THE PREPARATION OF CERTAIN NITROGEN AND SULFUR CONTAINING POLYCYCLIC HETEROCYCLES BY THE REACTION OF ARYNES POSSESSING CHARGED GROUPS WITH α-LITHIO-α-CYANO-*o*-TOLUNITRILE AND α-LITHIO-3-THIENYLACETONITRILE

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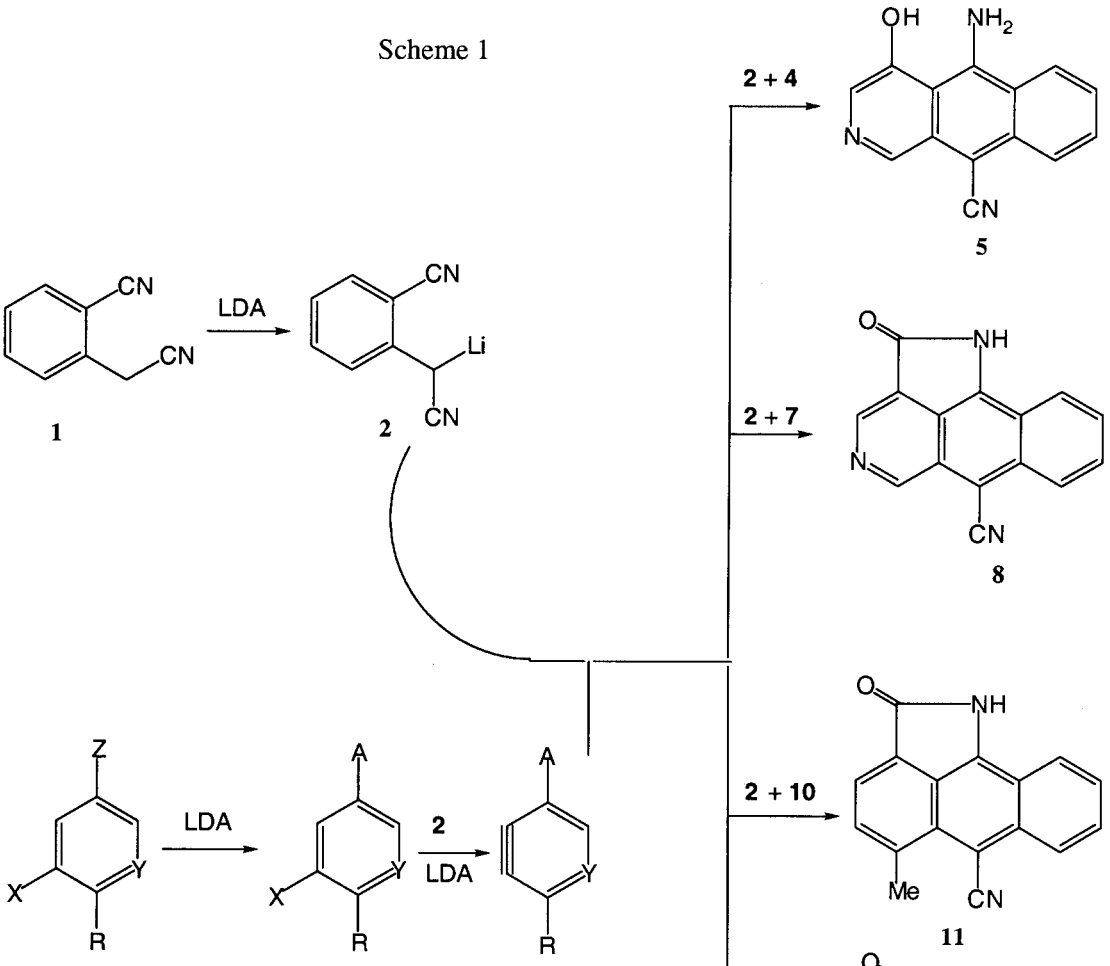
Abstract - The synthesis of a wide variety of polycyclic heterocycles by the reaction of arynes or hetarynes possessing charged substituents with lithiated 3-thiopheneacetonitrile (**22**) or α-cyano-*o*-tolunitrile (**2**) is reported. Specific heterocycles prepared include: 9-aminonaphtho[2,3-*b*]thiophen-8-yl]methanol from 2,3-dehydrobenzyl oxide and **22**; 5-amino-4-hydroxybenzo[*g*]isoquinoline-10-carbonitrile from 3,4-dehydropyridine-oxide and **2**; 4-aza-2-oxodibenzo[*cd,g*]indole-6-carbonitrile from 2,3-dehydronicotinamide and **2**; and 5-methyl- and 5-methoxy-2-oxo-1,2-dihydrodibenzo[*cd,g*]indole-2-carbonitrile from 4-methyl- and 4-methoxy-benzyne-3-carboylate, respectively and **2**. Possible mechanisms for these reactions are discussed.

We have shown that certain monocyclic arynes react with α-lithio-*o*-cyano-*o*-tolunitrile to give 9-amino-10-cyanoanthracenes.[1] More recently, several monocyclic arynes and hetarynes with charged substituents (CO_2Li,[2,3] CONHLi,[4,5] CH_2OLi[5], OLi[6]) have been found to react with aryl-acetonitriles under similar conditions to give rearranged nitriles or simple aryne addition products. We report here the extension of this methodology to the synthesis of nitrogen containing poly-cyclic heterocycles by treating arynes having charged or neutral substituents with α-lithio-α–cyano-*o*-tolunitrile or α-lithiothienylacetonitrile. The initial study involved the LDA-mediated reactions of α-cyano-*o*-tolunitrile (**1**) with 5-chloro-3-pyridinol (**3**), bromonicotinamide (**6**), and 3-bromo-4-methyl- (**9**) and 3-bromo-4-methoxybenzoic acids (**12**), as shown in Scheme 1. The reactions were carried

out using a reverse addition procedure, in which the dinitrile (**1**) was added to a solution containing the lithiated haloarene (**3'**, **6'**, **9'**, or **12'**) and excess LDA at -70 °C. During the addition, α-lithio-α-cyano-*o*-tolunitrile (**2**), which was formed by the reaction of **1** with LDA, assisted in the generation of the lithium aryne (**4**, **7**, **10**, or **13**).

Scheme 1



3 Z = OH, Y = N, R = H, X = Cl **3'** A = OLi, Y = N, R = H, X = Cl **4** A = OLi, Y = N, R = H

6 Z = $CONH_2$, Y = N, R = H, X = Br **6'** A = CONHLi, Y = N, R = H, X = Br **7** Z = CONHLi, Y = N, R = H

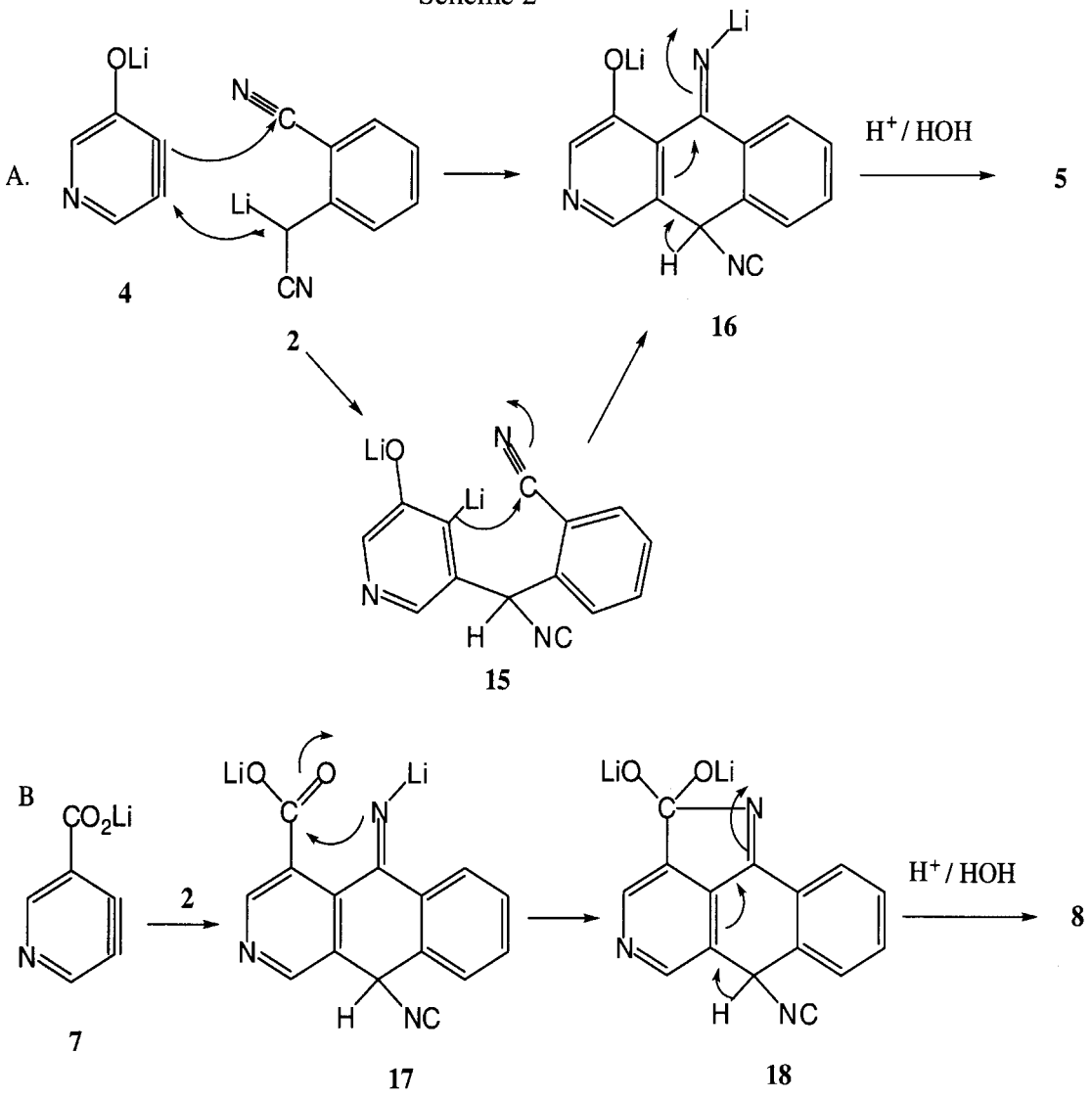
9 Z = CO_2H, Y = CH, R = Me, X = Br **9'** A = CO_2Li, Y = CH, R = Me, X = Br **10** Z = CO_2Li, Y = CH, R = Me

12 Z = CO_2H, Y = CH, R = OMe, X = Br **12'** A = CO_2Li, Y = CH, R = OMe, X = Br **13** Z = CO_2Li, Y = CH, R = OMe

The reaction of **2** with **4** gave, after quenching with dilute acid, the tricyclic heterocycle 5-amino-4-hydroxybenzo[*g*]isoquinoline-10-carbonitrile (**5**), in 54% yield. In like manner, the reaction of **2** with

lithium 3,4-dehydronicotinamidate (**7**) gave the tetracyclic amide, 4-aza-2-oxodibenzo[*cd,g*]indol-6-carbonitrile (**8**) in 59% yield, while 4-methylbenzyne-3-carboxylate (**10**) and 6-methoxy-benzyne-3-carboxylate (**13**) reacted with **2** to give 5-methyl- (**11**) and 5-methoxy-2-oxo-1,2-dihydrodibenzo[*cd,g*]indole-6-carbonitrile (**14**) in 36% and 44% yields, respectively. A likely mechanism for the formation of tricyclic heterocycle (**5**) is shown in Scheme 2. Part A involves the

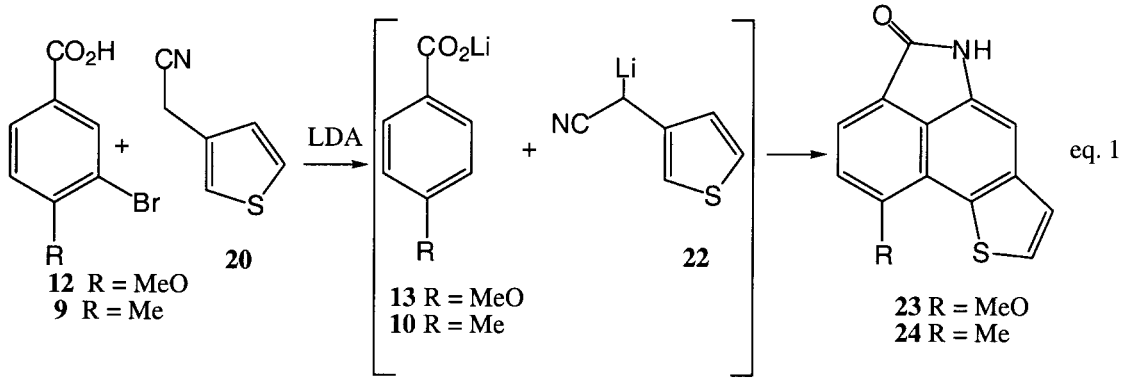
Scheme 2



addition of aryne (**4**)to the dinitrile (**2**)to give adduct (**16**) by either a non-synchronous [4+2] cycloaddition or a two-step process *via* the aryne-nitrile adduct (**15**). Both processes are consistent with the regioselective nature of the addition. Adduct (**16**) is then converted to product (**5**) during quenching. This mechanism is similar to that proposed for the preparation of anthra-quinones by the reaction of arynes with α-lithiated ethyl cyanoacetate.[7] The mechanism for the formation of heterocycle (**8**) is shown in Scheme 2, part B. In this case, the initially formed tricyclic adduct (**17**) from the reaction of **2** with **7** contains the N-Li and CO_2Li groups. The close proximity

of these two groups enables **17** to cyclizes to intermediate (**18**), which is then converted to **8** during acid quenching. Compounds (**11**) and (**14**) would be formed similarly.

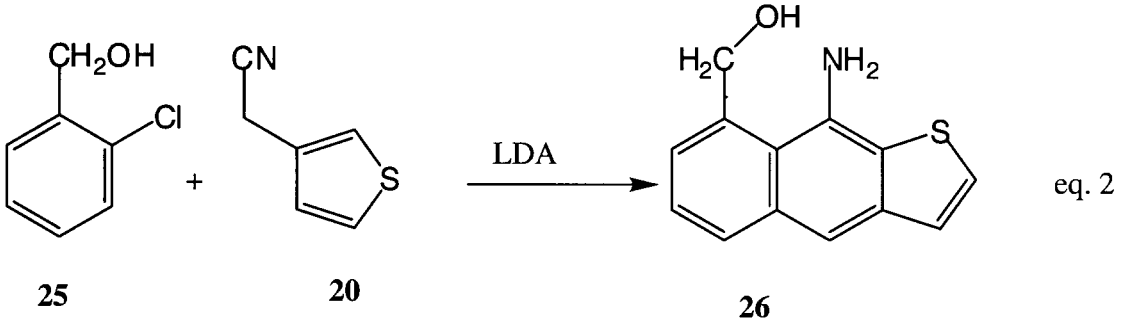
The use of lithiated 3-thienylacetonitrile as 1,4-dipolar synthon in arynic reactions was also studied. In a previous investigation,[8] we found that the reaction of lithiated 3-thienylacetonitrile (**22**), generated from 3-thienylacetonitrile (**20**) and LDA, with benzyne-3-carboxylates (**13**) and (**10**) gave products whose spectral properties indicated them to be 5-methoxy- (**23**) and 5-methylthieno[2,3-*f*]indol-2-one (**24**), respectively (see eq. 1).



eq. 1

A [4 + 2] cycloaddition mechanism was proposed to account for these products, the key step of which involved the addition of C-2 of the thiophene ring to the carbon of the cyano group.

To obtain more information on the use of lithiated 3-thienylacetonitrile (**22**) as a 1,4-dipolar synthon in arynic [4+2] cycloaddition reactions, the reaction of 2-chlorobenzyl alcohol (**25**) with **20** in the presence of LDA was carried out. As shown in eq. 2, 9-aminonaphtho[2,3-*b*]thiophen-8-yl-methanol (**26**) was obtained in 74% yield. In addition to IR, ^{1}H NMR and ^{13}C NMR spectroscopic analyses, the structure of **26** was also ascertained by X-Ray diffractometry. The ORTEP of **26** is



eq. 2

25 **20** **26**

shown in Figure 1.

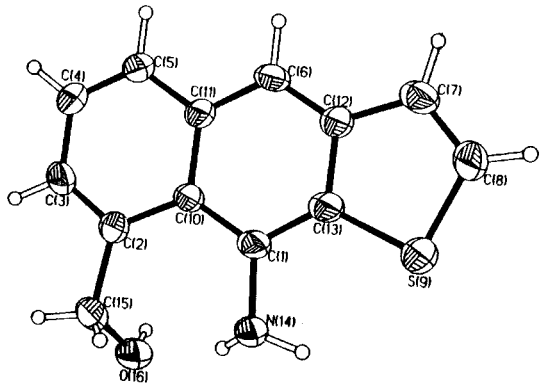
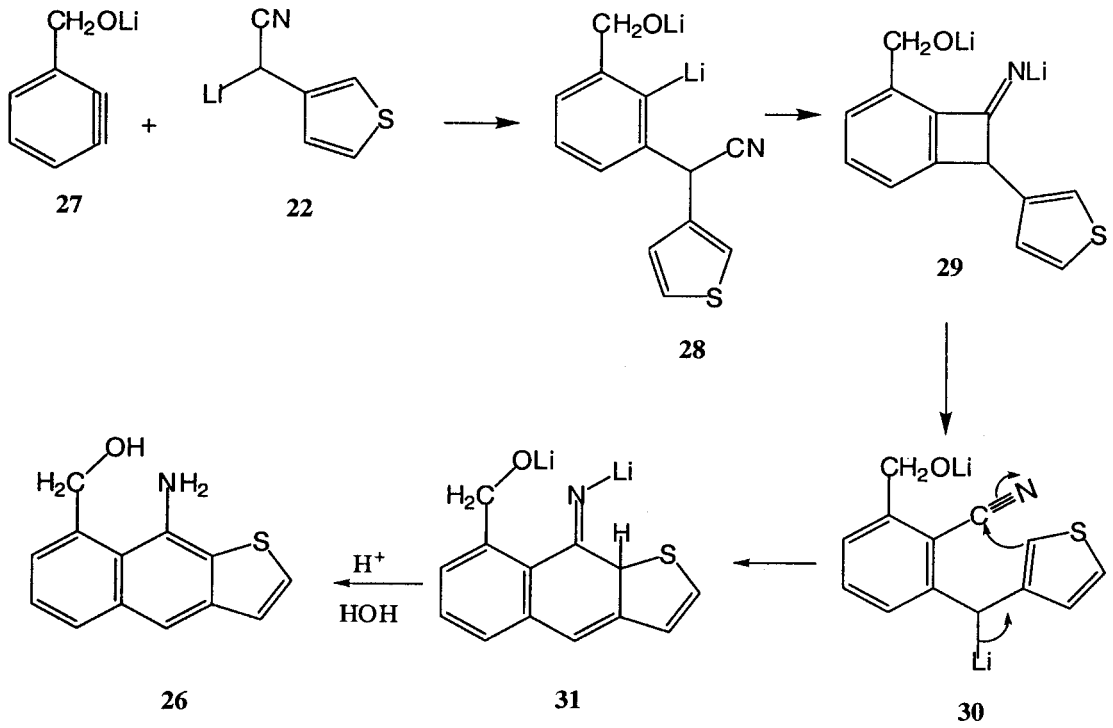


Figure 1 ORTEP of compound (**26**)

A possible mechanism to account for the formation of **26** is outlined in Scheme 3. As shown, lithium 2,3-dehydrobenzyl oxide (**27**) and α-lithio-3-thienylacetonitrile (**22**) react to form adduct (**28**).

Scheme 3



This adduct is then converted to intermediate (**30**) *via* the lithiated benzocyclobutanimine (**29**). The conversion to starting materials (**27**) and (**21**) to intermediate (**29**) is the well-documented tandem-addition rearrangement pathway, essentially a non-concerted [2+2] cycloaddition, which was first proposed by Meyers *et al.*[10] Nucleophilic addion by C-2 of the thiophene ring to the adjacent cyano group leads to the tricyclic imine (**31**), which is converted to product (**26**) during proton quench. The nucleophilic addition by C-2 of the thiophene ring, which is unprecedented, is probably enhanced by the α-lithiated methylene carbon in a manner similar to the nucleophilic activation of an α-carbon by a nitrogen lone pair electrons in the Stork enamine reaction.[11]

The confirmation of the structure of **26** by X-Ray crystallographic analysis and the similarity of preparation of the linear tricyclic thieno derivative (**26**) and the angular thieno derivatives (**23**) and (**24**) call into question our previous assignment of the latter two heterocycles.[8] Although single crystals could not be grown for X-Ray analysis of **23** and **24**, careful reevaluation of their ^{1}H NMR spectra confirmed the original structural assignments. For example, the chemical shift of the 5-methoxyl in **23** occurs at δ 4.18 ppm, which is considerably downfield from that (δ 3.8 ppm) generally observed for an aromatic methoxyl group. This downfield shift is consistent with the 5-methoxy group being situated near a sulfur atom. For example, strong non-bonding attractive O.....S interactions have been observed in ketene-S,N-acetals.[12] Furthermore, the chemical shifts of the aromatic 6-hydrogen adjacent to the nitrogen atom of the amide group in **23** and **24** (δ 8.21 ppm and 8.03 ppm, respectively) are very close to that (δ 8.11 ppm) of the similarly located aromatic 10-hydogen in **8**.

The difference in mechanisms of the reaction of 3-thiophene anion (**22**) with benzyne 3-carboxylates and 3-benzyloxide probably reflects the relative ability of the respective charged substituents, i.e. CO_2^- and CH_2O^-, to assist in the [4+2] or [2+2] cycloaddition pathway. Thus, the carboxylate group (which ends up as part of the cyclic amide) provides an electrophilic carbonyl site which is suitably situated to cyclize with and stabilize the emerging C=NLi group in the [4+2] pathway. The CH_2O^- group obviously affords no such interaction, and thus the usual [2+2] pathway is observed.

In conclusion, we have demonstrated another example of the use of aryne chemistry in the synthesis of multicyclic heterocycles. In addition, a general method for preparing fused thiophene rings using α-lithio-3-thienylacetonitrile as a 1,4-dipolar synthon has been developed.

EXPERIMENTAL

General Data: Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IRTM 550 FTIR spectrophotometer, and the ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. Elemental analyses were obtained from E + R Microanalytical Laboratories, Inc., Corona, NY. High resolution MS were performed by the Washington University

Mass Spectrometry Resource, an NIH Research Resource (Grant Np. (41RR0954). Diisopropylamine was refluxed and distilled from calcium hydride. THF was distilled from Na/benzophenone immediately before use. n-BuLi was purchased from Aldrich Chemical Company as a solution in hexanes. The haloarenes, α-cyano-*o*-tolunitrile. and 3-thienylacetonitrile were also purchased from Aldrich Chemical Company. The glassware was heated overnight in an oven at 125 °C prior to use. All the benzyne reactions were done under an atmosphere of dry O_2-free N_2 via balloon.

General procedure for aryne reactions. In a flame-dried flask flushed with nitrogen, fresh LDA (1.6 g,15 mmol) was prepared by adding n-BuLi (15 mmol, 6 mL of 2.5 M solution in hexanes) to a solution of diisopropylamine (1.5 g, 15 mmol) in THF (30 mL) at -70 °C. After stirring for 10 min, the appropriate aryne precursor (5 mmol) in THF (15 mL) was added dropwise over 20 min, and the stirring was continued for 10 min at -70 °C. The appropriate nitrile (5 mmol) was then added during which time the solution developed a deep red color. After addition, the solution was stirred for an additional 30 min, and then allowed to warm to rt, stirred overnight, and quenched with sat. aq. NH_4Cl (30 mL). The solvent, THF, was removed under reduced pressure, and the residue was neutralized with 6% HCl and extracted with methylene chloride (3 X 20 mL). The combined extracts were washed with 6% HCl (1 X 20 mL), brine (2 X 20 mL), dried (Na_2SO_4), and then concentrated (rotary evaporator) to provide the crude solid product. The mixture was subjected to flash column chromatography (silica gel) using a mixture of hexane/acetone (6:4) as the eluent to give a solid product, which was recrystallized from EtOAc. The mp, elemental analyses and NMR spectral data of isolated compounds (**5**, **8**, **11**, **14**, **26**) are given below.

5-Amino-4-hydroxybenzo[*g*]isoquinoline-10-carbonitrile (5): yellow solid, mp 225-226 °C; IR(Nujol) 3471, 3372, 3351 cm^{-1}; ^1H NMR(DMSO-d_6) δ 4.43 (s, 2 H), 7.21-7.35 (m, 4 H), 8.92 (s, 1 H), 8.96 (s, 1 H), 11.70 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 127.0, 129.1, 129.3, 134.0, 136.7, 139.7, 142.5, 145.8, 157.6, 168.8, 169.5. Anal. Calcd for $C_{14}H_9N_3O$; C, 71.48; H. 3.86; N, 17.86. Found: C, 71.55; H, 3.90; N, 17.88.

4-Aza-2-oxodibenzo[*cd,g*]indole-6-carbonitrile (8): brown solid, mp 321 °C; IR (Nujol) 1770 and 1745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.61 (t, J = 7.4 Hz, 1 H), 7.82 (t, J = 7.4 Hz, 1 H), 8.11 (d, J = 8.0 Hz, 1 H), 8.52 (d, J = 8.0 Hz, 1 H), 8.60 (s, 1 H) 9.51 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 113.6, 118.2, 119.3, 124.4, 125.1, 125.9, 129.2, 130.0, 131.0, 134.5, 139.1, 141.9, 148.5, 153.2 172.3. Anal. Calcd for $C_{15}H_7N_3O$; C, 73.46; H, 2.88; N, 17.13. Found: C, 73.50; H, 2.95; N, 17.20.

5-Methyl-2-oxo-1,2-dihydrodibenzo[*cd,g*]indole-2-carbonitrile (11): yellow solid, mp 316-318 °C; IR (Nujol) 1770 and 1745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.09 (s, 3 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 6.8 Hz, 1 H), 7.84 (t, *J* = 8.0 Hz, 1 H), 8.03 (d, *J* = 6.8 Hz, 1 H), 8.29 (d, *J* = 8.4 Hz, 1 H), 8.36 (d, *J* = 8.4 Hz, 1 H). Anal. Calcd for $C_{17}H_{10}N_2O$; C, 79.06; H, 3.90; N, 10.85. Found: C, 79.23; H, 3.92; N, 10.82.

5-Methoxy-2-oxo-1,2-dihydrodibenzo[*cd,g*]indole-2-carbonitrile (14): Yellow solid, mp 233-234 °C; IR (Nujol) 1773 and 1744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.18 (s, 3 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H), 8.26 (d, *J* = 8.8 Hz, 1 H), 8.31 (d, *J* = 8.8 Hz, 1 H), 11.91 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 5.70, 109.4, 118.4, 119.2, 120.6, 124.2, 126.0, 126.8, 126.0, 127.9, 130.3, 136.7, 139.0, 140.5, 150.0, 159.4, 168.7. Anal. Calcd for $C_{17}H_{10}N_2O_2$; C, 74.45; H, 3.67; N. 10.21. Found: C, 74.35; H, 3.68; N, 10.10.

9-Aminonaphtho[2,3-*b*]thiophen-8-ylmethanol (26): green solid, mp 129-130 °C; ^1H NMR (acetone-d_6) δ 5.16 (d, *J* = 5.2 Hz, 2 H), 5.30 (t, *J* = 5.2 Hz, 1 H), 6.15 (s, 2 H), 7.30 (m, 2 H), 7.45 (d, *J* = 5.6 Hz, 1 H), 7.67 (d, *J* = 5.6 Hz, 1 H), 7.82 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ 71.1, 117.4, 124.3, 128.4, 129.1, 130.0, 132.3, 132.6, 135.4, 140.1. Anal. Calcd for $C_{13}H_{11}NOS$; C, 68.10; H, 4.84; N.6.11; S, 13.98. Found: C, 68.15; H, 4.90; N, 6.18; S, 14.03.

X-Ray Single Crystal Analysis of 26. All data shown in Table 1 were collected on a Nicolet

Table 1 X-Ray data collection and processing parameters for 26.

formula	$C_{13}H_{11}NOS$	T (K)	228
crystal dmns, cm^{-3}	0.40 X 0.30 X 0.10	decay, %	2.86
Space group	$P2_1/n$	Data collected	1358
a (Å)	14.846(1)	Unique reflections	1055
b (Å	4.558(1)	R_{int}	0.057
c (Å)	16.220(2)	Parameters	155
β	105.134(5)	R, R_W	0.057, 0.081
V (Å)	1059.5(3)	(Δ/σ)	>0.01
Z-value	4	ρ_{max}; $\rho_{max}eÅ^{-3}$	0.25; - 0.70
D calc ($g\text{-}cm^3$)	1.437	GOF	1.93

R3m/V diffractometer using the θ-2θ scan technique, Mo-Kα radiation (λ = 0.71073 Å), scan speed 3.0-15 deg min^{-1}, scan range 3.5-35.00° and a graphite monochromator. Data were corrected for Lorentz, absorption, and polarization effects. The structures were solved by direct methods using SHELXS-86;[13] the model was refined using full-matrix least-squares methods.

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