DOI: 10.1002/ejoc.200901036

Synthesis of Novel Substituted Phenanthrenes and Polycyclic Heteroarenes by Pd-Catalyzed, Direct, Intramolecular Arylation/Heteroarylation

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Keywords: Cyclization / Heteroarenes / Palladium / Phenanthrenes / Polycycles

A novel route to substituted phenanthrenes and polycyclic heteroarenes by direct, Pd-catalyzed, intramolecular arylation/heteroarylation of 2-(2-bromoaryl/heteroaryl)-3-(aryl/heteroaryl)-3-(methylthio)acrylonitriles has been reported.

Introduction

Angularly fused polycyclic aromatics such as phenanthrene and its heterocyclic analogs are an important class of compounds, since their structural motifs are present in many biologically active natural products[1] such as the phenanthrene analogs of combretastatin A-4,[2] an exceptionally strong inhibitor of tubulin polymerization.[2a] Similarly, a number of polycyclic heteroarenes such as benzothiophenes and benzobis(thiophenes) such as benzo[1,2-*b*:4,5,-*b'*]dithiophene (BDT)[3a] and their polycyclic aromatic derivatives exhibit remarkable electrochemical and optical properties making them useful candidates in materials science[3,4] for optoelectronic devices, organic conductors,[3c,4b] narrow-band-gap polymers[3b] and field-effect transistors.[3e,3f] A few of the angularly fused naphtho[2,1-*b*]-furan, naphtho[2,1-*b*]thiophene, benzothienofuran and benzodithiophene derivatives are known to exhibit significant antiproliferative activity.[5,6]

Among other angularly fused heteroaromatics, carbazoles[7] and their benzo- and hetero-fused analogs (especially those fused to the *a* or *c* face of the carbazole nucleus) display a wide range of biological activity. Thus, a number of naphtho[*a*]-fused carbazoles[8,9] show significant cell-growth inhibition of a range of tumor cell lines,[8a–8c] whereas a benzo[*c*]carbazole derivative displayed a promising selectivity profile for the inhibition of an intercyclin-dependant kinase.[10] Similarly, hetero[*a*]-fused carbazoles such as granulatimide[11a,11b] and isogranulatimide[11c] act as G2 check-point inhibitors,[11] whereas a pyrido[*a*]carbazole-derived organometallic[12] was shown to be the inhibitor of glycogen synthase kinase 3. Furostifoline and eustifoline D, two furo-fused carbazole alkaloids,[13] are used as Chinese folk medicine for various ailments, whereas the indolo[2,3-*a*]carbazole alkaloids[7,14] such as staurosporine and its related natural and synthetic analogs,[9a,15,16] have been identified as some of the most potent D1-CDK4 inhibitors and are presently under clinical trial.

Because of the importance of these angularly fused polyarenes and related heteroarenes in medicinal chemistry as well as in materials science, a number of powerful methodologies, especially those involving biaryl (or heterobiaryl) bond construction, have been developed for this class of compounds in recent decades.[17,18] The most important methods for biaryl (or heterobiaryl) bond construction involve photochemical methods,[19] metal-catalyzed cross-coupling[9a,9d,18,20] and most recently, biomimetic oxidative coupling[18,21] and radical-mediated coupling reactions.[22]

During the course of our continued interest in the chemistry of polarized ketene dithioacetals as versatile building blocks for substituted and fused aromatic and heteroaromatic compounds,[23,24] we became interested in exploring the synthetic applications of another class of related organosulfur compounds of type **1** [i.e. 2- and 3-(aryl/heteroaryl)-3-(methylthio)acrylonitriles]. We have recently reported an interesting anionic domino rearrangement of these intermediates in the presence of *n*-butyllithium, leading to a new general synthesis of 2-(aryl/heteroaryl)-1-(*o*-cyanoaryl)-acetylenes.[25] Also, we have developed an efficient route to 2-(aryl/heteroaryl)-3-cyanobenzo[*b*]thiophenes by the tributyltin hydride (TBTH)-induced, intramolecular, radical cyclization of these compounds.[26] In continuation of these studies, we further examined the Pd^0-catalyzed, direct, intramolecular arylation of intermediates **1**, providing a facile access to functionalized phenanthrenes and a variety of angularly fused heteroaryl scaffolds (Scheme 3). We have successfully accomplished this goal, and the results are presented in this paper.

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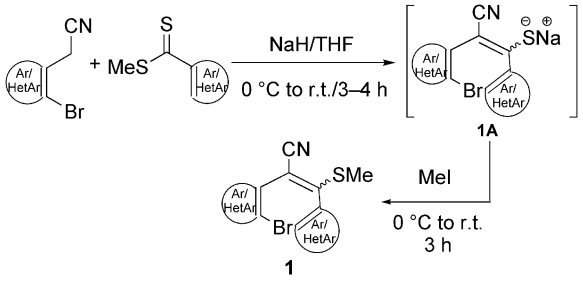
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901036.

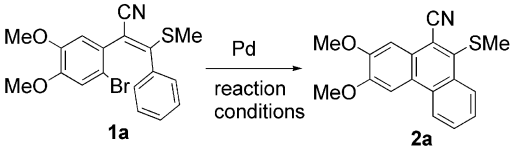
Results and Discussion

We prepared the desired (*o*-bromoaryl/heteroaryl)acrylonitriles **1a**–**p**, according to the general methodology developed in our laboratory,[25,26] by the base-induced condensation of (2-bromoaryl/heteroaryl)acetonitriles with various aryl/heteroaryl dithioesters followed by in situ *S*-methylation of the resulting enethiolate salts **1A** with methyl iodide (Scheme 1). The ^{1}H NMR spectra of **1a**–**p** revealed that we isolated **1a**, **1e**–**g** and **1o** as pure stereoisomers, whereas we found the other products to be inseparable mixtures of (*E*)/(*Z*) isomers with ratios varying from 1:1.2 to 1:4.4. The X-ray analysis of **1a** and **1g** established the (*Z*) configuration for these compounds. Nevertheless, the NMR analysis of either (*E*)/(*Z*) mixtures or of pure **1e**,**f** and **1o** did not allow us to determine the double-bond configuration in these compounds, which also underwent thermal (*Z*)/(*E*) isomerization, probably due to the push-pull character of the double bond in **1**.[26,27]



Scheme 1. Synthesis of (*o*-bromoaryl/heteroaryl)acrylonitriles **1a**–**p**.

We selected the acrylonitrile **1a** as the model substrate for optimizing reaction conditions for the intramolecular, Heck-type arylation by changing Pd catalysts, ligands, bases, solvents and additives (Scheme 2), and the results are shown in Table 1. As is evident from Table 1, we obtained the best yield of any phenanthrene (**2a**, 82%) when we heated **1a** with $Pd(OAc)_2$ (20 mol-%), triphenylphosphane (40 mol-%) and K_2CO_3 (2.5 equiv.) as base in DMF at 110–115 °C (24 h, Table 1, Entry 5). We confirmed the structure of phenanthrene **2a** with the help of spectral and analytical data.

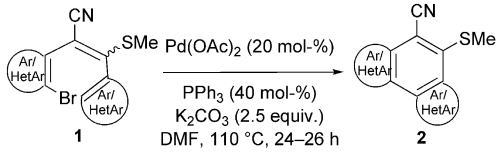


Scheme 2. Synthesis of phenanthrene **2a**.

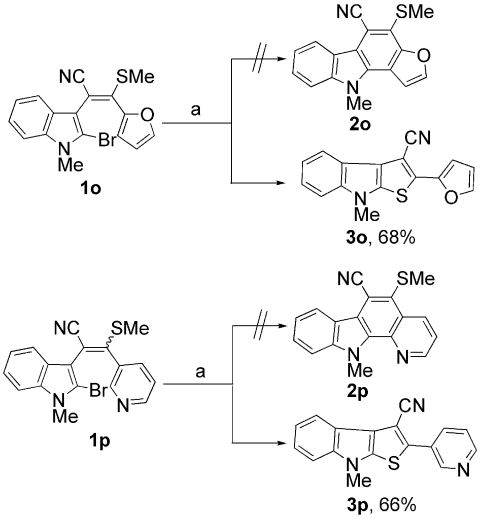
We used these optimized reaction conditions throughout our study of the intramolecular, Pd-catalyzed cyclization of other (aryl/heteroaryl)acrylonitriles **1b**–**p**, and the results are depicted in Schemes 3 and 4 and Table 2. Thus, the intramolecular, Heck-type arylation of sterically crowded, trimethoxylated, diarylacrylonitrile **1b** furnished the trimethoxyphenanthrene **2b**, a combrestatin analog,[2b] in 62% yield (Table 2, Entry 1).

Table 1. Pd-catalyzed, intramolecular, Heck arylation of **1a** to **2a**.

Entry	Reaction conditions	Yield of **2a** [%]
1	$Pd(OAc)_2$ (10 mol-%), nBu_4NBr (1 equiv.), K_2CO_3 (2.5 equiv.), DMF, 110 °C, 40 h	no reaction
2	$Pd(PPh_3)_4$ (4 mol-%), Et_3N (2.5 equiv.), CH_3CN, 100 °C, 38 h	34
3	$Pd(OAc)_2$ (10 mol-%), PPh_3 (20 mol-%), K_2CO_3 (2.5 equiv.), DMF, 110 °C, 24 h	56
4	$Pd(OAc)_2$ (20 mol-%), PPh_3 (40 mol-%), Na_2CO_3 (2.5 equiv.), DMF, 110 °C, 24 h	48
5	$Pd(OAc)_2$ (20 mol-%), PPh_3 (40 mol-%), K_2CO_3 (2.5 equiv.), DMF, 110 °C, 24 h	82
6	$Pd(PPh_3)_4$ (5 mol-%), KOAc (1.05 equiv.), DMA, 130 °C, 28 h	no reaction



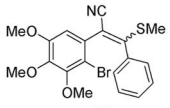
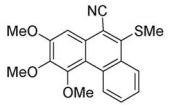
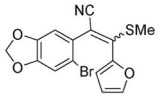
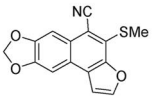
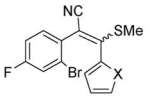
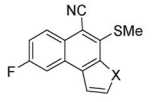
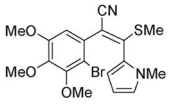
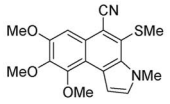
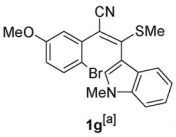
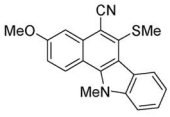
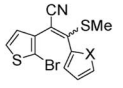
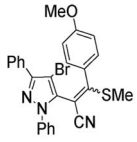
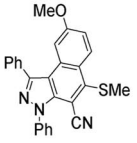
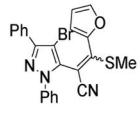
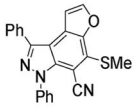
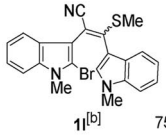
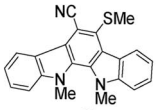
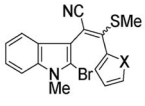
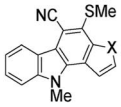
Scheme 3. Synthesis of phenanthrenes and polycyclic heteroarenes **2**.



Scheme 4. Pd^0-catalyzed, intramolecular cyclization of **1o**,**p**. Reaction conditions: (a) $Pd(OAc)_2$ (20 mol-%), PPh_3 (40 mol-%) K_2CO_3 (2.5 equiv.), DMF, 110 °C, 24 h.

Similarly, the corresponding 2-arylacrylonitriles **1c**–**f**, bearing a five-membered heterocyclic ring at the 3-position, underwent facile Pd^0-catalyzed, intramolecular cyclization under these conditions, yielding substituted naphtho[2,1-*b*]-furan **2c**, naphtho[2,1-*b*]thiophene **2d** and benzo[*e*]indole derivatives **2e**,**f** in 58–74% yields (Table 2, Entries 2–5). We prepared the substituted benzo[*a*]carbazole derivative **2g** in 68% yield when we subjected the 2-(2-bromo-5-methoxyphenyl)-3-[3-(*N*-methyl-3-indolyl)]acrylonitrile (**1g**) to Pd-catalyzed cyclization under identical conditions (Table 2, Entry 6).

Table 2. Pd^0-catalyzed, intramolecular cyclization of **1b**–**n**.

Entry	1	% Yield 1	2	% Yield 2[c]
1	 **1b**[b]	71%	 **2b**	62%
2	 **1c**[b]	72%	 **2c**	74%
3	 **1d**,[b] X = S	80%	 **2d**	61%
4	**1e**,[a] X = NMe	78%	**2e**	59%
5	 **1f**[a]	76%	 **2f**	58%
6	 **1g**[a]	82%	 **2g**	68%
7	 **1h**,[b] X = S	76%	 **2h**	78%
8	**1i**,[b] X = O	78%	**2i**	68%
9	 **1j**[b]	85%	 **2j**	65%
10	 **1k**[b]	84%	 **2k**	70%
11	 **1l**[b]	75%	 **2l**	72%
12	 **1m**,[b] X = S	81%	 **2m**	73%
13	**1n**,[b] X = NMe	80%	**2n**	71%

[a] Pure (*Z*) isomer. [b] Mixtures of (*E*)/(*Z*) isomers. [c] Yields calculated on the basis of either pure isomer or (*E*)/(*Z*) mixtures of isomers.

We next extended this Pd-catalyzed, intramolecular, Heck-type heteroarylation protocol to acrylonitriles **1h**–**p**, with a brominated heterocyclic ring as the electrophilic partner in this cyclization, as shown in Table 2, Entries 7–13. Thus, we obtained the regiospecifically substituted thieno[2,3-*e*]benzo[*b*]thiophene **2h** and the novel thieno-[2,3-*e*]benzo[*b*]furan **2i** in high yields from the corresponding acyclic precursors **1h**,**i** under the standard reaction conditions (Table 2, Entries 7–8). The extension of the reaction to 2-(4-bromo-1,3-diphenyl-5-pyrazolyl)-3-(4-methoxyphenyl)- and -3-(2-furyl)acrylonitriles **1j**,**k** under identical conditions provided novel highly substituted benzo[*e*]indazole **2j** and the corresponding furo[3,2-*e*]indazole **2k** in 65% and 70% yields, respectively (Table 2, Entries 9–10).

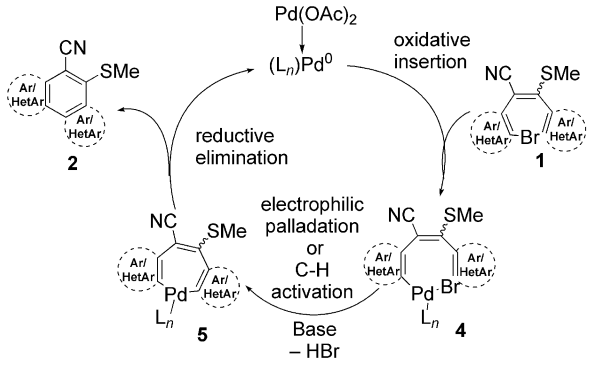
We next extended the intramolecular, Heck heteroarylation strategy to 2-(2-bromo-3-indolyl)-3-(heteroaryl)acrylonitriles **1l**–**p** with a view to synthesizing indolo[2,3-*a*]- and other heterocyclo[2,3-*a*]-fused carbazole frameworks **2l**–**p** because of the wide spectrum of biological activity displayed by this class of compounds. Thus, 2-(2-bromoindolyl)-3-(3-indolyl)acrylonitrile **1l** underwent facile Pd-catalyzed cyclization under the previously described reaction conditions to yield the desired 5-cyano-6-(methylthio)-indolo[2,3-*a*]carbazole derivative **2l** in 72% yield (Table 2, Entry 11). Similarly, we obtained the novel substituted thieno[3,2-*a*]- and pyrrolo[3,2-*a*]carbazole frameworks **2m** and **2n** in high yields by subjecting the respective 2-(2-bromo-3-indolyl)-3-(2-thienyl)- and -3-(2-pyrrolyl)acrylonitrile precursors **1m**–**n** to catalytic cyclization under these conditions (Table 2, Entries 12–13).

Interestingly, the attempted intramolecular Heck heteroarylation of the related 3-(2-furyl)acrylonitrile **1o** under the reported conditions did not furnish the desired furo[3,2-*a*]-carbazole **2o**. Instead, we isolated 3-cyano-2-furylthieno-[3,2-*b*]indole **3o** (68%) as the product on the basis of its spectral and analytical data (Scheme 4).

Similarly, the 2-(2-bromo-3-indolyl)-3-(3-pyridyl)acrylonitrile **1p** failed to furnish the expected pyrido[3,2-*a*]carbazole **2p** under these conditions and yielded only 3-cyano-2-(3-pyridyl)thieno[3,2-*b*]indole **3p** in 66% yield (Scheme 4).[28]

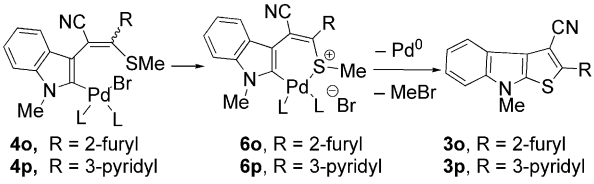
The mechanistic pathway for the Pd-catalyzed, intramolecular arylation of **1** to **2** is shown in Scheme 5. Thus, the oxidative addition of the C–Br bond of **1** to the Pd^0 species affords the (aryl)Pd complex **4**. The formation of an intramolecular C–C bond may proceed either by the electrophilic palladation of the arene[29,30] in **4** or by C–H activation involving the oxidative addition of (aryl)Pd species **4** to the neighboring aryl C–H bond,[30b] to give seven-membered palladacycle **5**, which undergoes reductive elimination to afford the product **2**, regenerating the active Pd^0 species. However, there is growing evidence of an electrophilic pathway in the direct arylation of heterocyclic arenes.[30,31]

The failure of 3-(2-furyl)- and 3-(3-pyridyl)acrylonitriles **1o**,**p** to afford furo- and pyrido-fused carbazoles **2o**,**p** under the present reaction conditions appears to be due to the combined effect of the reduced electrophilicity of the C–Br



Scheme 5. Mechanism for the formation of **2a**–**n**.

bond of the electron-rich 2-bromoindole along with a reduced nucleophilicity of the π-deficient, 3-pyridyl and 2-furyl heterocyclic rings, resulting in the failure to form palladacycle intermediate **5** by electrophilic displacement on Pd complexes **4o**,**p** (Scheme 5).[32] Therefore, the reaction takes a different course with the formation of cyclopalladated thioether complexes **6o**,**p** by the intramolecular nucleophilic attack of the electron-rich methylthio group on the Pd-insertion complexes **4o**,**p** (Scheme 6). The subsequent demethylation of the activated metal-bonded methylthio group in **6o**,**p** by some nucleophilic species followed by a subsequent reductive elimination affords the corresponding thienoindoles **3o**,**p** in good yields (Scheme 6). The formation of these kinds of cyclopalladated thioether complexes leading to thioheterocycles has been reported in the literature.[33]



Scheme 6. Mechanism for the formation of **3o**,**p**.

Conclusions

We have reported an efficient synthesis of a diverse array of novel aryl/heteroaryl-annulated scaffolds by Pd-catalyzed, direct, intramolecular arylation of easily accessible, novel, functionalized, *o*-bromodiaryl/heteroarylstilbene precursors. To the best of our knowledge, there is only one report of phenanthrene synthesis by a Pd-catalyzed direct arylation of *cis*-(*o*-chlorophenyl)stilbene,[30a] whereas other examples of biaryl construction by Pd-catalyzed cross coupling employ 1,2-(*o*-haloaryl/heteroaryl)-substituted heterocycles as precursors.[8b,9a,11c,18b,18c]

Experimental Section

General: Unless otherwise noted, all reactions were carried out in oven-dried glassware under N_2 in anhydrous solvents. Wherever appropriate, all reagents were purified prior to use according to the guidelines of Vogel, Perrin or Armarego.[34] ^{1}H (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were recorded with Jeol JNM-LA 400 FT-NMR and Jeol JNM-LA 500 FT-NMR spectrometers with $CDCl_3$ and [D_6]DMSO as the solvents. Tetramethylsilane was used as an internal reference. Melting points were recorded with a Mel-Temp melting point apparatus (capillary method) and are uncorrected. The IR spectra were recorded with a Perkin–Elmer 1320 spectrophotometer. The FAB mass spectra were recorded with a JEOL SX 102/DA-6000 Mass Spectrometer/Data System. HRMS (ESI) data were recorded with a Waters Micromass Q-TOF Premier Mass Spectrometer and a Bruker Daltonics APEXII FTICR spectrometer. Chromatographic purification was conducted by column chromatography on 100–200 mesh silica gel obtained from Acme Synthetic Chemicals (India).

General Procedure for the Preparation of 3-(Aryl/heteroaryl)-2-(2-bromoaryl/heteroaryl)-3-(methylthio)-2-propenenitriles (1a–p):[25,26] To a stirred suspension of NaH (0.44 g, 11.0 mmol, 60%) in dry THF (15 mL) under N_2 was added a solution of the corresponding (2-bromoaryl/heteroaryl)acetonitrile (5.0 mmol) in dry THF (15 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and a solution of the corresponding dithioester (5.0 mmol) in dry THF (15 mL) was added dropwise at 0 °C over 15–20 min. The reaction mixture was further stirred at room temperature for 3 h and cooled to 0 °C. MeI (0.46 mL, 7.5 mmol) was added dropwise at 0 °C to the reaction mixture, which was further stirred for 3 h. The reaction mixture was poured into ice-cold water. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure to give crude adducts **1a**–**p**, which were purified by column chromatography using hexane/EtOAc as the eluent.

2-(2-Bromo-3,4,5-trimethoxyphenyl)-3-(methylthio)-3-phenyl-2-propenenitrile (1b): Obtained as a 4:1 inseparable mixture of geometrical isomers; yield 71% (1.48 g); white solid; m.p. 80–82 °C; R_f = 0.50 (hexane/EtOAc, 8:2). IR (CH_2Cl_2): $\tilde{\nu}$ = 2937, 2204, 1562, 1481, 1385, 1346, 1251, 1106, 1011, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 3 H, Ar-H), 7.14–7.12 (m, 2 H, Ar-H), 6.75 (s, 0.2 H, Ar-H), 6.21 (s, 0.8 H, Ar-H), 3.92 (s, 0.60 H, OCH_3), 3.92 (s, 0.60 H, OCH_3), 3.88 (s, 0.60 H, OCH_3), 3.81 (s, 2.40 H, OCH_3), 3.79 (s, 2.40 H, OCH_3), 3.53 (s, 2.40 H, OCH_3), 2.06 (s, 2.40 H, SCH_3), 1.87 (s, 0.60 H, SCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4, 161.4, 153.3, 152.5, 151.9, 151.2, 144.0, 143.3, 135.0, 134.4, 130.2, 130.1, 129.6, 129.5, 129.3, 129.13, 129.12, 128.9, 128.8, 128.6, 117.5, 116.8, 111.4, 111.1, 109.9, 108.7, 61.3, 61.23, 61.17, 56.4, 56.12, 56.11, 16.36, 16.35 ppm. HRMS-ESI: calcd. for $C_{19}H_{19}BrNO_3S$ [M + H]$^+$ 420.0269; found 420.0266.

General Procedure for the Pd-Catalyzed Cyclization of 3-(Aryl/heteroaryl)-2-(2-bromoaryl/heteroaryl)-3-(methylthio)-2-propenenitriles (1a–p): A solution of the corresponding 3-(aryl/heteroaryl)-2-(2-bromoaryl/heteroaryl)-3-(methylthio)-2-propenenitrile **1a**–**p** (1 mmol) in dry DMF (5 mL, degassed with argon) was added to a suspension of $Pd(OAc)_2$ (20 mol-%), $(Ph_3)_3P$ (40 mol-%) and K_2CO_3 (2.5 mmol) in dry DMF (10 mL, degassed with argon) under argon at room temperature. The reaction mixture was heated at 110 °C for 24–26 h, and the reaction was monitored by TLC. The mixture was cooled to room temperature, poured into water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried with Na_2SO_4. The solvent was removed under reduced pres-

sure to give crude products **2a**–**n** and **3o**,**p**, which were purified by column chromatography on silica gel using hexane/EtOAc as the eluent.

2,3-Dimethoxy-9-(methylthio)phenanthrene-10-carbonitrile (2a): Yield 82% (0.25 g); white solid; m.p. 151–152 °C; R_f = 0.45 (hexane/EtOAc, 6:1). IR (KBr): $\tilde{\nu}$ = 2927, 2198, 1598, 1554, 1513, 1440, 1372, 1244, 1216, 1173, 1025, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2 H, Ar-H), 7.17–7.15 (m, 2 H, Ar-H), 6.93 (s, 1 H, Ar-H), 6.34 (s, 1 H, Ar-H), 3.81 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 2.08 (s, 3 H, SCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 149.5, 148.0, 134.3, 129.4, 128.9, 128.5, 126.6, 116.8, 115.1, 114.7, 114.6, 108.6, 56.0, 55.9, 16.2 ppm. MS: *m*/*z* (%) = 310 (74) [M + 1], 154 (100). HRMS-ESI: calcd. for $C_{18}H_{16}NO_2S$ [M + H]$^+$ 310.0902; found 310.0903.

4-(Methylthio)-3,7,9-trioxadicyclopenta[*a*,*g*]naphthalene-5-carbonitrile (2c): Yield 74% (0.21 g); white solid; m.p. 199–200 °C; R_f = 0.56 (hexane/EtOAc, 6:1). IR (KBr): $\tilde{\nu}$ = 2924, 2216, 1473, 1267, 1236, 1037, 859, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.61 (s, 1 H, Ar-H), 7.39 (s, 1 H, Ar-H), 7.18 (d, *J* = 1.9 Hz, 1 H, Ar-H), 6.15 (s, 2 H, OCH_2O), 2.78 (s, 3 H, SCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 148.9, 147.2, 127.5, 127.1, 125.8, 123.5, 117.1, 108.2, 106.1, 103.1, 101.9, 100.9, 18.2 ppm. MS: *m*/*z* (%) = 283 (100) [M$^+$]. HRMS-ESI: calcd. for $C_{15}H_{10}NO_3S$ [M + H]$^+$ 284.0381; found 284.0380.

7,8,9-Trimethoxy-3-methyl-4-(methylthio)benzo[*e*]indole-5-carbonitrile (2f): Yield 58% (0.20 g); white solid; m.p. 164–165 °C; R_f = 0.23 (hexane/EtOAc, 9:1). IR (KBr): $\tilde{\nu}$ = 2930, 2209, 1509, 1455, 1344, 1252, 1126, 1060, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H, Ar-H), 7.34 (d, *J* = 2.9 Hz, 1 H, Ar-H), 7.23 (d, *J* = 1.2 Hz, 1 H, Ar-H), 4.33 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.00 (s, 3 H, NCH_3), 2.59 (s, 3 H, SCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 149.3, 142.7, 133.7, 130.9, 126.9, 126.2, 126.1, 118.5, 118.2, 110.9, 104.3, 101.5, 61.2, 60.5, 56.0, 37.9, 21.6 ppm. MS: *m*/*z* (%) = 342 (100) [M]$^+$. HRMS-ESI: calcd. for $C_{18}H_{19}N_2O_3S$ [M + H]$^+$ 343.1116; found 343.1117.

4-(Methylthio)thieno[2,3-*e*]benzo[*b*]thiophene-5-carbonitrile (2h): Yield 78% (0.20 g); white solid; m.p. 157–158 °C; R_f = 0.49 (hexane/EtOAc, 19:1). IR (KBr): $\tilde{\nu}$ = 2921, 2217, 1463, 1346, 1311, 1095, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 5.4 Hz, 1 H, Ar-H), 7.68 (d, *J* = 5.4 Hz, 1 H, Ar-H), 7.65 (d, *J* = 5.4 Hz, 1 H, Ar-H), 7.63 (d, *J* = 5.6 Hz, 1 H, Ar-H), 2.69 (s, 3 H, SCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 138.5, 135.7, 134.8, 133.0, 132.7, 127.4, 123.3, 122.7, 117.0, 108.5, 19.3 ppm. MS: *m*/*z* (%) = 262 (100) [M + 1]$^+$, 261 (98) [M]$^+$. HRMS-ESI: calcd. for $C_{12}H_8NS_3$ 261.9819; found 261.9816.

4-(Methylthio)-6,8-diphenylfuro[3,2-*e*]indazole-5-carbonitrile (2k): Yield 70% (0.27 g); white solid; m.p. 219–220 °C; R_f = 0.56 (hexane/EtOAc, 6:1). IR (KBr): $\tilde{\nu}$ = 2927, 2218, 1592, 1499, 1307, 1144, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.87 (d, *J* = 7.3 Hz, 2 H, Ar-H), 7.59–7.48 (m, 8 H, Ar-H), 7.17 (d, *J* = 2.0 Hz, 1 H, Ar-H), 2.78 (s, 3 H, SCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 148.4, 148.3, 146.5, 138.4, 137.7, 132.4, 129.8, 129.7, 128.9, 128.8, 128.6, 127.8, 123.4, 115.3, 114.1, 107.1, 93.6, 18.2 ppm. MS: *m*/*z* (%) = 382 (100) [M + 1]$^+$, 381 (80) [M]$^+$. HRMS-ESI: calcd. for $C_{23}H_{16}N_3OS$ 382.1014; found 382.1014.

11,12-Dimethyl-6-(methylthio)-11,12-dihydro-11,12-diazaindeno[2,1-*a*]fluorene-5-carbonitrile (2l): Yield 72% (0.26 g); light yellow solid; m.p. 199–200 °C; R_f = 0.46 (hexane/EtOAc, 6:1). IR (KBr): $\tilde{\nu}$ = 2913, 2205, 1530, 1467, 1330, 1321, 1255, 1240, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (d, *J* = 8.0 Hz, 1 H, Ar-H), 8.77 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.62–7.51 (m, 4 H, Ar-H), 7.43–7.35 (m, 2 H, Ar-H), 4.22 (s, 3 H, NCH_3), 4.17 (s, 3 H, NCH_3), 2.58 (s, 3 H, SCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 143.7, 131.6, 129.1, 127.8, 127.0, 126.6, 124.0, 123.8, 123.4, 122.1, 121.3, 121.2, 120.9, 118.6, 110.2, 110.0, 103.3, 36.8, 36.6, 19.8 ppm. MS: *m*/*z* (%) = 355 (100) [M]$^+$. HRMS-ESI: calcd. for $C_{22}H_{18}N_3S$ [M + H]$^+$ 356.1221; found 356.1223.

2-(2-Furyl)-8-methyl-1-thia-8-azacyclopenta[*a*]indene-3-carbonitrile (3o): Yield 68% (0.19 g); yellow solid; m.p. 111–112 °C; R_f = 0.69 (hexane/EtOAc, 9:1). IR (KBr): $\tilde{\nu}$ = 2924, 2214, 1497, 1459, 736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 7.8, 0.7 Hz, 1 H, Ar-H), 7.46 (t, *J* = 0.98 Hz, 1 H, Ar-H), 7.35 (d, *J* = 1.2 Hz, 1 H, Ar-H), 7.34 (d, *J* = 3.2 Hz, 1 H, Ar-H), 7.27–7.23 (m, 1 H, Ar-H), 7.08 (d, *J* = 3.4 Hz, 1 H, Ar-H), 6.55 (dd, *J* = 3.5, 1.8 Hz, 1 H, Ar-H), 3.82 (s, 3 H, NCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1, 142.3, 142.0, 141.2, 134.2, 123.4, 121.6, 120.6, 120.4, 119.2, 115.5, 112.5, 109.4, 108.1, 94.8, 32.3 ppm. HRMS-ESI: calcd. for $C_{16}H_{11}N_2OS$ [M + H]$^+$ 279.0592; found 279.0592.

8-Methyl-2-(3-pyridyl)-1-thia-8-azacyclopenta[*a*]indene-3-carbonitrile (3p): Yield 66% (0.19 g); yellow solid; m.p. 191–192 °C; R_f = 0.23 (hexane/EtOAc, 7:3). IR (KBr): $\tilde{\nu}$ = 2921, 2219, 1495, 1469, 1410, 1327, 1089, 728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (br. s, 1 H, Ar-H), 8.65 (br. s, 1 H, Ar-H), 8.20 (d, *J* = 7.8 Hz, 1 H, Ar-H), 8.07 (dd, *J* = 7.9, 0.9 Hz, 1 H, Ar-H), 7.39–7.38 (m, 2 H, Ar-H), 7.31–7.25 (m, 2 H, Ar-H), 3.88 (s, 3 H, NCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 147.1, 142.1, 142.0, 139.3, 134.8, 129.3, 124.1, 123.9, 122.8, 120.7, 120.5, 119.3, 115.3, 109.5, 98.9, 32.4 ppm. HRMS-ESI: calcd. for $C_{17}H_{12}N_3S$ [M + H]$^+$ 290.0752; found 290.0755.

Supporting Information (see footnote on the first page of this article): General experimental procedures, characterization data of **1c**,**d**, **1f**, **1h**–**p**, **2b**, **2d**,**e**, **2g**, **2i**,**j**, **2m** and **2n** and copies of ^{1}H NMR and ^{13}C NMR spectra of **2a**–**n** and **3o**,**p**.

Acknowledgments

A. K. Y. thanks the Council of Scientific and Industrial Research (CSIR) New Delhi for a Senior Research Fellowship. Financial assistance under the Department of Science and Technology (DST) project is also acknowledged.

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Received: September 9, 2009
Published Online: November 18, 2009

