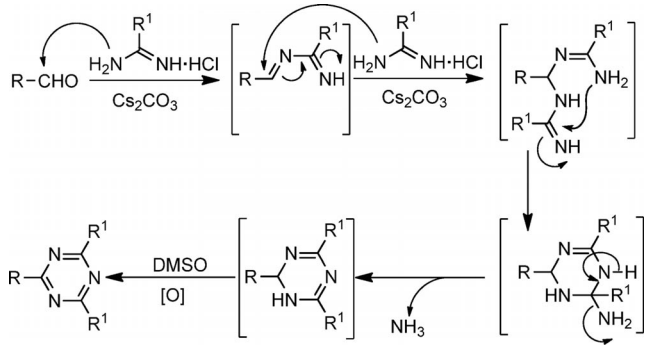
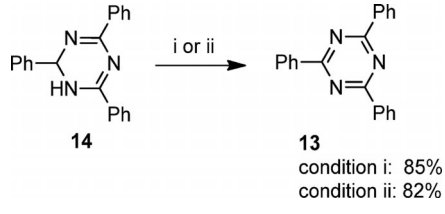


Figure 4. Plausible mechanism for the formation of 1,3,5-triazines from aldehyde.



Scheme 5. Reagents and conditions: (i) Cs_2CO_3 (2.0 equiv.), DMSO (2 mL), 90 °C, 6 h; (ii) DMSO (2 mL), 90 °C, 24 h.

Conclusions

In summary, we have developed a one-step synthesis for 2-amino-5*H*-pyrimido[5,4-*b*]indoles from 3-haloindole-2-carbaldehydes. The synthesis of this indole-fused system was achieved under basic conditions, though the presence of copper and a ligand facilitated the rate of reaction and the formation of the product. In contrast, upon reaction with similar substrates, the substituted amidines gave substituted 2-(1,3,5-triazin-2-yl)-1*H*-indoles through a cascade sequence. On the basis of the results, this methodology was extended to direct the transformation of simple benzaldehydes into 2,4,6-trisubstituted 1,3,5-triazines. The role of DMSO as an oxidant to assist the transformation of 1,3,5-dihydrotriazine to 1,3,5-triazine was demonstrated.

Experimental Section

General Methods: The melting points were measured using capillary tubes with a Precision melting point apparatus containing silicon oil. The IR spectroscopic data were recorded with a Perkin–Elmer RX I FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with either a Bruker DPX-200 or a Bruker Avance DRX-300 FT spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESI-MS data were recorded with a MICROMASS Quadro-II LCMS system. The HRMS spectra were recorded as ESI-HRMS with an Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer. The room temperatures varied between 20 and 35 °C. All of the solvents and chemicals were used as procured from the suppliers.

General Procedure for the Preparation of 5*H*-Pyrimido[5,4-*b*]indol-2-amines, Exemplified by 5*H*-Pyrimido[5,4-*b*]indol-2-amine (6): To a solution of 3-iodoindole-2-carbaldehyde (0.3 g, 1.1 mmol) and guanidine hydrochloride (0.21 g, 2.2 mmol) in DMSO (2 mL) were added CuI (0.021 g, 0.11 mmol), 1,10-phenanthroline (0.025 g, 0.22 mmol), and Cs_2CO_3 (0.72 g, 2.2 mmol). The reaction mixture was heated at 90 °C for the mentioned time in a sealed tube under nitrogen. Thereafter, water (50 mL) and ethyl acetate (25 mL) were added, and the reaction mixture was filtered through a bed of Celite. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (35 mL), dried with anhydrous Na_2SO_4, and concentrated under vacuum. Column chromatography of the crude product over basic alumina (EtOAc/hexanes, 1:1) furnished the pure 5*H*-pyrimido[5,4-*b*]indol-2-amine (**6**) as a brown solid (0.138 g, 68%).

5*H*-Pyrimido[5,4-*b*]indol-2-amine (6): Table 1, Entry 10. R_f = 0.46 (EtOAc/hexanes, 1:1, v/v), m.p. > 250 °C (EtOAc). IR (KBr): $\tilde{\nu}_{max}$ = 3421 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.49 (br. s, 2 H, NH$_2$), 7.14 (t, J = 7.1 Hz, 1 H, Ar), 7.27 (t, J = 7.8 Hz, 1 H, Ar), 7.34 (d, J = 7.8 Hz, 1 H, Ar), 7.89 (d, J = 7.5 Hz, 1 H, Ar), 8.87 (s, 1 H, Ar), 11.41 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 105.6, 111.0, 119.2, 120.2, 120.6, 124.7, 137.5, 150.1, 158.0, 162. ppm. MS (ESI): m/z = 185.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{10}H_9N_4$ [M + H]$^+$ 185.0827; found 185.0822.

8-Fluoro-5*H*-pyrimido[5,4-*b*]indol-2-amine: Table 2, Entry 4. Brown solid (0.132 g from 0.3 g), R_f = 0.43 (EtOAc/hexanes, 1:1, v/v), m.p. > 250 °C (EtOAc). IR (KBr): $\tilde{\nu}_{max}$ = 3433 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.59 (br. s, 2 H, NH$_2$), 7.29–7.33 (m, 2 H, Ar), 7.72–7.76 (m, 1 H, Ar), 8.89 (s, 1 H, Ar), 11.45 (br. s, 1 H, N) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 105.3, 105.7, 111.6, 111.7, 111.9, 112.0, 115.6, 121.6, 122.8, 133.9, 151.1, 158.7, 162.4, 167.1 ppm. MS (ESI): m/z = 203.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{10}H_8FN_4$ [M + H]$^+$ 203.0733; found 203.0728.

8-Bromo-5*H*-pyrimido[5,4-*b*]indol-2-amine: Table 2, Entry 6. Brown solid (0.144 g from 0.3 g), R_f = 0.40 (EtOAc/hexanes, 1:1, v/v), m.p. > 250 °C (EtOAc). IR (KBr): $\tilde{\nu}_{max}$ = 3423 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.64 (br. s, 2 H, NH$_2$), 7.38–7.47 (m, 2 H, Ar), 8.13 (s, 1 H, Ar), 8.93 (s, 1 H, Ar), 11.57 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 103.5, 112.8, 121.8, 123.3, 125.5, 126.9, 137.1, 151.2, 162.5, 167. ppm. MS (ESI): m/z = 263.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{10}H_7BrN_4$ [M + H]$^+$ 262.9932; found 262.9936.

8-Methoxy-5*H*-pyrimido[5,4-*b*]indol-2-amine: Table 2, Entry 8. Brown solid (0.147 g from 0.3 g), R_f = 0.34 (EtOAc/hexanes, 1:1, v/v), m.p. > 250 °C (EtOAc). IR (KBr): $\tilde{\nu}_{max}$ = 3435 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.79 (s, 3 H, OCH$_3$), 6.44 (br. s, 2 H, NH$_2$), 6.88 (d, J = 7.7 Hz, 1 H, Ar), 7.23 (d, J = 8.4 Hz, 1 H, Ar), 7.51 (s, 1 H, Ar), 8.85 (s, 1 H, Ar) 11.23 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.6, 103.4, 111.7, 112.9, 121.3, 132.0, 150.4, 154.3, 158.3, 162.0, 167.2 ppm. MS (ESI): m/z = 215.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{11}N_4O$ [M + H]$^+$ 215.0933; found 215.0929.

7,8-Dimethoxy-5*H*-pyrimido[5,4-*b*]indol-2-amine: Table 2, Entry 9. Brown solid (0.148 g from 0.3 g), R_f = 0.24 (EtOAc/hexanes, 1:1, v/v), m.p. > 250 °C (EtOAc). IR (KBr): $\tilde{\nu}_{max}$ = 3415 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.80 (s, 3 H, OCH$_3$), 3.81 (s, 3 H, OCH$_3$), 6.37 (br. s, 2 H, NH$_2$), 6.91 (s, 1 H, Ar), 7.54 (s, 1 H, Ar), 8.76 (s, 1 H, Ar), 11.26 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 55.7, 56.2, 95.6, 103.6, 106.4, 112.3, 132.0, 144.6, 148.1, 148.2, 157.7, 160.7 ppm. MS (ESI): m/z = 245.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{13}N_4O_2$ [M + H]$^+$ 245.1039; found 245.1042.

General Procedure for the Preparation of 2-(4,6-Dimethyl-1,3,5-triazin-2-yl)-1*H*-indoles as Exemplified by 2-(4,6-Dimethyl-1,3,5-triazin-2-yl)-1*H*-indole (9): To a solution of 3-iodoindole-2-carbaldehyde (0.3 g, 1.1 mmol) and acetamidine hydrochloride (0.21 g, 2.2 mmol) in DMSO (2 mL) was added Cs_2CO_3 (0.72 g, 2.2 mmol), and the reaction mixture was heated at 90 °C for the mentioned time in a sealed tube under nitrogen. Thereafter, water (50 mL) and ethyl acetate (25 mL) were added, and the reaction mass and the organic layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (35 mL), dried with anhydrous Na_2SO_4, and concentrated under vacuum. Column chromatography of the crude product product over silica gel (60–120 mesh, EtOAc/hexanes, 1:4) furnished the pure 2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1*H*-indole (**9**) as a yellow solid (0.183 g, 74%).

2-(4,6-Dimethyl-1,3,5-triazin-2-yl)-1*H*-indole (9): Scheme 3. R_f = 0.53 (EtOAc/hexanes, 1:4, v/v), m.p. 208–210 °C (diethyl ether). IR (KBr): $\tilde{\nu}_{max}$ = 3401 (NH) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.66 (s, 6 H, 2 CH$_3$), 7.15 (t, J = 7.3 Hz, 1 H, Ar), 7.31 (t, J = 7.5 Hz, 1 H, Ar), 7.44 (d, J = 8.2 Hz, 1 H, Ar), 7.60 (d, J = 0.8 Hz, 1 H, Ar), 7.71 (d, J = 8.0 Hz, 1 H, Ar), 9.45 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$ + [D$_6$]DMSO): δ = 25.1, 107.2, 111.9, 119.8, 121.4, 124.2, 127.6, 133.2, 137.5, 164.8, 175.4 ppm. MS (ESI): m/z = 225.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{13}N_4$ [M + H]$^+$ 225.1141; found 225.1143.

2-(4,6-Dimethyl-1,3,5-triazin-2-yl)-5-fluoro-1*H*-indole: Table 3, Entry 1. Yellow solid (0.320 g from 0.3 g), R_f = 0.51 (EtOAc/hexanes,

1:4, v/v), m.p. 219–220 °C (diethyl ether). IR (KBr): $\tilde{\nu}_{max}$ = 3412 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 6 H, 2 CH_3), 7.07 (dt, ^1J = 9.1 Hz, ^2J = 2.3 Hz, 1 H, Ar), 7.33–7.39 (m, 2 H, Ar), 7.54 (s, 1 H, Ar), 9.45 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$ + [D_6]DMSO): δ = 24.6, 104.6, 105.0, 105.3, 106.4, 112.2, 112.7, 127.1, 134.0, 134.5, 156.0, 164.3, 175.0 ppm. MS (ESI): *m*/*z* = 243.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{12}FN_4$ [M + H]$^+$ 243.1046; found 243.1040.

5-Bromo-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1*H*-indole: Table 3, Entry 2. Brown solid (0.301 g from 0.3 g), R_f = 0.50 (EtOAc/hexanes, 1:4, v/v), m.p. 225–226 °C (diethyl ether). IR (KBr): $\tilde{\nu}_{max}$ = 3409 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 6 H, 2 CH_3), 7.30–7.40 (m, 2 H, Ar), 7.51 (s, 1 H, Ar), 7.84 (s, 1 H, Ar), 9.48 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + [D_6]DMSO): δ = 24.4, 105.5, 111.9, 113.4, 122.8, 126.0, 128.4, 134.0, 135.7, 164.0, 174.9 ppm. MS (ESI): *m*/*z* = 303.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{12}BrN_4$ [M + H]$^+$ 303.0245; found 303.0242.

2-(4,6-Dimethyl-1,3,5-triazin-2-yl)-5-methoxy-1*H*-indole: Table 3, Entry 3. Pale yellow solid (0.344 g from 0.3 g), R_f = 0.48 (EtOAc/hexanes, 1:4, v/v), m.p. 213-214 °C (diethyl ether). IR (KBr): $\tilde{\nu}_{max}$ = 3396 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 6 H, 2 CH_3), 3.87 (s, 3 H, OCH_3), 6.99 (d, *J* = 8.6 Hz, 1 H, Ar), 7.10 (s, 1 H, Ar), 7.33 (d, *J* = 8.9 Hz, 1 H, Ar), 7.50 (s, 1 H, Ar), 9.37 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + [D_6]DMSO): δ = 23.9, 53.8, 100.2, 105.5, 112.1, 114.6, 126.6, 132.3, 132.5, 152.6, 163.7, 174.2 ppm. MS (ESI): *m*/*z* = 255.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{15}N_4O$ [M + H]$^+$ 255.1246; found 255.1251.

2-(4,6-Dimethyl-1,3,5-triazin-2-yl)-5,6-dimethoxy-1*H*-indole: Table 3, Entry 4. Yellow solid (0.307 g from 0.3 g), R_f = 0.42 (EtOAc/hexanes, 1:4, v/v), m.p. 231–232 °C (diethyl ether). IR (KBr): $\tilde{\nu}_{max}$ = 3391 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 6 H, 2 CH_3), 3.94 (s, 6 H, 2 OCH_3), 6.88 (s, 1 H, Ar), 7.06 (s, 1 H, Ar), 7.48 (s, 1 H, Ar), 9.36 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 56.2, 56.3, 94.0, 102.6, 108.6, 116.5, 121.8, 132.1, 132.5, 133.1, 146.3, 150.3, 176.0 ppm. MS (ESI): *m*/*z* = 285.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{17}N_4O_2$ [M + H]$^+$ 285.1352; found 285.1355.

2-(4,6-Diphenyl-1,3,5-triazin-2-yl)-1*H*-indole (10): Scheme 3. Off-white solid (0.34 g from 0.3 g), R_f = 0.72 (EtOAc/hexanes, 1:4, v/v), m.p. 181–182 °C (hexanes). IR (KBr): $\tilde{\nu}_{max}$ = 3465 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.1 Hz, 1 H, Ar), 7.35 (t, *J* = 7.4 Hz, 1 H, Ar), 7.50–7.63 (m, 7 H, Ar), 7.75 (s, 1 H, Ar), 7.78 (s, 1 H, Ar), 8.73 (d, *J* = 6.5 Hz, 4 H, Ar), 9.53 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.4, 112.0, 120.9, 122.6, 125.3, 128.7, 128.8, 129.1, 132.7, 134.5, 136.1, 137.6, 166.1, 171.5 ppm. MS (ESI): *m*/*z* = 349.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{23}H_{17}N_4$ [M + H]$^+$ 349.1453; found 349.1455.

2-(4,6-Diphenyl-1,3,5-triazin-2-yl)-5-fluoro-1*H*-indole: Table 3, Entry 5. Yellow solid (0.566 g from 0.3 g), R_f = 0.71 (EtOAc/hexanes, 1:4, v/v), m.p. 188–190 °C (hexanes). IR (KBr): $\tilde{\nu}_{max}$ = 3486 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10 (dt, ^1J = 9.0 Hz, ^2J = 2.3 Hz, 1 H, Ar), 7.37–7.46 (m, 2 H, Ar), 7.56–7.63 (m, 6 H, Ar), 7.73 (s, 1 H, Ar), 8.73 (d, *J* = 6.5 Hz, 4 H, Ar), 9.54 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 106.6, 106.9, 108.0, 108.1, 112.7, 112.8, 114.1, 114.4, 128.8, 128.9, 129.1, 132.8, 134.1, 135.9, 136.0, 156.8, 160.0, 165.9, 171.5 ppm. MS (ESI): *m*/*z* = 367.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{23}H_{16}FN_4$ [M + H]$^+$ 367.1359; found 367.1355.

5-Bromo-2-(4,6-diphenyl-1,3,5-triazin-2-yl)-1*H*-indole: Table 3, Entry 6. Brown solid (0.493 g from 0.3 g), R_f = 0.68 (EtOAc/hexanes, 1:4, v/v), m.p. 201–202 °C (hexanes). IR (KBr): $\tilde{\nu}_{max}$ = 3438 (NH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 7.42 (dd, ^1J = 8.7 Hz, ^2J = 1.8 Hz, 1 H, Ar), 7.58 (d, *J* = 8.8 Hz, 1 H, Ar), 7.65–7.73 (m, 7 H, Ar), 7.96 (s, 1 H, Ar), 8.78 (d, *J* = 6.7 Hz, 4 H, Ar), 12.31 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 106.9, 112.8, 114.7, 124.1, 127.3, 128.8, 128.9, 129.6, 133.1, 135.3, 135.5, 136.9, 165.8, 170.9 ppm. MS (ESI): *m*/*z* = 427.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{23}H_{16}BrN_4$ [M + H]$^+$ 427.0558; found 427.0554.

2-(4,6-Diphenyl-1,3,5-triazin-2-yl)-5-methoxy-1*H*-indole: Table 3, Entry 7. Yellow solid (0.576 g from 0.3 g), R_f = 0.63 (EtOAc/hexanes, 1:4, v/v), m.p. 195–197 °C (hexanes). IR (KBr): $\tilde{\nu}_{max}$ = 3506 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 7.02 (dd, ^1J = 8.9 Hz, ^2J = 2.3 Hz, 1 H, Ar), 7.15 (d, *J* = 1.9 Hz, 1 H, Ar), 7.41 (d, *J* = 8.9 Hz, 1 H, Ar), 7.56–7.62 (m, 6 H, Ar), 7.70 (s, 1 H, Ar), 8.73 (d, *J* = 6.3 Hz, 4 H, Ar), 9.45 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.9, 102.7, 107.9, 112.8, 116.9, 128.8, 129.1, 132.7, 133.0, 134.9, 136.1, 154.9, 166.1, 171.5 ppm. MS (ESI): *m*/*z* = 379.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{19}N_4O$ [M + H]$^+$ 379.1559; found 379.1562.

2-(4,6-Diphenyl-1,3,5-triazin-2-yl)-5,6-dimethoxy-1*H*-indole: Table 3, Entry 8. Yellow solid (0.525 g from 0.3 g), R_f = 0.53 (EtOAc/hexanes, 1:4, v/v), m.p. 218–220 °C (hexanes). IR (KBr): $\tilde{\nu}_{max}$ = 3447 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 6 H, 2 OCH_3), 6.91 (s, 1 H, Ar), 7.08 (s, 1 H, Ar), 7.44–7.47 (m, 1 H, Ar), 7.53–7.60 (m, 5 H, Ar), 7.63 (d, *J* = 1.2 Hz, 1 H, Ar), 8.70 (d, *J* = 6.3 Hz, 4 H, Ar), 9.43 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1, 56.2, 93.9, 102.6, 108.3, 121.8, 126.6, 128.6, 128.9, 132.5, 132.8, 133.0, 136.3, 146.1, 150.0, 165.7, 171.1 ppm. MS (ESI): *m*/*z* = 409.3 [M + H]$^+$. HRMS (ESI): calcd. for $C_{25}H_{21}N_4O_2$ [M + H]$^+$ 409.1665; found 409.1662.

Supporting Information (see footnote on the first page of this article): Spectroscopic details of the compounds in Tables 4 and 2 (continued) and copies of the ^1H and ^{13}C NMR spectra for all of the compounds are provided.

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[11] Crystals were coated with a light hydrocarbon oil and mounted in a 100 K dinitrogen stream of a Bruker SMART APEX CCD diffractometer equipped with a CRYO Industries low-temperature apparatus. Intensity data were collected using graphite-monochromated Mo-K_α radiation. The data integration and reduction were processed with SAINT software. An absorption correction was applied. The structures were solved by the direct method using SHELXS-97 and refined on F^2 by a full-matrix least-squares technique using the SHELXL-97 program package. The non-hydrogen atoms were refined anisotropically. In the refinement, the hydrogens were treated as riding atoms using the SHELXL default parameters. The crystal data of 2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1*H*-indole (crystallized from DMSO): $C_{13}H_{12}N_4$, M = 224.27, orthorhombic, space group $P21$, a = 6.3334(15) Å, b = 9.561(2) Å, c = 18.021(4) Å, α = 90.00, β = 90.00 (7), γ = 90.00, V = 1091.3(4) Å^3, Z = 4, D_x = 1.365 g cm^{-3}, μ (Mo-K_α) = 0.086 mm^{-1}, F (000) = 472.0, yellow block crystals with dimensions 0.22 × 0.20 × 0.18 mm, 7140 reflections measured (R_{int} = 0.0376), 2677 unique, wR_2 = 0.1926, conventional R = 0.0614 on F^2 values of 2677 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 000), S = 1.063 for all data and 154 parameters. All of these software packages were the integrated WINGX software package. CCDC-873222 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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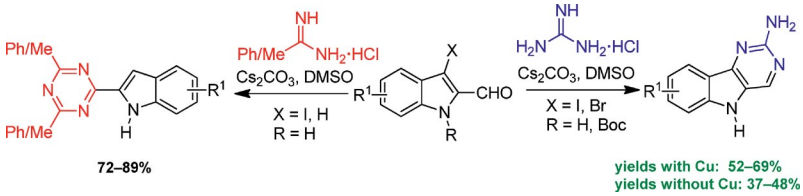

The synthesis of 2-amino-5*H*-pyrimido[5,4-*b*]indoles from 3-haloindole-2-carbaldehyde and guanidine hydrochloride is described. In contrast, 3-haloindole-2-carbaldehydes or indole-2-carbaldehydes react with substituted amidine hydrochlorides to give 2-(1,3,5-triazin-2-yl)-1*H*-indole derivatives in excellent yields. The latter protocol was used to prepare 2,4,6-trisubstituted 1,3,5-triazines.

Keywords: Nitrogen heterocycles / Fused-ring systems / Synthetic methods / Copper

