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Synthesis of N-Functionalized/NH-Multisubstituted Indoles, Thienopyrroles, Pyrroloindoles, and Pyrazolopyrroles via Sequential One-Pot Base-Mediated and Copper-Catalyzed Inter- and Intramolecular Amination of 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitriles

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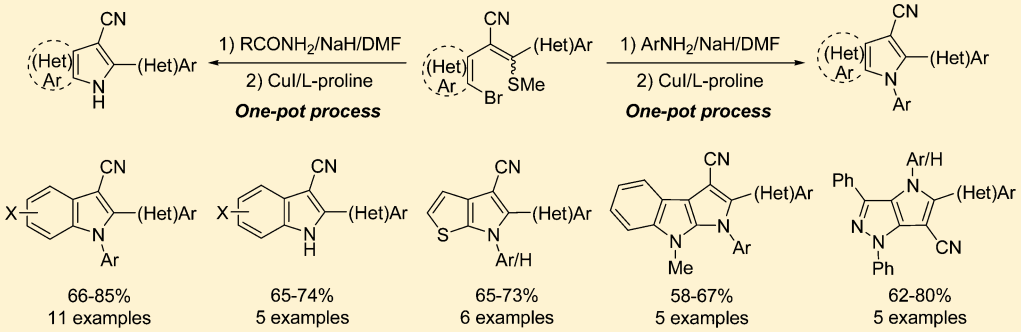
Supporting Information



ABSTRACT: A novel, efficient route to substituted 1-*N*-(het)aryl/NH-2-(het)aryl-3-cyanoindoles and related pyrrolo-fused heterocycles such as thienopyrroles, pyrroloindoles, and pyrazolopyrroles has been reported. The overall protocol involves sequential cycloamination of readily available 2-[2-bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitrile precursors with primary amines or amides via two key C−N bond-forming processes, one base-mediated intermolecular and the other Cu-catalyzed intramolecular arylamination leading to N(1)−C(2) and N(1)−C(7a) bond formation, respectively, in a two-step one-pot procedure.

INTRODUCTION

The indole structural motif[1] has been generally recognized as a "privileged structure" in medicinal chemistry because of the presence of this heterocyclic scaffold in numerous therapeutic agents,[2] as well as in natural products,[3] displaying a wide range of biological and pharmacological activity. Therefore, the development of new efficient and practical methods for synthesis of functionalized indoles has attracted the attention of synthetic organic chemists over the past several decades.[4] While classical approaches to indoles are based on a condensation and cyclization sequence, transition-metal-catalyzed C−C and C−N bond-formation reactions have recently enabled the development of alternative methodologies toward modular indole synthesis.[4,5] In this context, palladium-catalyzed transformations for the synthesis of indole backbone starting from *o*-alkynylanilines,[5,6] as well as Pd-catalyzed coupling of *o*-haloanilines with terminal alkynes,[5,7] have been studied extensively. These methods generally afford 3-unsubstituted indoles; however, in some cases, subsequent functionalization of the 3-position can be performed in a one-pot manner, via either Pd-catalyzed arylation,[6c,d] alkenylation,[6e] alkylation,[6f,g] or alkynation.[6h,i] Palladium-catalyzed reaction of *o*-haloanilines with internal alkynes[2e,5,8] based on Larock's protocol[8a] provides direct synthesis of 2,3-substituted indoles, which, although it is an efficient protocol for the synthesis of complex indoles,[8d] frequently displays poor regioselectivity for many substrates, requiring fine-tuning of individual reaction conditions and ligands to obtain optimal results.[8,8b] Synthesis of 2-substituted indoles by palladium-catalyzed tandem intramolecular C−N and intermolecular C−C bond formation cross-coupling strategy,[9a−c] using *o*-*gem*-dihalovinylaniline substrates, has also been reported.[9] With emerging interest in the Ullman Goldberg reaction[10] and also due to the lower cost of copper catalysts, several new efficient routes to indole synthesis have also been developed via copper-catalyzed reactions.[11] Significant breakthroughs have also been made in recent years by several research groups[12] for developing direct approaches for indole synthesis by transition-metal-catalyzed oxidative C−H activa-

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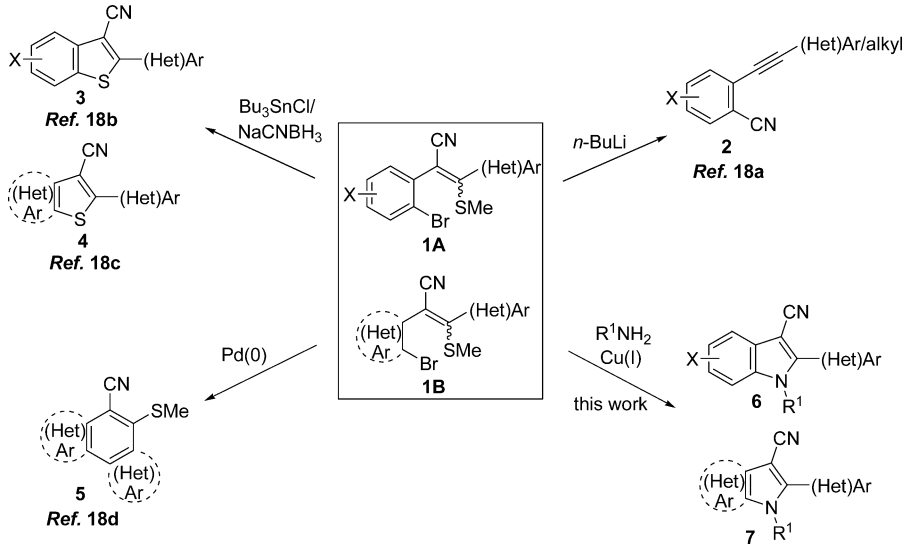
Scheme 1. 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitriles as Versatile Synthons for Heterocyclic Synthesis



tion. However, the synthesis of N-functionalized multisubstituted indoles has not received much attention.[2e,6f,12d,13]

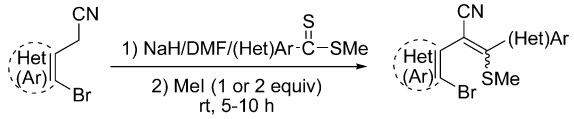
Ackermann and co-workers[14] have reported a useful route to indole framework via palladium-catalyzed tandem N-arylation−hydroamination of *o*-alkynylhaloarene precursors. Willis and co-workers[15] have reported an efficient route to N-functionalized indoles via palladium-catalyzed inter- and intramolecular alkenyl−arylamination reaction of a broad range of 2-(2-haloalkenyl)aryl halides as well as the corresponding alkenyl triflates. Application of Cu-catalyzed amination methodology for construction of the indole ring via a key N(1)−C(7a) bond formation has also been demonstrated by several workers.[11a,c,16]

As part of our own research efforts directed toward design and development of new synthetic methods for substituted and fused five- and six-membered heterocycles, utilizing polarized ketene dithioacetals and other newly developed organosulfur synthons,[17] we have recently reported in a series of papers synthesis and application of a new class of organosulfur building blocks such as 2-[2-bromo(het)aryl]-3-(het)aryl/alkyl-3-(methylthio)acrylonitriles with the general structures **1A** and **1B** (Scheme 1). Thus, we have previously shown that these intermediates (**1A**) undergo a novel unexpected anionic domino rearrangement in the presence of *n*-butyllithium, leading to a general synthesis of 2-(het)aryl/alkyl-1-(*o*-cyano)-arylacetylenes **2**.[18a] Also, we have developed an efficient route for synthesis of 2-(het)aryl/alkyl-3-cyanobenzothiophenes **3**[18b] and the corresponding thienoheterocycles **4**[18c] by intramolecular radical cyclization of these intermediates (Scheme 1). It was further demonstrated that Pd(0)-catalyzed direct intramolecular (het)arylation of these intermediates provides facile access to functionalized phenanthrenes and a variety of novel angularly fused polycyclic heteroarenes **5**[18d] in good yields (Scheme 1). During the course of these studies, we became interested in employing intermediates **1A** and **1B** in a cascade inter- and intramolecular C−N bond formation−cyclization process with various primary amines, with a view to develop a novel synthesis of substituted indoles and hetero-fused pyrroles such as **6** and **7**, respectively (Scheme 1). We have successfully achieved this goal and herein describe a two-step one-pot protocol, involving base-mediated intermolecular N(1)−C(2) and Cu-catalyzed intramolecular N(1)−C(7a) bond formation with primary amines, which allows direct transformation of these easily accessible intermediates **1** into a variey of N-functionalized/NH multisubstituted indoles and their hetero-fused analogues.

RESULTS AND DISCUSSION

The desired 2-[2-bromo(het)aryl]-3-(het)aryl-3-(methylthio)-acrylonitrile precursors **1a−l** (Table 2), **13a−e** (Table 6), **16a−e** (Table 7), and **19a−d** (Table 8) were prepared according to previously developed methods in our laboratory,[18] by base-induced condensation of the corresponding 2-bromo-(het)-arylacetonitriles with (het)aryl dithioesters, followed by in situ S-methylation of the resulting enethiolate intermediates (Scheme 2).

Scheme 2. Synthesis of 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitrile Precursors



1, **13**, **16**, **19**

The general strategy for one-pot indole synthesis from **1** is shown in Scheme 3. The major expectation was that treatment of **1** with primary amines will furnish, under optimized conditions, enaminonitrile **8** via conjugate addition−elimination of amine on activated *β*-(methylthio)acrylonitrile double bond of **1**. The ortho bromo substituent in the benzene ring of **8** should offer the possibility to convert them (in situ or in two steps) into indole **6** by a copper- (or palladium-) catalyzed intramolecular N-arylamination−cyclization process.

Cyclization of acrylonitrile **1a** with 4-methoxyaniline was selected as a test reaction for optimization of reaction conditions for the synthesis of indole **6a** (Scheme 4, Table 1). We first focused on devising reaction conditions for a two-step process, that is, synthesis and isolation of enaminonitrile **8a** by conjugate addition−elimination on **1a** with 4-methoxyaniline and its subsequent copper- (or palladium-) catalyzed intramolecular arylamination to indole **6a** (Scheme 4, route a). Thus, optimization studies revealed that **1a** remained unaffected when reacted with 4-methoxyaniline in the

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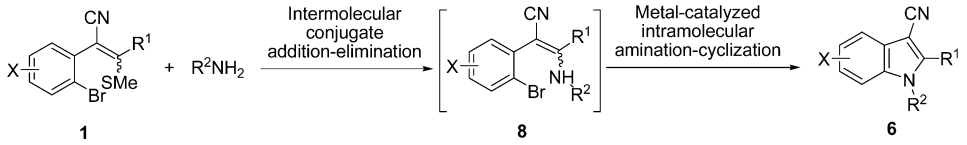
Scheme 3. Designed Strategy for Synthesis of Indole 6 from 1



Scheme 4. Synthesis of Indole 6a from 1a via Enaminonitrile 8a

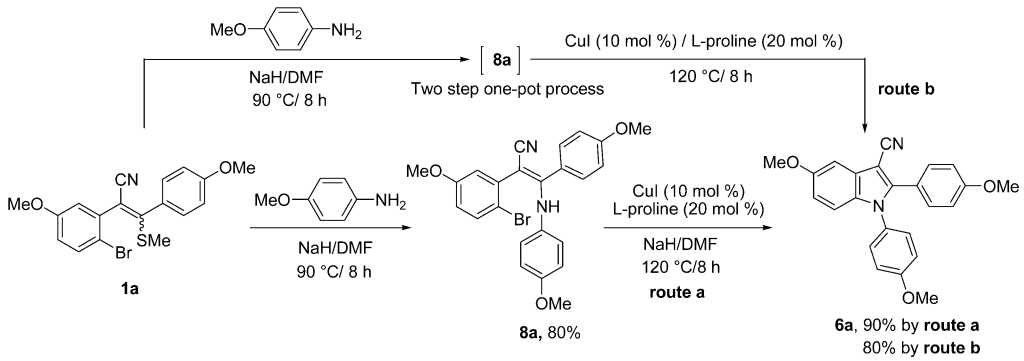
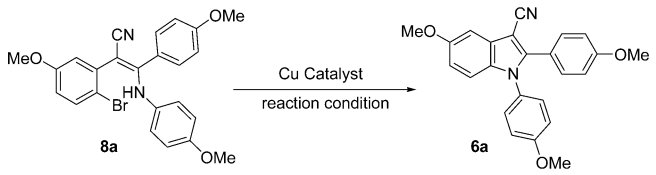


Table 1. Optimization of Reaction Conditions for Synthesis of 6a from 8a[a]



entry	Cu catalyst (10 mol %)	ligand (20 mol %)	base	solvent	temp, °C/time, h	% yield **6a**
1	CuI		*t*-BuOK	DMF	120/12	65
2	CuI	L-proline	*t*-BuOK	DMF	120/10	78
3	CuI	L-proline	NaH	DMF	120/8	90
4	CuI	phenanthroline	NaH	DMF	120/9	78
5	CuI	DMEDA	NaH	DMF	120/10	73
6	CuI	cyclohexane 1,2-diamine	NaH	DMF	120/10	75
7	CuI	ethylene glycol	K_3PO_4	2-propanol	80/12	68
8	CuI	ethylene glycol	K_3PO_4	DMF	120/10	78
9	CuI	L-proline	Cs_2CO_3	DMF	120/12	70
10	CuI	L-proline	K_2CO_3	DMF	120/12	55
11	CuBr	L-proline	NaH	DMF	120/10	78
12	CuOAc	L-proline	NaH	DMF	120/10	75
13	CuI (5 mol %)	L-proline	NaH	DMF	120/15	75

[a]Reactions were performed with **8a** (1 mmol) in 5 mL of solvent with 10 mol % Cu catalyst, 20 mol % ligand, and 1 equiv of base.

presences of bases like K_2CO_3 or Cs_2CO_3 in solvents like toluene, acetonitrile, or *N*,*N*-dimethylformamide (DMF), even at higher temperature, whereas with potassium *t*-butoxide in DMF at 120 °C, enaminonitrile **8a** could be obtained in maximum yield of 35% only, upon prolonged heating (24 h). On the other hand, when sodium hydride was employed as base in DMF at 90 °C, the reaction was complete within 8 h, furnishing enaminonitrile **8a** in 80% yield (Scheme 4). The ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data of **8a** revealed that it exists as a single (*E*) stereoisomer.

Having established the reaction conditions for formation of enaminonitrile **8a**, we next set out to examine its intramolecular arylamination cross-coupling to indole **6a** under the influence of various catalysts and ligands. In view of the lower costs of copper salts and related ligands, in comparison to palladium catalysts and phosphine ligands, we first evaluated copper-catalyzed intramolecular cyclization of **8a** to indole **6a**,[10,11,16] and these results are summarized in Table 1.

Copper-catalyzed "nitrogen ligand free" amination reactions are shown to proceed efficiently in the presence of *t*-BuOK as base.[14a,16a] We therefore first explored the possibility of accomplishing intramolecular aminoarylation of **8a** with inexpensive CuI as catalyst under these conditions, which afforded the desired indole **6a** in 65% yield (Table 1, entry 1). On the other hand, promising results could be achieved with proline ligand, affording indole **6a** in increased yield of 78% under identical conditions (entry 2). Furthermore, use of sodium hydride as base was found to be superior, furnishing indole **6a** in 90% yield within 8 h (entry 3). Preliminary studies revealed that DMF, among a variety of other solvents [toluene, dimethyl sulfoxide (DMSO), acetonitrile, *N*-methylpyrrolidone (NMP), and tetrahydrofuran (THF)], proved to give rise to optimal results. Use of representative ligands [phenanthroline,

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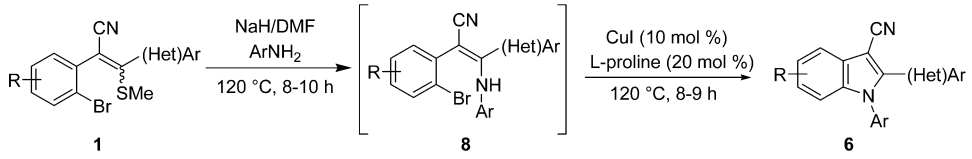
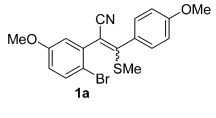
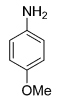
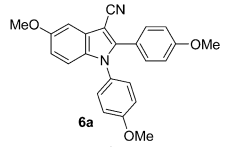
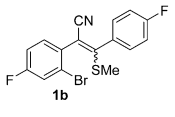
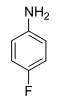
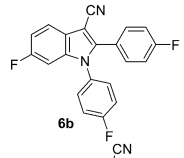
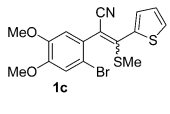
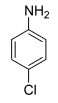
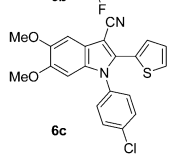
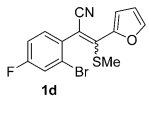
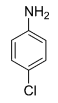
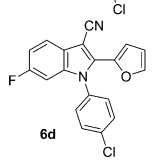
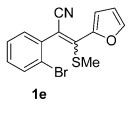
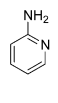
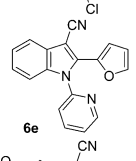
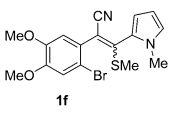
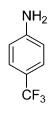
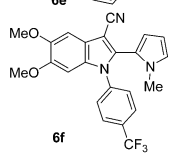
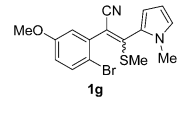
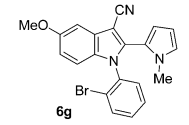
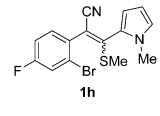
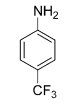
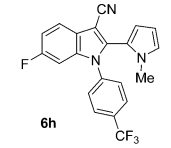
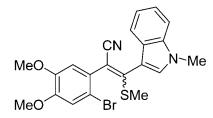
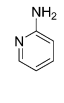
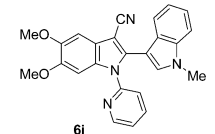
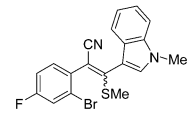
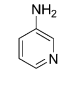
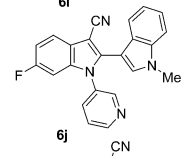
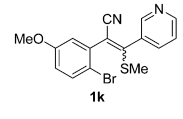
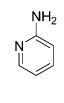
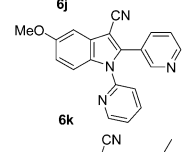
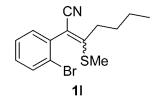
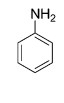
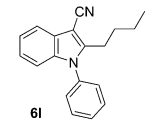
Table 2. One-Pot Two-Step Synthesis of 1,2,3-Trisubstituted Indoles 6 from 1[a]



entry	substrate	amine	product	yield (%)
1	 1a		 6a	80
2	 1b		 6b	85
3	 1c		 6c	74
4	 1d		 6d	75
5	 1e		 6e	75
6	 1f		 6f	68
7	 1g		 6g	78
8	 1h		 6h	71
9	 1i		 6i	75
10	 1j		 6j	78
11	 1k		 6k	66
12	 1l		 6l	0

[a]Reactions were performed with **1** (1 mmol) plus amine (1.1 mmol) in 10 mL of solvent and 2 equiv of 100% NaH, followed by addition of 10 mol % CuI and 20 mol % L-proline.

N,*N*′-dimethylethylenediamine (DMEDA), and cyclohexane-1,2-diamine] generally employed in Cu-catalyzed N-arylation also furnished the indole **6a** in 73−78% yield (entries 4−6). Similarly, ethylene glycol in the presence of K_3PO_4 as base in either 2-propanol or DMF was also found to be effective,[11c] providing **6a** in reasonably good yields (entries 7 and 8). Bases like Cs_2CO_3 and K_2CO_3 were found to be inferior in comparison to sodium hydride (entries 9 and 10), whereas alternative Cu sources could also be employed, with both CuBr and CuOAc found to be effective, although with reduced efficiency compared to CuI (entries 11 and 12 vs entry 3). Reducing the catalytic loading (5 mol %) resulted in decreased yield of **6a** even after 15 h of heating (entry 13).

With optimized reaction conditions for the two-step synthesis of indole **6a** from 2-(2-bromoaryl)acrylonitrile **1a** in hand (Table 1, entry 3), we next attempted one-pot sequence by subjecting in situ generated enaminonitrile **8a** to intramolecular arylamination by adding CuI (10 mol %) and proline (20 mol %) to the reaction mixture (from **1a** and 4-methoxyaniline in the presence of NaH in DMF) and further heating it at 120 °C (monitored by TLC). To our delight, the reaction was complete within 8 h and workup of the reaction mixture afforded indole **6a** in 80% yield (Scheme 4, route b). Despite the slightly reduced yield of indole **6a** in comparison with the two-step process, this sequential one-pot procedure was followed throughout our subsequent studies for the synthesis of 1-*N*-aryl-2-(het)arylindoles **6** (Table 2).

Having accomplished the optimal conditions for the two-step one-pot base-mediated amination−Cu-catalyzed intramolecular arylamination protocol, we set out to evaluate the scope and generality of this novel indole synthesis by varying the substituents on acrylonitrile precursors **1**, as well as on N-coupling partners, that is, anilines, following these optimized reaction conditions (Table 2). Thus, the reaction was equally facile with electron-donating and electron-withdrawing substituents on the aromatic ring of **1** (**1a**−**d**), yielding indoles **6a**−**d** in high yields (Table 2, entries 1−4). Also, by employing appropriate 3-(het)aryl-substituted acrylonitrile precursors (**1c**−**k**), the protocol could also be extended for synthesis of 2-(het)arylindoles bearing 2-thienyl (**6c**), 2-furyl (**6d** and **6e**), 2-(*N*-methylpyrrolyl) (**6f**−**h**), 3-(*N*-methylindolyl) (**6i** and **6j**), and 3-pyridyl (**6k**) moieties in good to excellent yields (entries 3−11). It should be noted that despite the broad application of palladium- (or copper-) catalyzed C−N cross-coupling/cyclization protocol for synthesis of 2-substituted indoles from the relevant acetylene precursors, not much attention

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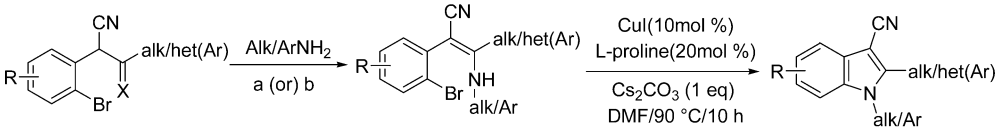
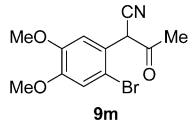
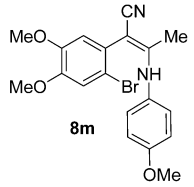
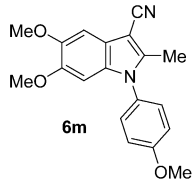
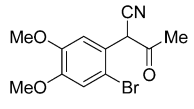
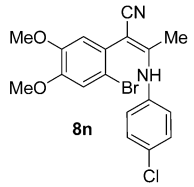
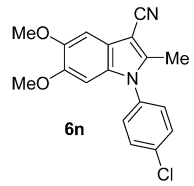
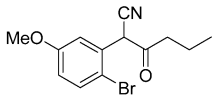
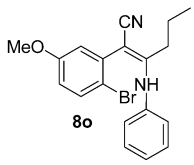
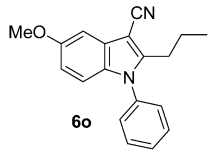
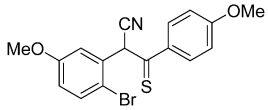
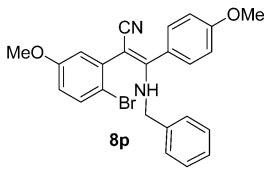
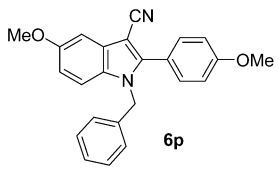
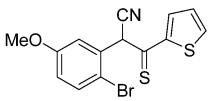
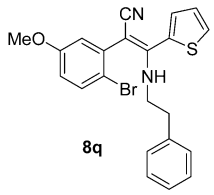
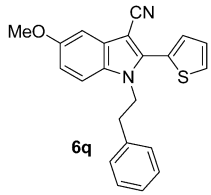
Table 3. Synthesis of 3-Cyano-2-alkyl-*N*-arylindoles 6m−o and 3-Cyano-2-(het)aryl-*N*-alkylindoles 6p and 6q[a]



9m, **9o**, X = O
9p-q, X = S

8m-q

6m-q

entry	substrate **9**	substrate **8**	product[c]	yield (%)
1	 **9m**	 **8m**	 **6m**	80
2	 **9m**	 **8n**	 **6n**	78
3	 **9o**	 **8o**	 **6o**	60
4	 **9p**	 **8p**	 **6p**	55
5	 **9q**	 **8q**	 **6q**	55

[a]AcOH/reflux, 6−7 h (for **8m−o**). [b]MeCN/rt, 5−6 h (for **8p** and **8q**). [c]Reactions were performed with **8** (1 mmol) in 5 mL of solvent with 10 mol % CuI, 20 mol % L-proline, and 1 equiv of Cs_2CO_3.

has been paid to extending this methodology for synthesis of biologically important 2-(het)arylindoles from the corresponding *o*-halo(het)arylacetylene substrates.[14g,16a] Also, extension of the reaction to a range of commercially available anilines, as N-coupling partners in the cyclization reaction, revealed that a wide variety of substitution pattern and functionalities are tolerated, as shown in Table 2. Thus, *N*-arylindoles containing both electron-donating (**6a**; entry 1) and electron-withdrawing groups (**6b−d**, **6f**, and **6h**; entries 2−4, 6, and 8) or bearing sterically constrained *o*-substituent (**6g**; entry 7) on the *N*-aryl moiety could be prepared efficiently in good yields following this procedure (Table 2). When the pyridyl-2- (or 3-) amines were used as the amine coupling partners, the corresponding *N*-pyridylindoles (**6e** and **6i−k**; entries 5 and 9−11) were also obtained in good yields (Table 2).

Further elaboration of the methodology for the synthesis of 2-alkylindole by treatment of 2-(2-bromophenyl)-3-(methylthio)hept-2-enenitrile (**1l**) with aniline under two-step one-pot conditions (NaH/CuI/proline) did not yield the desired indole **6l**, furnishing only an intractable reaction mixture (Table 2, entry 12). We therefore synthesized few 2-alkyl- (**6m−o**) and 1-*N*-alkyl- (**6p** and **6q**) indoles via the two-step procedure as depicted in Table 3. Thus, enaminonitriles **8m−q** were prepared by reaction of either α-ketonitriles[19] **9m** and **9o** or the corresponding thiocarbonyl analogues **9p** and **9q** with appropriate primary amines under varying conditions (Table 3). However, enaminonitriles **8m−q** failed to yield indoles **6m−q** when subjected to Cu-catalyzed intramolecular aminoarylation under previously described conditions (NaH/CuI/proline/DMF), affording only complex mixture of products. Optimization of reaction conditions—using weaker base such as Cs_2CO_3 instead of NaH in the presence of CuI catalyst and proline as ligand—afforded the corresponding 2-alkyl (**6m−o**) and 1-*N*-alkyl (**6p** and **6q**) indoles in moderate to good yields (Table 3).

In view of the importance of free N−H indoles among biologically active compounds,[2,20] besides the ease with which less nucleophilic amides can be N-arylated under copper

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Scheme 5. Synthesis of *N*-Acylenaminonitriles and Their Cu-Catalyzed Intramolecular N-Arylation−Hydrolysis to Indole 12a

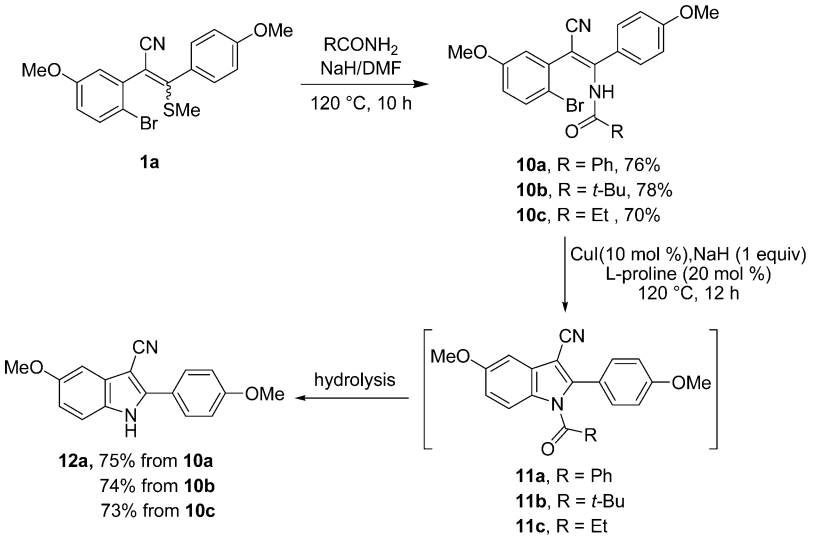
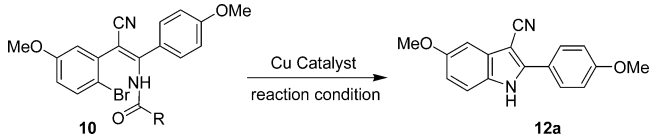


Table 4. Attempted Intramolecular N-Arylation of *N*-Acylenaminonitriles 10



entry	substrate	Cu catalyst (10 mol %)	ligand (20 mol %)	base (equiv)	solvent	temp, °C/time, h	% yield **12a**
1	**10a**	CuI	L-proline	NaH (1)	DMF	120/12	75
2	**10b**	CuI	L-proline	NaH (1)	DMF	120/12	74
3	**10a**	CuI	DMEDA	K_2CO_3 (2)	toluene	110/24	70
4	**10a**	CuI	DMEDA	K_2CO_3 (2)	THF	80/12	62
5	**10b**	CuI	DMEDA	K_2CO_3 (2)	toluene	110/12	66
6	**10a**	CuTC	DMEDA	K_2CO_3 (2)	toluene	110/12	70
7	**10b**	CuTC	DMEDA	K_2CO_3 (2)	toluene	110/12	68
8	**10c**	CuI	DMEDA	K_2CO_3 (2)	toluene	110/12	64

catalysis,[10a−c] we further conceived of extending this protocol for the synthesis of *N*-acylindoles **11** and their subsequent hydrolysis to the corresponding NH indoles **12** (Scheme 5 and Table 4).[16a] Thus, the acrylonitrile substrate **1a** was reacted with either benzamide, trimethylacetamide, or propionamide in the presence of NaH/DMF (120 °C/10 h), yielding the corresponding *N*-acylenaminonitriles **10a−c** in good yields (Scheme 4). However, subsequent copper-catalyzed intramolecular N-arylation of **10a−c** under earlier described reaction conditions (CuI/proline/NaH) did not provide the expected *N*-acylindoles **11a−c**, but the product isolated from all these reactions was characterized as the hydrolyzed NH indole **12a** (Scheme 5). Attempted intramolecular N-arylation of *N*-acylenaminonitriles **10a−c** in the presence of various copper catalysts/ligands/bases under varying conditions also resulted in the formation of only NH indole **12a**, without any trace of the corresponding *N*-acylindoles **11a−c** (Table 4).

In view of our failure to isolate *N*-acylindoles **11**, we therefore focused our attention toward direct one-pot synthesis of N-unsubstituted 2-(het)arylindoles **12a−e** by reaction of the respective acrylonitrile precursors **1** with either benzamide or *t*-butylamide in the presence of sodium hydride in DMF and subsequent in situ treatment of the resulting *N*-acylenaminonitrile intermediates **10a−e** with CuI/proline in a one-pot procedure (Table 5). Following this protocol, 1-N-unsubstituted 3-cyanoindoles bearing various 2-(het)aryl moieties such as 2-(3-indolyl) (**12b** and **12c**), 2-(3-pyridyl) (**12d**), and 2-(2-thienyl) (**12e**) groups could be obtained in good to excellent overall yields (65−74%) (Table 5, entries 2−5).

With the successful synthesis of substituted indoles, we sought to extend our methodology to the synthesis of other heteroarylpyrroles such as thieno[2,3-*b*]pyrroles,[21] pyrrolo[2,3-*b*]indoles,[22] and pyrazolo[3,2-*c*]pyrroles,[23] which have important optical and electronic properties.[24] Also, bioisosteric replacement of indole arene ring by other heteroarenes in these pyrrolo-fused heterocycles is known to alter their biological profile by changing the binding sites as well as their bioavailability.[21a,25] Thus, thienopyrroles[21a,b,25] and pyrazolopyrroles[23a] are known to display a broad range of biological activity, whereas the hexahydropyrrolo[2,3-*b*]indole ring system is present in many biologically important alkaloids and in several marketed drugs and drug candidates.[26,27] It should be noted that these fused pyrroles are less stable than the corresponding indole derivatives and they cannot be synthesized by the usual classical methods employed for indole synthesis.[21]

Synthesis of Thieno[2,3-*b*]pyrroles 14a−f. We began this segment of our studies by examining the reaction of 2-(2-bromo-3-thienyl)-3-(methylthio)-3-(4-methoxyphenyl)-acrylonitrile **13a** with 4-methoxyaniline under the previously

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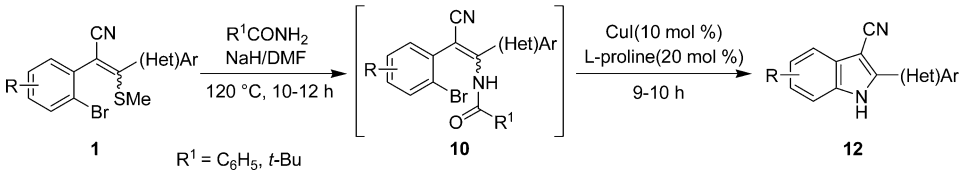
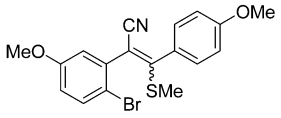
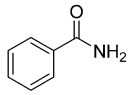
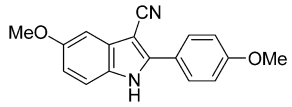
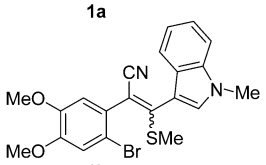
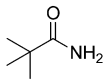
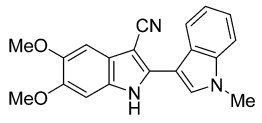
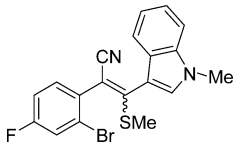
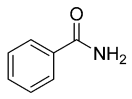
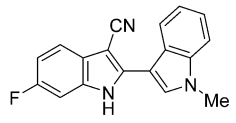
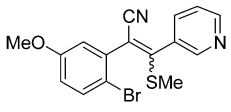
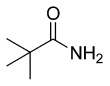
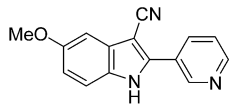
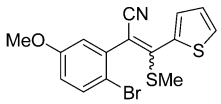
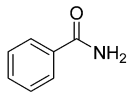
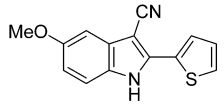
Table 5. Synthesis of 3-Cyano-2-(het)aryl-1-unsubstituted Indoles 12[a]



entry	substrate	amide	product	yield (%)
1	 1a		 12a	72
2	 1i		 12b	74
3	 1j		 12c	65
4	 1k		 12d	70
5	 1m		 12e	70

[a]Reaction was performed with **1** (1 mmol) plus amide (1.1 mmol) in 10 mL of solvent and 2 equiv of 100% NaH, followed by addition of 10 mol % CuI and 20 mol % L-proline.

described two-step one-pot double C−N amination reaction conditions (Table 6), which furnished the desired 4-cyano-5,6-bis(4-methoxyphenyl)thieno[2,3-*b*]pyrrole **14a** in 69% yield (Table 6). Similarly, the other substituted thieno[2,3-*b*]pyrroles **14b−e**, bearing a diverse range of 5-(het)aryl groups and *N*-aryl or *N*-(2-pyridyl) substituents, could also be prepared in 65−73% overall yields from the respective acrylonitrile precursors **13b−e** and appropriate anilines/pyridylamine (Table 6, entries 2−5). By subjecting one of the (2-bromothienyl)-acrylonitriles (**13e**) to one-pot inter- and intramolecular amination with benzamide under previously described conditions (Scheme 4, Table 5), it was also possible to synthesize 6-unsubstituted NH thieno[2,3-*b*]pyrrole **14f** in 72% yield (Table 6, entry 6).

Synthesis of Pyrrolo[2,3-*b*]indoles 18a−e. The scope of this novel pyrrole annulation protocol was next extended for the synthesis of pyrrolo-fused indoles **18** by employing the corresponding 2-[(2-bromo-1-*N*-methyl)-3-indolyl]acrylonitrile substrates **16a−e** and substituted anilines (Table 7). Under previously optimized reaction conditions, the corresponding 3-cyano-2-het(aryl)pyrrolo[2,3-*b*]indoles **18a−e** were obtained in moderate to good yields (58−67%) through intermediacy of enaminonitrile **17**, and no further attempts were made to improve the yields of the products (Table 7).

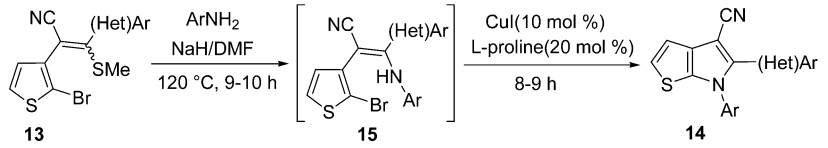
Synthesis of Substituted Pyrrolo[3,2-*c*]pyrazoles 21a−e. Further elaboration of the methodology revealed that the above reaction conditions and catalytic system are equally effective for the synthesis of annulated pyrrolopyrazoles such as **21**, which are shown to be useful subunits present in biologically relevant structures.[23a] Thus, 6-cyano-1,3-bis-(phenyl)-4,5-(het)arylpyrrolo[3,2-*c*]pyrazoles **21a−d** could be readily accessed in 62−80% overall yields by sequential inter- and intramolecular Cu-catalyzed amination of the corresponding 2-(4-bromo-1,3-bisphenyl-5-pyrazolyl)acrylonitrile precursors **19a−d** with various primary amines (Table 8, entries 1−4) through intermediacy of enaminonitrile **20**. The corresponding 4-N-unsubstituted pyrrolo[3,2-*c*]pyrazole derivative **21e** could also be prepared in good yield by cycloannulation of acrylonitrile precursor **19c** with benzamide under earlier described conditions (Table 8, entry 5).

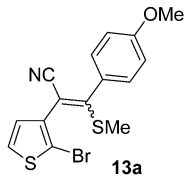
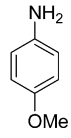
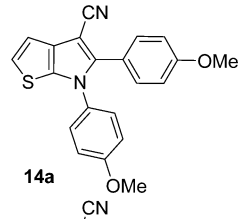
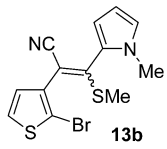
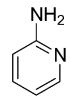
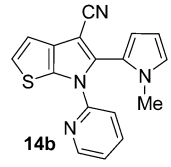
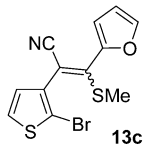
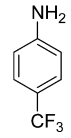
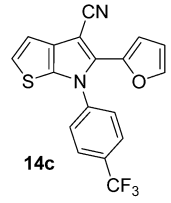
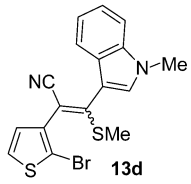
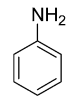
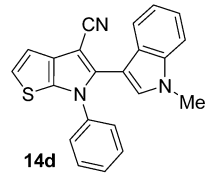
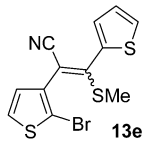
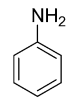
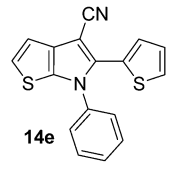
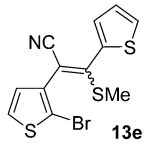
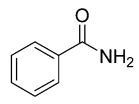
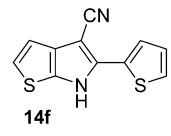
■ CONCLUSION

In summary, we have developed an efficient protocol for assembly of N-functionalized/NH-multisubstituted indoles from easily accessible acyclic 2-(2-bromoaryl)-3-[(methylthio)-(het)aryl]acrylonitrile precursors and primary amines, involving two key N(1)−C(2) and N(1)−C(7a) bond-forming processes, one base-mediated intermolecular conjugate addition

dx.doi.org/10.1021/jo501114a | J. Org. Chem. 2014, 79, 7961−7978

Table 6. Synthesis of Thieno[2,3-*b*]pyrroles 14[a]



entry	substrate	amine/amide	product[a]	yield (%)
1	 **13a**		 **14a**	69
2	 **13b**		 **14b**	67
3	 **13c**		 **14c**	67
4	 **13d**		 **14d**	73
5	 **13e**		 **14e**	65
6	 **13e**		 **14f**	72[b]

[a]Reactions were performed with **13** (1 mmol) plus amine (1.1 mmol) in 10 mL of DMF and 2 equiv of 100% NaH, followed by addition of 10 mol % CuI and 20 mol % L-proline. [b]In this reaction, benzamide (1.1 mmol) was used rather than amine.

and the other Cu-catalyzed intramolecular arylamination, in a sequential two-step one-pot procedure. The synthetic methodology is compatible with a variety of electronically and structurally varied primary amines including primary alkylamines by tuning the reaction conditions, thus allowing installation of a broad range of functionalized N units. The cyclization precursors **1** are assembled by condensation of 2-bromo(het)arylacetonitriles and (het)aryl dithioesters with variation of both components well tolerated, thus allowing efficient synthesis of diversely functionalized indoles. Of particular importance is the synthesis of indoles bearing a wide range of 2-(het)aryl moieties such as 2-thienyl, 2-furyl, 2-pyrrolyl, 3-pyridyl, and 3-indolyl groups, since most of the established palladium- (or copper-) catalyzed methods from either 2-amino(or 2-halo)arylacetylenes usually lead to 2-aryl- (or 2-alkyl-) indoles, with only a few exceptions.[7b,16a] Similarly, there are only a few reports of the synthesis of indoles bearing reactive functionalities at either 2- or 3- positions, prepared by earlier reported cross-coupling reactions. The 3-nitrile moiety in these newly synthesized indoles provides a useful functionality, which can undergo a rich array of chemical transformations to form other functional groups. 1,2-Disubstituted and 1,2,3-trisubstituted indoles generally display a broad range of biological activities (COX-II inhibitors, estrogen agonists and antagonists) and also find a range of applications in material science (electroluminescence) industries.[9a] N-substituted skeletons, especially N-arylindoles, represent an important subclass, due to their presence in many synthetically challenging pharmaceutically active compounds; however,

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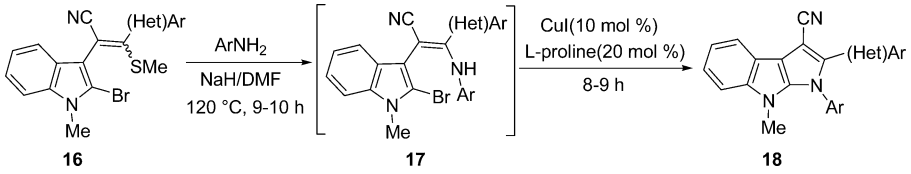
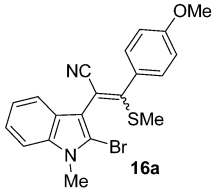
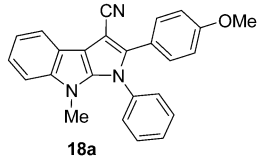
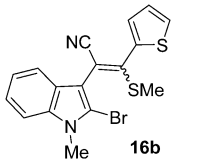
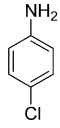
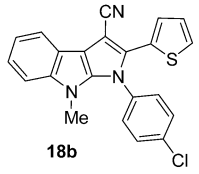
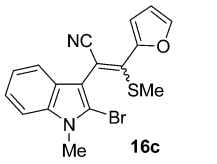
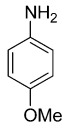
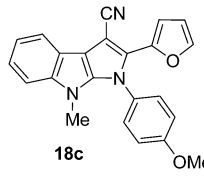
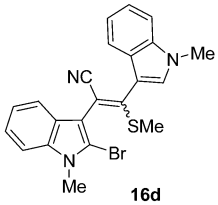
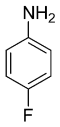
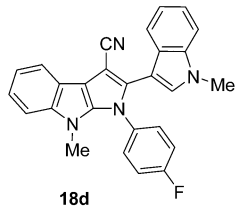
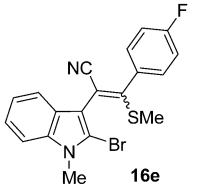
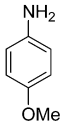
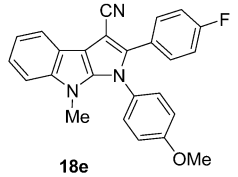
Table 7. Synthesis of Pyrrolo[2,3-*b*]indoles 18[a]



entry	substrate	amine	product	yield (%)
1	 **16a**		 **18a**	61
2	 **16b**		 **18b**	58
3	 **16c**		 **18c**	67
4	 **16d**		 **18d**	60
5	 **16e**		 **18e**	65

[a]Reactions were performed with **16** (1 mmol) plus amine (1.1 mmol) in 10 mL of DMF and 2 equiv of 100% NaH, followed by addition of 10 mol % CuI and 20 mol % L-proline.

strategic approaches to the *N*-aryl pattern of indole compounds are limited.[28a,b]

The broad scope of the methodology was further illustrated with the synthesis of biologically relevant N−H indoles by employing primary amides as coupling partners in this sequential one-pot C−N bond-forming reaction. We are still not in a position to give a rational explanation for our failure to isolate the corresponding *N*-acylindoles **11**, which may probably be due to steric hindrance by 2-(het)aryl group, thus facilitating the hydrolysis of **11** to the corresponding NH-indoles **12** during workup under these conditions.[29]

The protocol also enables the facile and efficient synthesis of hetero-fused pyrroles such as thieno[2,3-*b*]pyrrole, pyrrolo[2,3-*b*]indole, and pyrrolopyrazole structural motifs by subjecting the corresponding 2-[2-bromo(het)aryl)]acrylonitriles to sequential two-step one-pot cycloamination with various primary amines under identical conditions.

EXPERIMENTAL SECTION

General Information. All chemicals were commercially purchased and used without further purification. Solvents were dried according to standard procedures. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates and visualized with UV light. Column chromatography was performed with Merck 100−200 mesh silica gel. Nuclear magnetic resonance spectra were recorded on a (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$, DMSO-d_6, or acetone-d_6 as solvent. Chemical shifts were reported in δ ppm (parts per million) with residual solvent protons as internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6, and δ 2.05 for acetone-d_6 in ^{1}H NMR, δ 77.16 for $CDCl_3$, δ 39.5 for DMSO-d_6 and δ 29.84 for acetone-d_6 in ^{13}C NMR). Coupling constant (J) values are given in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), m (multiplet), and br (broad). Infrared spectra were recorded on a Fourier transform infrared (FTIR) instrument, and high-resolution mass spectra (HRMS) were measured on a quadrupole time-of-flight (Q-TOF) spectrometer. Melting points were recorded on an electrothermal

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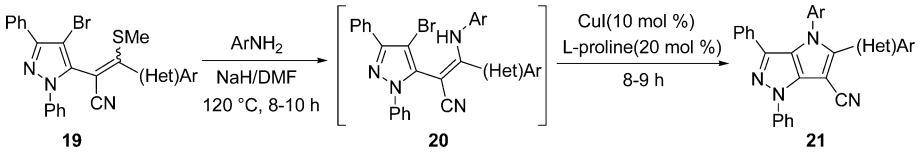
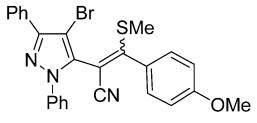
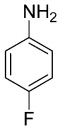
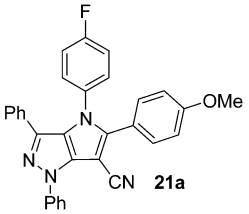
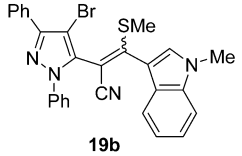
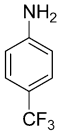
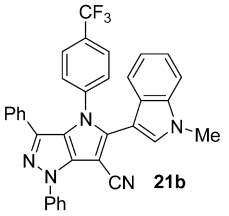
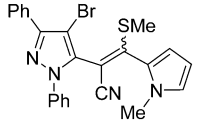
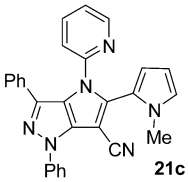
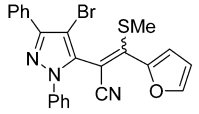
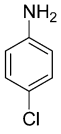
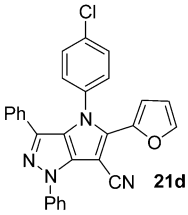
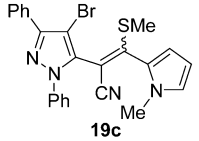
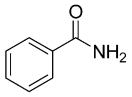
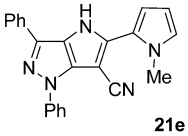
Table 8. Synthesis of Pyrrolo[3,2-*c*]pyrazoles 21a–e[a]



entry	substrate	amine/amide	product[a]	yield (%)
1	 **19a**		 **21a**	80
2	 **19b**		 **21b**	70
3	 **19c**		 **21c**	65
4	 **19d**		 **21d**	62
5	 **19c**		 **21e**	62[b]

[a]Reactions were performed with **19** (1 mmol) plus amine (1.1 mmol) in 10 mL of solvent and 2 equiv of 100% NaH, followed by addition of 10 mol % CuI and 20 mol % L-proline. [b]In this reaction, benzamide (1.1 mmol) was used rather than amine.

capillary melting point apparatus and are uncorrected. X-ray single-crystal data of **8a**, **6d**, and **18c** were collected on a diffractometer using Mo Kα radiation (λ = 0.7107 Å), at room temperature. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares against F^2 by use of SHELXL-97 software

Precursors Prepared According to Literature. The desired acrylonitrile precursors **1a–n**, **13a–e**, **16a–e**, and **19a–d** were prepared according to our earlier reported procedure[18] by reaction of the corresponding 2-bromo(het)arylacetonitrile (5.0 mmol) with the appropriate (het)aryl dithioester (5.0 mmol) by use of NaH (0.44 g, 11.0 mmol, 60%) in THF (15 mL), and subsequent alkylation with MeI (0.46 mL, 7.5 mmol). The known acrylonitrile precursors **1c**, **1e**, **1f**, **1h**, **13b–e**, **16b–d**, **19a**, **19b**, and **19d** were characterized by comparison of their spectral and analytical data with reported data,[18] whereas spectral and analytical data for the unknown precursors **1a**, **1b**, **1d**, **1g**, **1i–m**, **13a**, **16a**, **16e**, and **19c** are given below. Enaminonitriles **8m–o** were prepared according to a reported procedure[19a] by refluxing corresponding ketonitriles **9m** or **9o** and the appropriate anilines in glacial acetic acid for 6–7 h. Spectral and analytical data for the unknown enaminonitriles **8m** and **8n** are given below, whereas the enaminonitrile **8o** (obtained from ketonitrile **9o** and aniline) was found to be unstable and used as such without purification for further transformation. The corresponding thioketonitriles **9p** and **9q** were obtained by condensation of the respective 2-bromoarylacetonitrile and dithioesters in the presence of of sodium hydride in DMF[17e] and used as such without further purification.

*2-(2-Bromo-5-methoxyphenyl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile (**1a**).* Obtained as a 4:1 inseparable mixture of geometrical isomers, off-white solid (1.65 g, 85%): mp 66–68 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2207, 1608, 1249, 1028, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 0.2H), 7.48 (d, J = 8.8 Hz, 0.4H), 7.35 (d, J = 8.8 Hz, 0.8H), 7.11 (d, J = 8.8 Hz, 1.6H), 7.02 (d, J = 8.8 Hz, 0.4H), 6.94 (d, J = 3.2 Hz, 0.2H), 6.83 (dd, J = 8.8 Hz, 3.2 Hz, 0.2H), 6.74 (d, J = 8.8 Hz, 1.6H), 6.62 (dd, J = 8.8 Hz, 3.2 Hz, 0.8H), 6.49 (d, J = 3.2 Hz, 0.8H), 3.87 (s, 0.6H), 3.83 (s, 0.6H), 3.75 (s, 2.4H), 3.60 (s, 2.4H), 2.11 (s, 2.4 H), 1.91 (s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 161.4, 161.1, 160.5, 159.2, 158.7, 136.1, 135.3, 133.9, 133.6, 130.9, 130.5, 127.1, 126.4,

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117.63, 117.58, 117.1, 116.8, 116.7, 116.3, 114.7, 114.4, 114.1, 113.9, 107.9, 106.9, 55.7, 55.5, 55.4, 55.2, 16.51, 16.45; HRMS (ESI) m/z calcd for $C_{18}H_{16}BrNO_2S$ $[M + H]^+$ 390.0163 and 392.0143, found 390.0160 and 392.0145.

*2-(2-Bromo-4-fluorophenyl)-3-(4-fluorophenyl)-3-(methylthio)-acrylonitrile (**1b**).* Obtained as a single geometrical isomer, white solid (1.46 g, 80%); mp 91−92 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2207, 1602, 1482, 1230, 845; ^1H NMR (400 MHz, $CDCl_3$) δ 7.259 (dd, J = 8.0, 2.8 Hz, 1H), 7.138 (dd, J = 8.8, 5.2 Hz, 2H), 6.97−6.91 (m, 3H), 6.82 (td, J = 8.8, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.4, 161.9, 161.2, 160.9, 133.7, 133.6, 131.24, 131.19, 131.1, 130.2, 130.1, 124.8, 124.7, 120.6, 120.4, 116.6, 116.2, 116.0, 115.3, 115.0, 108.0, 16.5; HRMS (ESI) m/z calcd for $C_{16}H_{10}BrF_2NS$ $[M + H]^+$ 365.9764 and 367.9743, found 365.9760 and 367.9739

*2-(2-Bromo-4-fluorophenyl)-3-(furan-2-yl)-3-(methylthio)-acrylonitrile (**1d**).* Obtained as a 2:1 inseparable mixture of geometrical isomers, brown semisolid (1.26 g, 75%): R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2918, 2199, 1480, 1206, 876, 742; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.65 (m, 0.33H), 7.43 (dd, J = 8.0, 2.4 Hz 0.33H), 7.38−7.32 (m, 1.67H), 7.19 (dd, J = 8.8, 5.6 Hz, 0.67H), 7.14−7.10 (m, 0.67H), 7.00 (td, J = 8.4, 2.4 Hz, 0.67H), 6.59 (dd, J = 2.8, 1.6 Hz, 0.33H), 6.47 (d, J = 3.6 Hz, 0.67H), 6.36 (dd, J = 2.8, 1.2 Hz, 0.67H), 2.47 (s, 2H), 2.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.7, 161.4, 161.2, 149.9, 148.4, 147.8, 147.1, 145.7, 145.4, 132.9, 132.8, 132.6, 132.5, 131.9, 131.8, 131.13, 131.10, 124.6, 124.5, 124.4, 124.3, 121.0, 120.73, 120.72, 120.5, 117.5, 117.3, 116.3, 115.6, 115.40, 115.35, 115.2, 112.4, 112.3, 108.3, 105.8, 17.9, 17.0; HRMS (ESI) m/z calcd for $C_{14}H_9BrFNOS$ $[M + H]^+$ 337.9651 and 339.9630, found 337.9645 and 339.9624.

*2-(2-Bromo-5-methoxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)-3-(methylthio)acrylonitrile (**1g**).* Obtained as a single geometrical isomer, off-white solid (1.45 g, 80%): mp 105−106 °C; R_f 0.45 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2200, 1577, 1469, 1293, 1022, 726; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 9.0 Hz, 1H), 6.65 (dd, J = 9.0, 2.8 Hz, 1H), 6.59 (dd, J = 2.4, 2.0 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 6.13 (dd, J = 3.6, 2.0 Hz, 1H), 6.04 (dd, J = 3.6, 2.4 Hz, 1H), 3.60 (s, 3H), 3.43 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 153.0, 136.0, 134.1, 133.8, 126.4, 125.3, 117.1, 116.7, 114.8, 114.1, 109.1, 108.4, 55.6, 34.7, 16.3; HRMS (ESI) m/z calcd for $C_{16}H_{15}BrN_2OS$ $[M + H]^+$ 363.0167 and 365.0146, found 363.0168 and 365.0151

*2-(2-Bromo-4,5-dimethoxyphenyl)-3-(1-methyl-1H-indol-3-yl)-3-(methylthio)acrylonitrile (**1i**).* Obtained as a 3:1 inseparable mixture of geometrical isomers, pale yellow solid (1.66 g, 75%): mp 80−82 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2194, 1507, 1211, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 0.77H), 7.82 (d, J = 8.0 Hz, 0.23H), 7.57 (s, 0.77H), 7.39 (d, J = 8.0 Hz, 0.77H), 7.32 (td, J = 6.8, 2.8 Hz, 0.77H), 7.28−7.23 (m, 1.54H), 7.18−7.14 (m, 1H), 6.94 (s, 0.77H), 6.93 (s, 0.23H), 6.78 (s, 0.23H), 6.45 (m, 0.23H), 3.921 (s, 2.31H), 3.919 (s, 2.31H), 3.88 (s, 2.31H), 3.80 (s, 0.69H), 3.65 (s, 0.69H), 3.41 (s, 0.69H), 2.15 (s, 0.69H), 2.00 (s, 2.31); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 155.4, 150.0, 149.4, 148.8, 148.2, 137.4, 137.1, 131.1, 130.7, 128.4, 127.2, 126.5, 126.3, 122.9, 122.8, 121.2, 120.6, 120.2, 119.1, 118.1, 115.7, 115.3, 114.8, 114.7, 114.3, 114.1, 110.1, 109.9, 109.8, 109.6, 106.0, 104.5, 56.4, 56.3, 56.2, 55.9, 33.4, 33.3, 16.8, 16.7; HRMS (ESI) m/z calcd for $C_{21}H_{19}BrN_2O_2S$ $[M + H]^+$ 443.0429 and 445.0408, found 443.0425 and 445.0407.

*2-(2-Bromo-4-fluorophenyl)-3-(1-methyl-1H-indol-2-yl)-3-(methylthio)acrylonitrile (**1j**).* Obtained as a 3:1 inseparable mixture of geometrical isomers, off-white solid (1.56 g, 78%): mp 95−97 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2919, 2200, 1589, 1467, 1200, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88−7.86 (m, 0.75H), 7.74 (dt, J = 8.0, 0.8 Hz, 0.25H), 7.53 (s, 0.75H), 7.42−7.39 (m, 1.5H), 7.36−7.34 (m, 0.75H), 7.28 (td, J = 6.8, 0.8 Hz, 0.75H), 7.24−7.20 (m, 1.75H), 7.14−7.06 (m, 1H), 6.95 (dd, J = 8.8, 6.0 Hz, 0.25H), 6.74 (s, 0.25H), 6.72−6.67 (m, 0.25H), 3.84 (s, 2.25H), 3.61 (s, 0.75H), 2.12 (s, 2.25H), 1.95 (s, 0.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 163.1, 161.2, 160.6, 157.8, 156.1, 137.5, 137.2, 133.4, 133.3, 133.2, 132.78, 132.75, 131.61, 131.57, 131.3, 131.2, 126.23, 126.19, 124.96, 124.86, 124.8, 124.7, 123.0, 121.4, 120.9, 120.6, 120.5, 120.4, 120.2, 118.0, 118.8, 115.4, 115.2, 115.0, 110.2, 109.9, 109.7, 109.3, 104.6, 103.5, 33.5, 33.3, 16.93, 16.86; HRMS (ESI) m/z calcd for $C_{19}H_{14}BrFN_2S$ $[M + H]^+$ 401.0123 and 403.0103, found 401.0128 and 403.0110.

*2-(2-Bromo-5-methoxyphenyl)-3-(methylthio)-3-(pyridin-3-yl)-acrylonitrile (**1k**).* Obtained as a single geometrical isomer, pale yellow solid (1.08 g, 60%): mp 105−106 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2200, 1589, 1463, 1236, 1016, 770; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.0 Hz, 1H), 8.41 (s, 1H), 7.54 (dt, J = 7.6, 2.4 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.21 (dd, J = 7.6, 5.2 Hz, 1H), 6.64 (dd, J = 9.0, 3.2 Hz, 1H), 6.54 (d, J = 3.2 Hz, 1H), 3.63 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.5, 150.6, 149.7, 136.7, 135.0, 134.0, 130.8, 123.3, 117.7, 116.9, 116.4, 114.5, 110.4, 55.7, 16.6; HRMS (ESI) m/z calcd for $C_{16}H_{13}BrN_2OS$ $[M + H]^+$ 361.001 and 362.9990, found 361.0005 and 362.9990.

*2-(2-Bromophenyl)-3-(methylthio)hept-2-enenitrile (**1l**).* Obtained as a single geometrical isomer, pale yellow liquid (1.01 g, 65%): R_f 0.7 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2963, 2207, 1558, 1469, 1028, 757; ^1H NMR (400 MHz, DMSO-d_6) δ 7.56−7.73 (m, 1H), 7.49−7.45 (m, 1H), 7.38−7.34 (m, 2H), 2.81−2.79 (m, 2H), 2.33 (s, 3H), 1.63 (quintet, J = 7.2 Hz, 2H), 1.48 (sextet, J = 7.2 Hz, 2H), 0.975 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 133.6, 133.0, 131.9, 131.1, 128.5, 123.2, 116.8, 104.0, 33.1, 30.8, 21.6, 13.7, 13.6; HRMS (ESI) m/z calcd for $C_{14}H_{16}BrNS$ $[M + H]^+$ 310.0265 and 312.0245, found 310.0256 and 312.0236.

*2-(2-Bromo-5-methoxyphenyl)-3-(methylthio)-3-(thiophen-2-yl)-acrylonitrile (**1m**).* Obtained as a 9:1 inseparable mixture of geometrical isomers, pale yellow solid (1.50 g, 82%): mp 62−64 °C; R_f 0.6 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2200, 1564, 1463, 1236, 1016, 713; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59−7.54 (m, 0.3H), 7.43 (d, J = 8.4 Hz, 0.9H), 7.39 (dd, J = 5.2, 1.2 Hz, 0.9H), 7.17 (dd, J = 4.8, 3.2 Hz, 0.1H), 7.03 (dd, J = 3.6, 1.2 Hz, 0.9H), 6.94 (d, J = 2.8 Hz, 1H), 6.91 (dd, J = 5.2, 3.6 Hz, 0.9H), 6.84 (dd, J = 8.8, 3.2 Hz, 0.1H), 6.76−6.71 (m, 1.8H), 3.83 (s, 0.1H), 3.70 (s, 0.9H), 2.43 (s, 0.9H), 2.08 (s, 0.1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 151.8, 137.4, 135.7, 133.9, 131.6, 130.9, 130.6, 130.0, 127.9, 127.6, 117.3, 117.0, 116.9, 116.8, 116.6, 114.7, 110.1, 55.7, 55.6, 18.1, 17.2; HRMS (ESI) m/z calcd for $C_{15}H_{12}BrNOS_2$ $[M + H]^+$ 365.9622 and 367.9601, found 365.9620 and 367.9602.

*2-(2-Bromothiophen-3-yl)-3-(4-methoxyphenyl)-3-(methylthio)-acrylonitrile (**13a**).* Obtained as a single geometrical isomer, off-white solid (1.42 g, 78%): mp 101−102 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2200, 1602, 1255, 827; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 9.2 Hz, 2H), 7.03 (d, J = 5.8 Hz, 1H), 6.79 (d, J = 9.2 Hz, 2H), 6.45 (d, J = 5.8 Hz, 1H), 3.79 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 160.9, 134.6, 131.3, 129.3, 126.6, 126.3, 117.0, 114.2, 113.2, 102.0, 55.4, 16.8; HRMS (ESI) m/z calcd for $C_{15}H_{12}BrNOS_2$ $[M + H]^+$ 365.9622 and 367.9601, found 365.9618 and 367.9599.

*2-(2-Bromo-1-methyl-1H-indol-3-yl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile (**16a**).* Obtained as a 2:1 inseparable mixture of geometrical isomers, pale yellow solid (1.34 g, 65%): mp 86−88 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2200, 1608, 1457, 1249, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 0.33H), 7.53 (d, J = 8.8 Hz, 0.67H), 7.44 (d, J = 8.0 Hz, 0.67H), 7.34 (d, J = 8.0 Hz, 0.33H), 7.30−7.27 (m, 0.33H), 7.22−7.15 (m, 3H), 7.09−7.02 (m, 1.32H), 6.66 (d, J = 8.8 Hz, 1.32H), 3.88 (s, 0.99H), 3.83 (s, 0.99H), 3.71 (s, 2.01H), 3.66 (s, 2.01H), 2.16 (s, 2.01H), 1.89 (s, 0.99H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 161.0, 160.4, 160.1, 136.9, 136.7, 131.2, 128.0, 127.4, 126.4, 125.8, 122.8, 122.6, 120.8, 119.3, 118.9, 118.2, 118.1, 115.8, 115.6, 114.5, 113.9, 110.0, 109.8, 109.6, 109.0, 100.6, 99.6, 55.5, 55.3, 31.9, 31.8, 17.0, 16.7; HRMS (ESI) m/z calcd for $C_{20}H_{17}BrN_2OS$ $[M + H]^+$ 413.0323 and 415.0303, found 413.0326 and 415.0305.

*2-(2-Bromo-1-methyl-1H-indol-3-yl)-3-(4-fluorophenyl)-3-(methylthio)acrylonitrile (**16e**).* Obtained as a 3:2 inseparable mixture of geometrical isomers, off-white solid (1.45 g, 73%): mp 134−136 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2168, 1467, 1223, 740; ^1H

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NMR (400 MHz, $CDCl_3$) δ 7.59−7.55 (m, 1.2H), 7.42 (d, J = 8.0 Hz, 0.6H), 7.37 (d, J = 8.0 Hz, 0.4H), 7.29 (dd, J = 7.2, 1.2 Hz, 0.4H), 7.24−7.16 (m, 3.6H), 7.08 (ddd, J = 8.0, 6.8, 1.6 Hz, 0.6H), 6.85 (t, J = 8.8 Hz, 1.2H), 3.84 (s, 1.2H), 3.66 (s, 1.8H), 2.14 (s, 1.8H), 1.88 (s, 1.2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 163.4, 163.0, 161.5, 160.9, 159.9, 136.4, 136.2, 131.64, 131.60, 131.33, 131.29, 131.24, 131.20, 130.63, 130.60, 125.2, 124.7, 122.5, 122.4, 120.58, 120.56, 118.6, 117.8, 117.4, 117.1, 116.2, 116.0, 115.8, 115.74, 115.66, 115.4, 110.7, 110.5, 108.2, 107.4, 100.1, 99.1, 31.8, 31.7, 16.0, 15.7; HRMS (ESI) m/z calcd for $C_{19}H_{14}BrFN_2S$ $[M + H]^+$ 401.0123 and 403.0103, found 401.0110 and 403.0091.

*2-(4-Bromo-1,3-diphenyl-1H-pyrazol-5-yl)-3-(1-methyl-1H-pyrrol-2-yl)-3-(methylthio)acrylonitrile (**19c**).* Obtained as a 1:1 inseparable mixture of geometrical isomers, brown solid (1.54 g, 65%): mp 72−74 °C; R_f 0.35 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2207, 1495, 1306, 959, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.01 (m, 1H), 7.96−7.94 (m, 1H), 7.63−7.61 (m, 1H), 7.52−7.36 (m, 6H), 7.20−7.19 (m, 1H), 6.80 (t, J = 2.0 Hz, 0.5 H), 6.80 (t, J = 2.0 Hz, 0.5H), 6.55 (t, J = 2.0 Hz, 0.5H), 6.41 (dd, J = 4.0, 1.6 Hz, 0.5H), 6.21 (dd, J = 3.6, 2.8 Hz, 0.5H), 5.93 (dd, J = 3.6, 2.8 Hz, 0.5H), 5.77 (dd, J = 3.6, 2.0 Hz, 0.5H), 3.62 (s, 1.5H), 2.94 (s, 1.5H), 2.03 (s, 1.5H), 1.83 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 157.8, 149.9, 149.4, 139.6, 139.1, 135.6, 135.1, 131.62, 131.55, 129.4, 129.2, 128.83, 128.78, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.90, 127.8, 127.4, 125.4, 124.8, 124.45, 124.47, 116.5, 116.4, 115.5, 114.8, 109.7, 109.3, 97.6, 97.1, 96.4, 95.1, 34.7, 34.1, 16.4, 16.1; HRMS (ESI) m/z calcd for $C_{24}H_{19}BrN_4S$ $[M + H]^+$ 475.0592 and 477.0572, found 475.0586 and 477.0566

*(E)-2-(2-Bromo-4,5-dimethoxyphenyl)-3-(4-methoxyphenylamino)but-2-enenitrile (**8m**).* Obtained from ketonitrile **9m** and 4-methoxyaniline, off-white solid (261 mg, 65%): mp 119−120 °C, R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3329, 2939, 2179, 1600, 1508, 1245, 1023, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.89 (s, 3H), 6.83 (d, J = 8.8 Hz, 2H), 6.01 (br s, 1H), 3.88 (s, 6H), 3.79 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.6, 150.0, 149.4, 131.4, 127.7, 124.8, 121.4, 116.3, 116.2, 115.0, 114.5, 81.4, 56.37, 56.35, 55.6, 17.9; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrN_2O_3$ $[M + H]^+$ 403.0657 and 405.0637, found 403.0656 and 405.0638.

*(E)-2-(2-Bromo-4,5-dimethoxyphenyl)-3-(4-chlorophenylamino)but-2-enenitrile (**8n**).* Obtained from ketonitrile **9m** and 4-chloroaniline, off-white solid (284 mg, 70%): R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3327, 2926, 2190, 1608, 1497, 1206, 1026, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 7.10 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 6.07 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.2, 149.4, 137.3, 131.6, 129.5, 126.4, 124.4, 120.8, 116.2, 116.1, 114.7, 83.9, 56.40, 56.36, 18.0; HRMS (ESI) m/z calcd for $C_{18}H_{16}BrClN_2O_2$ $[M + H]^+$ 407.0162 and 409.0141, found 407.0153 and 409.0131.

General Procedure for Synthesis of Enaminonitriles 8p and 8q. A solution of thioketonitrile **9p** or **9q** (1.0 mmol) and aliphatic amine (1.0 mmol) in CH_3CN (10 mL) was stirred at room temperature for 5−6 h (monitored by TLC). The reaction mixture was concentrated under reduced pressure and the residue was diluted with ice-cold water (20 mL), extracted with EtOAc (2 × 20 mL), and dried over Na_2SO_4, followed by removal of the solvent to give crude **8p** or **8q**. These were found to be unstable and were utilized for the next step without purification.

Procedure for Synthesis of (*E*)-2-(2-Bromo-5-methoxyphenyl)-3-(4-methoxyphenyl)-3-(4-methoxyphenylamino)-acrylonitrile (8a). A solution of **1a** (390 mg, 1.0 mmol) in dry DMF (5 mL) was added to a stirred suspension of 4-methoxyaniline (135 mg, 1.1 mmol) and NaH (44 mg, 1.1 mmol, 100%) in DMF (10 mL) at room temperature, followed by heating at 120 °C for 8 h (monitored by TLC). The reaction mixture after cooling was poured into ice-cold water (50 mL) and extracted with EtOAc (2 × 50 mL), and the organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography over silica gel with 30% EtOAc/hexane to give pure **8a**: off-white solid (0.348 g, 75%): mp 118−120 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 3296, 2932, 2193, 1582, 1514, 1252, 1030, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.50 (m, 3H), 7.03 (d, J = 3.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 8.8, 3.2 Hz, 1H), 6.64−6.58 (m, 4H), 6.10 (br s, 1H), 3.82 (s, 3H), 3.81 (S, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 159.8, 157.3, 156.4, 134.7, 133.0, 131.7, 125.0, 124.6, 121.6, 117.7, 116.1, 114.2, 114.1, 84.7, 55.8, 55.5, 55.4; HRMS (ESI) m/z calcd for $C_{24}H_{21}BrN_2O_3$ $[M + Na]^+$ 487.0633 and 489.0613, found 487.0638 and 489.0702.

Procedure for Copper-Catalyzed Cyclization of Enaminonitrile 8a to 5-Methoxy-1,2-bis(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (6a). To a stirred solution of enaminonitrile **8a** (232 mg, 0.5 mmol) in DMF (5 mL) were added CuI (9 mg, 0.05 mmol), L-proline (12 mg, 1.0 mmol), and NaH (20 mg, 0.5 mmol, 100%), and the reaction mixture was heated at 120 °C with constant stirring for 8 h (monitored by TLC). It was then poured into ice-cold water (20 mL), extracted with EtOAc (3 × 10 mL), washed with brine (1 × 10 mL), and dried over Na_2SO_4, followed by removal of the solvent. The resulting crude product was purified by column chromatography over silica gel with 12% EtOAc/hexane as eluent to give pure **6a**: white solid (0.172 mg, 90%): mp 141−142 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2930, 2205, 1607, 1470, 1246, 1021, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 9.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 9.2, 2.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.5, 156.5, 147.4, 132.9, 131.3, 129.7, 129.2, 128.5, 121.4, 117.3, 115.0, 114.6, 114.3, 112.6, 100.6, 85.9, 56.0, 55.7, 55.4; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2O_3$ $[M + H]^+$ 385.1552, found 385.1533.

General Procedure for Two-Step One-Pot Synthesis of Indoles 6a−k, Thieno[2,3-*b*]pyrroles 14a−e, Pyrrolo[2,3-*b*]-indoles 18a−c, and Pyrrolo[3,2-*c*]pyrazoles 21a−d. A solution of respective 2-[2-bromo(het)aryl]-3-(het)aryl/(methylthio)-acrylonitriles **1**, **13**, **16**, or **19** (1.0 mmol) in dry DMF (5 mL) was added to a stirred suspension of the corresponding aniline (1.1 mmol) and NaH (80 mg, 2.0 mmol, 100%) in DMF (10 mL) at room temperature, followed by further heating at 120 °C for 8−10 h (monitored by TLC). After consumption of starting materials, CuI (19 mg, 0.1 mmol) and L-proline (23 mg, 0.2 mmol) were added to the reaction mixture and it was further heated at the same temperature for 8−9 h (monitored by TLC). It was then cooled to room temperature, poured into ice-cold water (50 mL), and extracted with EtOAc (2 × 50 mL), and the combined extracts were washed with water (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulting crude products were purified by column chromatography over silica gel with EtOAc/hexane as eluent.

*6-Fluoro-1,2-bis(4-fluorophenyl)-1H-indole-3-carbonitrile (**6b**).* Obtained from acrylonitrile **1b** and 4-fluoroaniline, white solid (295 mg, 85%): mp 167−168 °C; R_f 0.7 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3070, 2220, 1608, 1507, 1230, 1155, 845, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.8, 5.2 Hz, 1H), 7.33 (dd, J = 8.8, 5.2 Hz, 2H), 7.20−7.09 (m, 5H), 7.08−7.03 (m, 2H), 6.90 (dd, J = 9.2, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 163.7, 162.4, 162.2, 161.2, 160.0, 146.88, 146.85, 138.0, 137.9, 132.23, 132.20, 131.9, 131.8, 129.8, 129.7, 124.6, 124.5, 123.7, 121.0, 120.9, 117.4, 117.1, 116.4, 116.2, 115.9, 112.3, 112.3, 112.1, 98.4, 98.1, 87.8; HRMS (ESI) m/z calcd for $C_{21}H_{11}F_3N_2$ $[M + H]^+$ 349.0953, found 349.0948.

*1-(4-Chlorophenyl)-5,6-dimethoxy-2-(thiophen-2-yl)-1H-indole-3-carbonitrile (**6c**).* Obtained from acrylonitrile **1c** and 4-chloroaniline, white solid (291 mg, 74%): mp 195−196 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2936, 2207, 1486, 1275, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.34 (dd, J = 2.8, 1.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.03 (dd, J = 5.2, 3.6 Hz, 1H), 6.50 (s, 1H), 3.98 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 147.9, 138.9, 135.7, 135.2, 132.4, 130.4, 130.2, 129.9, 129.6, 128.6, 127.6, 120.8, 116.8, 100.6, 94.2, 86.9, 56.6, 56.5; HRMS (ESI) m/z calcd for $C_{21}H_{15}ClN_2O_2S$ $[M + H]^+$ 395.0621 and 397.0592, found 395.0597 and 397.0560.

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*1-(4-Chlorophenyl)-6-fluoro-2-(furan-2-yl)-1H-indole-3-carbonitrile (**6d**).* Obtained from acrylonitrile **1d** and 4-chloroaniline, white solid (252 mg, 75%): mp 180−182 °C; R_f 0.4 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 2938, 2220, 1621, 1489, 1192, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.8, 4.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.08 (td, J = 8.8, 2.0 Hz, 1H), 6.73 (dd, J = 8.8, 2.0 Hz, 1H), 6.41 (dd, J = 3.6, 2.0 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.1, 144.4, 143.3, 138.4, 138.3, 137.39, 137.36, 135.9, 135.2, 130.4, 129.5, 123.9, 120.9, 120.8, 115.7, 112.7, 112.3, 112.1, 111.9, 98.1, 97.9, 85.5; HRMS (ESI) m/z calcd for $C_{19}H_{10}ClFN_2O$ $[M + H]^+$ 337.0544 and 339.0514, found 337.0532 and 339.0508.

*2-(Furan-2-yl)-1-(pyridin-2-yl)-1H-indole-3-carbonitrile (**6e**).* Obtained from acrylonitrile **1e** and 2-aminopyridine, white solid (213 mg, 75%): mp 120−121 °C; R_f 0.4 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3052, 2919, 2220, 1476, 1445, 1244, 1022, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, J = 4.8, 1.2 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 7.6, 1.2 Hz, 1H), 7.74 (dq, J = 8.0, 1.6 Hz, 1H), 7.54 (ddd, J = 8.0, 4.8, 0.4 Hz, 1H), 7.40 (dd, J = 1.6, 0.4 Hz, 1H), 7.36 (td, J = 7.2, 1.2 Hz, 1H), 7.30 (td, J = 7.2, 1.2 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.58 (dd, J = 3.2, 0.4 Hz, 1H), 6.44 (dd, J = 3.2, 1. Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.4, 144.4, 143.3, 138.1, 136.8, 135.9, 134.1, 127.7, 125.2, 124.3, 123.6, 119.9, 115.9, 113.3, 112.0, 111.0, 86.2; HRMS (ESI) m/z calcd for $C_{18}H_{11}N_3O$ $[M + H]^+$ 286.0980, found 286.0979.

*5,6-Dimethoxy-2-(1-methyl-1H-pyrrol-2-yl)-1-(4-(trifluoromethyl)phenyl)-1H-indole-3-carbonitrile (**6f**).* Obtained from acrylonitrile **1f** and 4-(trifluoromethyl)aniline, white solid (290 mg, 68%): mp 184−185 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2944, 2215, 1494, 1329, 1164, 718; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (s, 1H), 6.75 (s, 1H), 6.69 (t, J = 2.4 Hz, 1H), 6.13−6.12 (m, 2H), 4.0 (s, 3H), 3.85 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 147.9, 140.3, 137.4, 131.0, 130.6, 130.2, 127.5, 127.0, 126.93, 126.89, 125.3, 125.1, 120.7, 120.4, 116.2, 114.5, 109.1, 100.8, 94.3, 90.0, 56.57, 56.55, 34.8; HRMS (ESI) m/z calcd for $C_{23}H_{18}F_3N_3O_2$ $[M + H]^+$ 426.1429, found 426.1423.

*1-(2-Bromophenyl)-5-methoxy-2-(1-methyl-1H-pyrrol-2-yl)-1H-indole-3-carbonitrile (**6g**).* Obtained from acrylonitrile **1g** and 2-bromoaniline, white solid (315 mg, 78%): mp 188−190 °C; R_f 0.4 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 2950, 2207, 1489, 1205, 1028, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.4, 1.2 Hz, 1H), 7.43 (td, J = 7.2, 1.2 Hz, 1H), 7.35−7.31 (m, 2H), 7.24 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 9.2, 2.4 Hz, 1H), 6.86 (d, J = 9.2 Hz, 1H), 6.73 (dd, J = 2.4, 1.6 Hz, 1H), 6.03 (dd, J = 3.6, 2.4 Hz, 1H), 5.95 (dd, J = 3.6, 1.6 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 140.0, 136.3, 134.0, 132.0, 131.2, 130.9, 128.6, 128.3, 125.8, 123.2, 120.8, 116.6, 115.1, 114.0, 112.7, 108.7, 100.7, 88.0, 56.0, 35.4; HRMS (ESI) m/z calcd for $C_{21}H_{16}BrN_3O$ $[M + H]^+$ 406.0555 and 408.0535, found 406.0556 and 408.0538.

*6-Fluoro-2-(1-methyl-1H-pyrrol-2-yl)-1-[4-(trifluoromethyl)-phenyl]-1H-indole-3-carbonitrile (**6h**).* Obtained from acrylonitrile **1h** and 4-(trifluoromethyl)aniline, white solid (272 mg, 71%): mp 131−132 °C; R_f 0.6 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2220, 1615, 1489, 1325, 1161, 1060, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.8, 5.2 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.14 (td, J = 8.8, 2.4 Hz, 1H), 7.00 (dd, J = 9.2, 2.4 Hz, 1H), 6.72 (dd, J = 2.4, 1.6 Hz, 1H), 6.17 (dd, J = 3.6, 1.6 Hz, 1H), 6.14 (dd, J = 3.6, 2.4 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.1, 140.1,140.0, 139.7, 137.1, 137.0, 131.0, 130.7, 127.5, 127.11, 127.07, 127.03, 127.0, 125.9, 123.9, 121.1, 121.0, 119.9, 115.5, 115.0, 112.5, 112.2, 109.4, 98.4, 98.1, 90.3, 35.0; HRMS (ESI) m/z calcd for $C_{21}H_{13}F_4N_3$ $[M + H]^+$ 384.1124, found 384.1112.

*5,6-Dimethoxy-2-(1-methyl-1H-indol-3-yl)-1-(pyridin-2-yl)-1H-indole-3-carbonitrile (**6i**).* Obtained from acrylonitrile **1i** and 2-aminopyridine, off-white solid (306 mg, 75%): mp 213-215 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2207, 1589, 1469, 1236, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 4.8, 1.2 Hz, 1H), 7.47 (td, J = 8.0, 2.0 Hz, 1H), 7.45 (s, 1H), 7.30−7.28 (m, 2H), 7.22−7.14 (m, 3H), 7.04 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 4.0 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.2, 148.4, 147.5, 140.5, 138.5, 137.1, 131.1, 130.3, 125.9, 122.7, 122.6, 121.6, 121.2, 120.7, 120.0, 117.5, 109.7, 104.4, 100.4, 96.0, 87.7, 56.5, 56.4, 33.4; HRMS (ESI) m/z calcd for $C_{25}H_{20}N_4O_2$ $[M + H]^+$ 409.1665, found 409.1655.

*6-Fluoro-2-(1-methyl-1H-indol-3-yl)-1-(pyridin-3-yl)-1H-indole-3-carbonitrile (**6j**).* Obtained from acrylonitrile **1j** and 3-aminopyridine, pale yellow solid (285 mg, 78%): mp 190−192 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2220, 1583, 1489, 1243, 1028, 745; ^1H NMR (400 MHz, DMSO) δ 8.60 (d, J = 2.4 Hz, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 7.99 (ddd, J = 8.4, 2.4, 1.6 Hz, 1H), 7.78 (dd, J = 8.8, 5.2 Hz, 1H), 7.62 (s, 1H), 7.51−7.47 (m, 2H), 7.29−7.24 (m, 2H), 7.18 (td, J = 8.0, 0.8 Hz, 1H), 7.14 (dd, J = 9.6, 2.0 Hz, 1H), 6.99 (td, J = 7.6, 0.8 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.8, 149.5, 148.4, 137.5, 137.4, 137.1, 134.6, 134.0, 130.8, 125.6, 124.4, 124.2, 122.9, 121.0, 120.6, 120.5, 119.9, 116.3, 112.0, 111.8, 110.0, 102.9, 98.0, 97.8, 88.0, 33.4; HRMS (ESI) m/z calcd for $C_{23}H_{15}FN_4$ $[M + Na]^+$ 389.1178, found 389.1177.

*5-Methoxy-1-(pyridin-2-yl)-2-(pyridin-3-yl)-1H-indole-3-carbonitrile (**6k**).* Obtained from acrylonitrile **1k** and 2-aminopyridine, pale yellow solid (215 mg, 66%): mp 190−192 °C; R_f 0.4 (4:1 EtOAc/hexane); IR (KBr, cm^{-1}) 3064, 2938, 2220, 1589, 1465, 1211, 1022, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 8.617 (ddd, J = 8.8, 2.0, 0.8 Hz, 1H), 8.61 (br s, 1H), 8.49 (s, 1H), 7.85 (dt, J = 8.0, 2.0 Hz, 1H), 7.77 (td, J = 8.0, 2.0 Hz, 1H), 7.44 (dd, J = 8.8, 0.4 Hz, 1H), 7.37 (dd, J = 4.8, 0.8 Hz, 1H), 7.35 (dd, J = 4.8, 0.8 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.05 (dt, J = 8.0, 0.8 Hz, 1H), 6.99 (dd, J = 9.2, 3.6 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 150.2, 150.1, 150.0, 149.98, 142.8, 138.9, 136.9, 132.2, 128.6, 125.8, 123.7, 122.1, 116.2, 115.9, 113.3, 100.8, 89.5, 56.0; HRMS (ESI) m/z calcd for $C_{20}H_{14}N_4O$ $[M + H]^+$ 327.1246, found 327.1233.

*5,6-Bis(4-methoxyphenyl)-6H-thieno[2,3-b]pyrrole-4-carbonitrile (**14a**).* Obtained from acrylonitrile **13a** and 4-methoxyaniline, white solid (248 mg, 69%): mp 89−90 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2920, 2215, 1619, 1517, 1243, 1031, 835; ^1H NMR (400 MHz, DMSO-d_6) δ 7.33−7.24 (m, 6H), 7.02 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 9.2 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.2, 131.2, 130.9, 130.0, 126.6, 121.8, 120.1, 117.0, 116.9, 115.0, 114.9, 114.22, 114.16, 85.9, 55.5, 55.3; HRMS (ESI) m/z calcd for $C_{21}H_{16}N_2O_2S$ $[M + H]^+$ 361.1011, found 361.1025.

*5-(1-Methyl-1H-pyrrol-2-yl)-6-(pyridin-2-yl)-6H-thieno[2,3-b]-pyrrole-4-carbonitrile (**14b**).* Obtained from acrylonitrile **13b** and 2-aminopyridine, white solid (203 mg, 67%); mp 104−105 °C; R_f 0.4 (1:4 EtOAc/hexane): IR (KBr, cm^{-1}) 2928, 2230, 1588, 1462, 1439, 1360, 718; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 3.6 Hz, 1H), 7.57 (t, J = 7.0 Hz, 1H), 7.23−7.14 (m, 3H), 6.83 (br s, 1H), 6.48 (br s, 1H), 6.30 (d, J = 8.0 Hz, 2H), 3.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 148.4, 138.8, 134.9, 129.6, 125.2, 123.7, 121.5, 121.2, 115.8, 115.7, 113.7, 113.2, 112.5, 109.4, 92.8, 34.5; HRMS (ESI) m/z calcd for $C_{17}H_{12}N_4S$ $[M + H]^+$ 305.0861, found 305.0855.

*5-(Furan-2-yl)-6-[4-(trifluoromethyl)phenyl]-6H-thieno[2,3-b]-pyrrole-4-carbonitrile (**14c**).* Obtained from **13c** and 4-(trifluoromethyl)aniline, white solid (240 mg, 67%); mp 158−160 °C; R_f 0.6 (1:9 EtOAc/hexane): IR (KBr, cm^{-1}) 2215, 1314, 1125, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.37 (dd, J = 2.0, 0.4 Hz, 1H), 7.17 (d, J = 5.2 Hz, 1H), 7.04 (d, J = 5.2 Hz, 1H), 6.62 (dd, J = 3.6, 0.4 Hz, 1H), 6.46 (dd, J = 3.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 142.9, 141.6, 138.4, 135.5, 131.0, 130.8, 127.1, 127.09, 127.05, 127.02, 126.98, 125.6, 121.4, 117.1, 115.6, 111.8, 111.7, 87.1; HRMS (ESI) m/z calcd for $C_{18}H_9F_3N_2OS$ $[M + H]^+$ 359.0466, found 359.0445.

*5-(1-Methyl-1H-indol-3-yl)-6-phenyl-6H-thieno[2,3-b]pyrrole-4-carbonitrile (**14d**).* Obtained from acrylonitrile **13d** and aniline, brown solid (257 mg, 73%); mp 191−192 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2920, 2215, 1596, 1510, 1235, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 6H), 7.25 (s, 1H), 7.19−7.14 (m, 3H), 7.01 (d, J = 5.2 Hz, 1H), 6.95 (dd, J = 7.6, 5.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 139.0, 137.1, 136.8, 130.4, 129.9, 129.6, 127.9, 126.0, 124.5, 122.3, 120.3, 120.2, 119.8, 117.14, 117.06,

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109.5, 104.4, 86.9, 33.29; HRMS(ESI) m/z calcd for $C_{22}H_{15}N_3S$ $[M + H]^+$ 354.1065, found 354.1055.

*6-Phenyl-5-(thiophen-2-yl)-6H-thieno[2,3-b]pyrrole-4-carbonitrile (**14e**).* Obtained from acrylonitrile **13e** and aniline, pale yellow solid (198 mg, 65%): mp 206−207 °C; R_f 0.6 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 3125, 2922, 2218, 1495, 714; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.46 (m, 3H), 7.36−7.32 (m, 3H), 7.22 (dd, J = 3.6, 0.8 Hz, 1H), 7.16 (d, J = 5.2 Hz, 1H), 7.02−7.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.9, 138.0, 130.5, 130.2, 130.1, 129.32, 129.31, 128.3, 127.5, 126.4, 121.0, 117.1, 116.5, 87.2; HRMS (ESI) m/z calcd for $C_{17}H_{10}N_2S_2$ $[M + H]^+$ 307.0364, found 307.0354.

*2-(4-Methoxyphenyl)-8-methyl-1-phenyl-1,8-dihydropyrrolo[2,3-b]indole-3-carbonitrile (**18a**).* Obtained from acrylonitrile **16a** and aniline, off-white solid (230 mg, 61%): mp 180−181 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2220, 1495, 1255, 751; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.47−7.46 (m, 3H), 7.36−7.33 (m, 2H), 7.28−7.24 (m, 3H), 7.21 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 9.2 Hz, 2H), 3.78 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 141.2, 140.7, 139.8, 136.5, 131.2, 129.7, 129.5, 129.0, 122.1, 122.0, 120.3, 119.6, 119.3, 117.9, 114.1, 109.5, 107.2, 84.2, 55.4, 30.6; HRMS (ESI) m/z calcd for $C_{25}H_{19}N_3O$ $[M + H]^+$ 378.1606, found 378.1599.

*1-(4-Chlorophenyl)-8-methyl-2-(thiophen-2-yl)-1,8-dihydropyrrolo[2,3-b]indole-3-carbonitrile (**18b**).* Obtained from acrylonitrile **16b** and 4-chloroanilne, off-white solid (224 mg, 61%): mp 255−256 °C; R_f 0.6 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2213, 1558, 1482, 1085, 739; ^{1}HNMR (400 MHz, acetone-d_6) δ 7.84 (br d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.55 (dd, J = 5.2, 0.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.33 (td, J = 7.2, 1.2 Hz, 1H), 7.28−7.25 (m, 2H), 7.11 (dd, J = 5.2, 3.6 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 141.8, 141.1, 136.6, 135.5, 134.5, 132.3, 131.2, 130.7, 129.6, 128.7, 128.0, 123.0, 120.9, 119.8, 119.1, 117.3, 110.8, 107.6, 85.5, 30.6; HRMS (ESI) m/z calcd for $C_{22}H_{14}ClN_3S$ $[M + H]^+$ 388.0675 and 390.0646, found 388.0667 and 390.0630.

*2-(Furan-2-yl)-1-(4-methoxyphenyl)-8-methyl-1,8-dihydropyrrolo[2,3-b]indole-3-carbonitrile (**18c**).* Obtained from acrylonitrile **16c** and 4-methoxyaniline, pale yellow solid (245 mg, 67%): mp 225−226 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2963, 2213, 1526, 1249, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dt, J = 4.0, 1.6 Hz, 1H), 7.39−7.37 (m, 3H), 7.27−7.20 (m, 3H), 7.05 (d, J = 8.8 Hz, 2H), 6.30 (dd, J = 3.6, 1.6 Hz, 1H), 5.90 (d, J = 3.6, 0.4 Hz, 1H), 3.92 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 144.1, 143.2, 140.5, 140.2, 130.3, 130.2, 127.8, 122.0, 120.0, 118.3, 117.9, 116.7, 114.9, 111.7, 110.3, 108.5, 106.1, 81.1, 55.6, 29.8; HRMS (ESI) m/z calcd for $C_{23}H_{17}N_3O_2$ $[M + H]^+$ 368.1399, found 368.1398.

*1-(4-Fluorophenyl)-8-methyl-2-(1-methyl-1H-indol-3-yl)-1,8-dihydropyrrolo[2,3-b]indole-3-carbonitrile (**18d**).* Obtained from acrylonitrile **16d** and 4-fluoroaniline, brown solid (250 mg, 60%): mp 250−251 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 2211, 1505, 1214, 735; ^1H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 7.2 Hz, 1H), 7.65 (dd, J = 8.8, 4.8 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.30−7.24 (m, 3H), 7.19 (q, J = 7.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 1H), 3.77 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 160.7, 139.9, 139.4, 136.2, 136.0, 131.99, 131.96, 131.1, 131.0, 126.5, 121.8, 121.4, 119.80, 119.75, 119.4, 118.5, 117.6, 117.3, 116.2, 116.0, 110.23, 110.19, 105.4, 102.6, 83.6, 32.7, 30.2; HRMS (ESI) m/z calcd for $C_{27}H_{19}FN_4$ $[M + H]^+$ 419.1672, found 419.1684.

*2-(4-Fluorophenyl)-1-(4-methoxyphenyl)-8-methyl-1,8-dihydropyrrolo[2,3-b]indole-3-carbonitrile (**18e**).* Obtained from acrylonitrile **16e** and 4-fluoroaniline, off-white solid (256 mg, 65%): mp 220−221 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2920, 2215, 1519, 1219, 744; ^1H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 6.8 Hz, 1H), 7.65 (dd, J = 8.8, 4.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.25−7.23 (m, 1H), 7.19 (td, J = 7.2, 0.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 160.8, 159.3, 141.1, 140.1, 139.6, 131.9, 131.8, 131.5, 131.4, 121.6, 121.2, 119.8, 118.4, 117.7, 117.2, 116.5, 116.3, 114.0, 110.3, 105.4, 82.6, 55.2, 30.1; HRMS (ESI) m/z calcd for $C_{25}H_{18}FN_3O$ $[M + H]^+$ 396.1512, found 396.1505.

*4-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1,3-diphenyl-1,4-dihydropyrrolo[3,2-c]pyrazole-6-carbonitrile (**21a**).* Obtained from acrylonitrile **19a** and 4-fluoroaniline, white solid (387 mg, 80%); mp 225−226 °C; R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 2223, 1604, 1517, 1251, 1181, 789; ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, J = 8.8, 1.2 Hz, 2H), 7.62 (br t, J = 7.6 Hz, 2H), 7.43−7.39 (m, 3H), 7.34 (d, J = 8.8 Hz, 2H), 7.30−7.25 (m, 1H), 7.24−7.16 (m, 4), 7.10 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.0, 160.7, 150.0, 139.8, 136.2, 134.9, 133.4, 133.3, 131.7, 131.0, 129.8, 129.7, 129.6, 128.7, 128.2, 128.1, 128.0, 126.6, 120.89, 120.85, 116.4, 116.2, 116.1, 114.4, 78.0, 55.5; HRMS (ESI) m/z calcd for $C_{31}H_{21}FN_4O$ $[M + H]^+$ 485.1778, found 485.1771.

*5-(1-Methyl-1H-indol-3-yl)-1,3-diphenyl-4-[4-(trifluoromethyl)-phenyl]-1,4 dihydropyrrolo[3,2-c]pyrazole-6-carbonitrile (**21b**).* Obtained from acrylonitrile **19b** and 4-(trifluoromethyl)aniline, white solid (373 mg, 67%); mp 261−263 °C; R_f 0.6 (1:9 EtOAc/hexane); IR (KBr, cm^{-1}) 2920, 2223, 1486, 1321, 1133, 1062, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.4, 1.2 Hz, 2H), 7.56 (dd, J = 8.8, 7.6 Hz, 2H), 7.40 (br d, J = 8.4 Hz, 2H), 7.37−7.32 (m, 2H), 7.248−7.245 (m, 1H), 7.23−7.10 (m, 9H), 7.01 (dd, J = 7.6, 7.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 140.5, 139.8, 137.0, 136.1, 135.2, 131.0, 130.9, 130.5, 130.1, 129.6, 128.9, 128.4, 128.1, 127.8, 127.4, 126.6, 126.23, 126.19, 126.16, 126.13, 122.9, 121.0, 120.9, 120.0, 116.2, 110.0, 103.3, 79.4, 33.5; HRMS (ESI) m/z calcd for $C_{34}H_{22}F_3N_5$ $[M + H]^+$ 558.1906, found 558.1902.

*5-(1-Methyl-1H-pyrrol-2-yl)-1,3-diphenyl-4-(pyridin-2-yl)-1,4-dihydropyrrolo[3,2-c]pyrazole-6-carbonitrile (**21c**).* Obtained from acrylonitrile **19c** and 2-aminopyridine, white solid (286 mg, 65%); mp 202−204 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 3053, 2223, 1580, 1502, 1470, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (ddd, J = 4.8, 2.0, 0.8 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.63 (td, J = 7.8, 2.0 Hz, 1H), 7.56 (dd, J = 8.4, 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.25−7.22 (m, 2H), 7.20−7.15 (m, 4H), 6.88 (dt, J = 8.0, 0.8 Hz, 1H), 6.68 (dd, J = 2.8, 1.4 Hz, 1H), 6.30 (dd, J = 3.6, 1.4 Hz, 1H), 6.14 (dd, J = 3.6, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 149.2, 141.3, 139.8, 138.3, 136.7, 134.6, 131.7, 129.6, 128.7, 128.1, 127.9, 127.4, 126.6, 125.3, 123.4, 120.94, 120.92, 120.3, 115.3, 114.8, 108.9, 81.4, 34.8; HRMS (ESI) m/z calcd for $C_{28}H_{20}N_6$ $[M + Na]^+$ 463.1647, found 463.1643.

*4-(4-Chlorophenyl)-5-(furan-2-yl)-1,3-diphenyl-1,4-dihydropyrrolo[3,2-c]pyrazole-6- carbonitrile (**21d**).* Obtained from acrylonitrile **19d** and 4-chloroaniline, off-white solid (285 mg, 62%); mp 128−130 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3058, 2226, 1489, 1085, 1016, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (td, J = 7.6, 1.2 Hz, 2H), 7.56 (dd, J = 8.4, 7.6 Hz, 2H), 7.43 (dd, J = 1.4, 0.6 Hz, 1H), 7.39−7.33 (m, 3H), 7.24−7.20 (m, 3H), 7.18−7.11 (m, 4H), 6.51 (dd, J = 3.4, 0.6 Hz, 1H), 6.44 (dd, J = 3.4, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.0, 139.6, 139.2, 136.3, 136.2, 135.5, 135.0, 130.7, 129.65, 129.59, 129.4, 128.8, 128.4, 128.3, 128.2, 126.8, 121.0, 115.4, 113.3, 111.8, 77.4; HRMS (ESI) m/z calcd for $C_{28}H_{17}ClN_4O$ $[M + H]^+$ 461.1169 and 463.1140, found 461.1163 and 463.1128.

General Procedure for Synthesis of 3-Cyano-2-alkyl-*N*-arylindoles 6m−o and 3-Cyano-2-(het)aryl-*N*-alkylindoles 6p and 6q from Enaminonitriles 8m−q. To a stirred solution of either pure (**8m** or **8n**) or crude (**8o−q**) enaminonitrile (0.5 mmol) in DMF (5 mL) were added CuI (9 mg, 0.05 mmol), L-proline (12 mg, 0.1 mmol), and Cs_2CO_3 (163 mg, 0.5 mmol, 1 equiv), and the reaction mixture was heated at 90 °C with constant stirring for 9−10 h (monitored by TLC). It was then poured into ice-cold water (20 mL) and extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with water (2 × 10 mL) and brine (1 × 10 mL) and dried over Na_2SO_4 followed by removal of the solvent. Th resulting crude products were purified by column chromatography over silica gel with EtOAc/hexane as eluent.

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*5,6-Dimethoxy-1-(4-methoxyphenyl)-2-methyl-1H-indole-3-carbonitrile (**6m**).* Obtained from enaminonitrile **8m**, white solid (128 mg, 80%); mp 131−132 °C; R_f 0.6 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 2919, 2220, 1608, 1482, 1224, 1022, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.8 Hz, 2H), 7.11 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.49 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.77 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 147.9, 147.1, 144.4 131.8, 128.98, 128.92, 119.76, 116.9, 115.3, 100.5, 94.5, 85.7, 56.5, 56.4, 55.8, 12.7; HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_3$ $[M + H]^+$ 323.1396, found 323.1383.

*1-(4-Chlorophenyl)-5,6-dimethoxy-2-methyl-1H-indole-3-carbonitrile (**6n**).* Obtained from enaminonitrile **8n**, white solid (127 mg, 78%): mp 185−186 °C; R_f 0.65 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2935, 2218, 1489, 1281, 1163, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H) 6.49 (s, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.3, 143.7, 135.3, 134.9, 131.6, 130.5, 129.1, 119.9, 116.6, 100.6, 94.2, 86.7, 56.5, 56.4, 12.7; HRMS (ESI) m/z calcd for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ 327.0900 and 329.0871, found 327.0880 and 329.0855.

*5-Methoxy-1-phenyl-2-propyl-1H-indole-3-carbonitrile (**6o**).* Obtained from enaminonitrile **8o**, colorless liquid (87 mg, 60%); R_f 0.65 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2967, 2211, 1480, 1248, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.53 (m, 3H), 7.32−7.30 (m, 2H), 7.15 (d, J = 2.4 Hz 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.82 (dd, J = 8.6, 2.4 Hz, 1H), 3.87 (s, 3H), 2.78 (t, J = 7.6 Hz, 2H), 1.57 (sextet, J = 7.2 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 150.1, 136.3, 132.5, 130.0, 129.3, 128.1, 127.9, 116.7, 113.8, 112.1, 100.5, 85.8, 56.0, 28.4, 22.5, 13.8; HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O$ $[M + H]^+$ 291.1497, found 291.1485.

*1-Benzyl-5-methoxy-2-(4-methoxyphenyl)-1H-indole-3-carbonitrile (**6p**).* Obtained from enaminonitrile **8p**, white solid (101 mg, 55%): mp 108−109 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2932, 2207, 1608, 1489, 1255, 1028, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 2H), 7.32−7.28 (m, 3H), 7.215 (d, J = 2.4 Hz 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.99−6.97 (m, 4H), 6.88 (dd, J = 8.8, 2.4 Hz, 1H), 5.32 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 156.2, 148.4, 136.5, 131.3, 131.0, 129.03, 128.7, 127.76, 125.8, 121.0, 117.0, 114.6, 114.4, 112.3, 100.8, 85.6, 55.8, 55.4, 48.4; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2O_2$ $[M + H]^+$ 369.1603, found 369.1603.

*5-Methoxy-1-phenethyl-2-(thiophen-2-yl)-1H-indole-3-carbonitrile (**6q**).* Obtained from enaminonitrile **8q**, yellow semisolid (103 mg, 58%): R_f 0.55 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2926, 2207, 1451, 1243, 1028, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.2, 1.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.226−7.19 (m, 4H), 7.17−7.14 (m, 2H), 6.99−6.94 (m, 3H), 4.44 (t, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.03 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 140.3, 137.3, 131.1, 130.5, 128.93, 128.9, 128.73, 128.7, 128.0, 127.2, 116.7, 115.1, 111.8,100.8, 87.09, 55.9, 46.5, 36.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}N_2OS$ $[M + H]^+$ 359.1218, found 359.1218.

General Procedure for Synthesis of *N*-Acylenaminonitriles 10a−c from 1a. To a stirred suspension of NaH (40 mg, 1.0 mmol, 100%) in dry DMF (10 mL) was added a solution of the appropriate amide (1.1 mmol) in DMF (5 mL) dropwise, followed by addition of **1a** (0.39 g, 1.0 mmol) in DMF (5 mL) at room temperature. The reaction mixture was heated at 120 °C with stirring for 9−11 h (monitored by TLC). It was then poured into ice-cold water (50 mL), extracted with EtOAc (2 × 50 mL), washed with water (2 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting crude N-acylenaminonitriles were purified by column chromatography over silica gel with EtOAc/hexane as eluent.

*(E)-N-[2-(2-Bromo-5-methoxyphenyl)-2-cyano-1-(4-methoxyphenyl)vinyl]benzamide (**10a**).* Obtained as a 70:30 mixture of geometrical isomers, white solid (324 mg, 76%): mp 140−144 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 3293, 2941, 2212, 1691, 1606, 1469, 1261, 1026, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 2.8 Hz, 1H), 6.57 (d, J = 2.8 Hz, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.6, 161.9, 161.2, 159.9, 159.1, 152.1, 134.7, 134.01, 133.96, 133.7, 133.2, 133.1, 132.9, 130.7, 130.4, 129.2, 129.1, 127.8, 127.5, 125.4, 125.1, 118.7, 118.0, 117.8, 117.2, 116.8, 116.6, 115.4, 114.3, 114.2, 114.0, 99.3, 98.3, 55.9, 55.7, 55.5, 55.4; HRMS (ESI) m/z calcd for $C_{24}H_{19}BrN_2O_3$ $[M + H]^+$ 463.0657 and 465.0637, found 463.0659 and 465.0639

*(E)-N-[2-(2-Bromo-5-methoxyphenyl)-2-cyano-1-(4-methoxyphenyl)vinyl]pivalamide (**10b**).* Obtained as a single geometrical isomer, white solid (345 mg, 78%): mp 184−186 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 3237, 2969, 2208, 1677, 1598, 1507, 1467, 1255, 1178, 1024, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.69 (m, 1H), 6.57 (d, J = 2.8 Hz, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 161.1, 159.0, 152.0, 134.0, 130.4, 125.4, 117.9, 117.1, 116.8, 115.3, 113.9, 99.4, 55.6, 55.3, 40.2, 27.5; HRMS (ESI) m/z calcd for $C_{22}H_{23}BrN_2O_3$ $[M + H]^+$ 443.0970 and 445.0950, found 443.0954 and 445.0937.

*(E)-N-(2-(2-Bromo-5-methoxyphenyl)-2-cyano-1-(4-methoxyphenyl)vinyl)propionamide (**10c**).* Obtained as 2:1 inseparable mixture of geometrical isomers, off-white solid (290 mg, 70%): mp 104−107 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 3234, 2929, 2203, 1687, 1595, 1251, 1023, 828; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 0.33H), 9.67 (s, 0.67H), 7.59−7.53 (m, 2.34H), 7.06 (dd, J = 8.8 Hz, 2.01H), 6.94−6.91(m, 1.32H), 6.86 (dd, J = 8.8, 2.4 Hz, 0.33H), 6.81 (d, J = 8.8 Hz, 0.67H), 6.66 (d, J = 2.4 Hz, 0.33H), 3.83 (s, 2.01H), 3.76 (s, 2.01H), 3.71 (s, 0.99H), 3.62 (s, 0.99H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 171.6, 161.1, 160.6, 158.7, 158.6, 152.0, 150.4, 135.1, 134.9, 133.9, 133.8, 130.9, 130.6, 126.8, 126.2, 119.1, 118.1, 117.0, 116.3, 115.4, 114.2, 113.7, 113.62, 113.59, 100.9, 98.4, 55.5, 55.45, 55.35, 55.22, 29.1, 28.9, 9.3, 9.2; HRMS (ESI) m/z calcd for $C_{20}H_{19}BrN_2O_3$ $[M + H]^+$ 415.0657 and 417.0637, found 415.0677 and 417.0642

General Procedure for Copper-Catalyzed Cyclization of *N*-Acylenaminonitriles 10a−c. *N*-Acylenaminonitriles **10a−c** (0.5 mmol) were subjected to copper-catalyzed cyclization under identical conditions as described for enaminonitrile **8a** in the presence of CuI (9 mg, 0.05 mmol), L-proline (12 mg, 0.1 mmol), and NaH (20 mg, 0.5 mmol, 100%) in DMF. Workup of the reaction mixture as described for **8a** afforded in all three reactions 5-methoxy-2-(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (**12a**): off-white solid (73−75%, Scheme 4): mp 224−225 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}); 3201, 2960, 2225, 1469, 1248, 1026, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.92 (dd, J = 8.8, 2.4 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.2, 145.2, 130.0, 129.8, 128.3, 122.2, 117.5, 115.0, 114.8, 112.5, 100.8, 83.1, 56.0, 55.6; HRMS (ESI) m/z calcd for $C_{17}H_{14}N_2O_2$ $[M + H]^+$ 279.1134, found 279.1122.

General Procedure for Two-Step One-Pot Synthesis of 3-Cyano-2-(het)aryl-1-N*H*-indoles 12, 14f, and 21e. To a stirred suspension of NaH (80 mg, 2.0 mmol, 100%) in dry DMF (5 mL) was added the appropriate amide (1.1 mmol) in DMF (5 mL) dropwise at room temperature, followed by addition of acrylonitrile **1**, **13e**, or **19c** (1.0 mmol) in DMF (10 mL). The reaction mixture was heated at 120 °C with stirring for 10 h, and after consumption of starting materials (monitored by TLC), CuI (19 mg, 0.1 mmol) and L-proline (23 mg, 0.2 mmol) were added and the reaction mixture was further heated (120 °C) for 9−10 h (monitored by TLC). Workup of the reaction mixture as described for preparation of *N*-arylindoles **6** afforded crude NH-indoles **12**, **14f**, and **21e**, which were further purified by column chromatography over silica gel with EtOAc/hexane as eluent.

*5,6-Dimethoxy-2-(1-methyl-1H-indol-3-yl)-1H-indole-3-carbonitrile (**12b**).* Obtained from **1i** and trimethylacetamide; white solid (244 mg, 74%): mp 138−140 °C; R_f 0.3 (1:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3335, 2931, 2203, 1639, 1452, 1205, 1017, 742; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.06 (s, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 147.2, 146.2, 139.8, 136.7, 129.62, 129.58, 127.4, 124.6, 122.3, 120.9, 120.3, 119.9, 117.8, 110.5, 104.6, 99.8, 95.9, 55.8, 55.7, 32.9; HRMS (ESI) m/z calcd for $C_{20}H_{17}N_3O_2$ $[M + H]^+$ 332.1399, found 332.1391.

*6-Fluoro-2-(1-methyl-1H-indol-3-yl)-1H-indole-3-carbonitrile (**12c**).* Obtained from **1j** and benzamide; off-white solid (187 mg, 65%): mp 255−256 °C; R_f 0.35 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3293, 2205, 1424, 1130, 740; ^1H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.0 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.58 (dd, J = 8.8, 5.2 Hz, 1H), 7.36−7.25 (m, 3H), 7.09 (td, J = 8.8, 2.4 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 158.1, 142.7, 136.8, 135.6, 135.5, 130.5, 124.7, 124.5, 122.5, 120.6, 119.9, 118.9, 117.1, 110.7, 110.0, 109.8, 104.0, 98.8, 98.6, 80.0, 33.0; HRMS (ESI) m/z calcd for $C_{18}H_{12}FN_3$ $[M + H]^+$ 290.1094, found 290.1077

*5-Methoxy-2-(pyridin-3-yl)-1H-indole-3-carbonitrile (**12d**).* Obtained from **1k** and trimethylacetamide; white solid (174 mg, 70%); mp 160−162 °C; R_f 0.3 (4:6 EtOAc/hexane); IR (KBr, cm^{-1}) 3458, 2925, 2212, 1598, 1474, 1212, 801; ^1H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, J = 2.0 Hz, 1H), 8.75 (dd, J = 4.6, 5.2 Hz, 1H), 8.25 (ddd, J = 8.6, 2.4, 1.6 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.65 (ddd, J = 8.6, 4.6, 0.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.20 (ddd, J = 9.0, 2.4, 0.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 152.0, 151.3, 148.2, 139.4, 135.6, 129.7, 127.4, 124.4, 124.3, 117.1, 114.5, 103.7, 102.3, 55.6; HRMS (ESI) m/z calcd for $C_{15}H_{11}N_3O$ $[M + H]^+$ 250.0980, found 250.0978.

*5-Methoxy-2-(thiophen-2-yl)-1H-indole-3-carbonitrile (**12e**).* Obtained from **1m** and benzamide; off-white solid (178 mg, 70%); mp 190−192 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (KBr, cm^{-1}) 3234, 2941, 2205, 1463, 1222, 1033, 811, 707; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (br s, 1H), 7.74 (dd, J = 3.6, 1.2 Hz, 1H), 7.47 (dd, J = 4.8, 1.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.19 (dd, J = 4.8, 3.6 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 8.8, 2.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 139.2, 131.5, 129.8, 129.6, 128.7, 127.4, 127.3, 116.8, 115.4, 112.6, 100.8, 83.7, 55.9; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_2OS$ $[M + H]^+$ 255.0592, found 255.0588.

*5-(Thiophen-2-yl)-6H-thieno[2,3-b]pyrrole-4-carbonitrile (**14f**).* Obtained from acrylonitrile **13e** and benzamide, gray solid (150 mg, 65%): mp 155−156 °C; R_f 0.35 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 3224, 2213, 1450, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (br s, 1H), 7.57 (dd, J = 3.6, 1.0 Hz, 1H), 7.38 (dd, J = 5.2, 1.0 Hz, 1H), 7.14 (dd, J = 5.2, 3.6 Hz, 1H), 7.08 (d, J = 5.2 Hz, 1H), 7.0 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 134.2, 132.4, 131.9, 128.4, 126.3, 125.9, 121..4, 116.9, 116.7, 83.2; HRMS (ESI) m/z calcd for $C_{11}H_6N_2S_2$ $[M + H]^+$ 231.0051, found 231.0045.

*5-(1-Methyl-1H-pyrrol-2-yl)-1,3-diphenyl-1,4-dihydropyrrolo[3,2-c]pyrazole-6-carbonitrile (**21e**).* Obtained from acrylonitrile **19c** and benzamide, brown solid (225 mg, 60%); mp 120−122 °C; R_f 0.35 (2:3 EtOAc/hexane): IR (KBr, cm^{-1}) 3404, 3064, 2953, 2211, 1601, 1497, 1275, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.55−7.52 (m, 2H), 7.50−7.46 (m, 2H), 7.38 (tt, J = 8.0, 1.2 Hz, 1H), 7.31 (tt, J = 8.0, 1.2 Hz, 1H), 6.86 (dd, J = 2.4, 1.6 Hz, 1H), 6.56 (dd, J = 3.6, 1.6 Hz, 1H), 6.27 (dd, J = 3.6, 2.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.9, 135.9, 134.9, 131.8, 129.6, 129.1, 128.5, 126.5, 126.4, 126.2, 125.7, 122.7, 120.6, 116.1, 113.1, 109.2, 77.8, 35.5; HRMS (ESI) m/z calcd for $C_{23}H_{17}N_5$ $[M + H]^+$ 364.1562, found 364.1549.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Fifty-nine figures showing ORTEP X-ray crystal structure displays for **8a**, **6d**, and **18c** and ^1H NMR and ^{13}C NMR spectra for all compounds (PDF); crystallographic data for **8a**, **6d**, and **18c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor C. N. R. Rao, JNCASR, on the occasion of his 80th birthday.

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(28) Recently, Zhao and co-workers have reported synthesis of *N*-aryl/alkyl-2-alkyl-3-cyanoindoles by PIFA-mediated intramolecular oxidative cyclization of the corresponding *N*-aryl/alkylenaminonitriles. However, substituent diversity at the 2-position of product indoles is limited to 2-methyl group with only one exception; besides, these 2-aryl-3-aryl/alkylamino-2-alkenenitriles are unstable and their isolation in pure form is experimentally difficult. (a) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919. For NBS-induced similar transformation, see (b) Yan, Q.; Luo, J.; Zhang-Negrerie, D.; Li, H.; Qi, X.; Zhao, K. *J. Org. Chem.* **2011**, *76*, 8690.

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