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A General Synthesis of Diaryl Cyclic Diamidines

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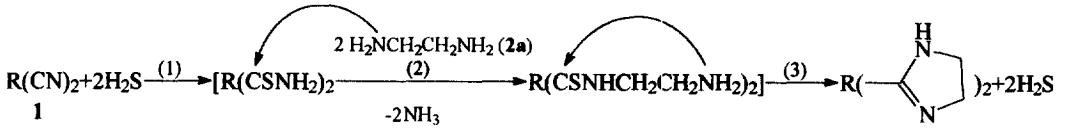
Abstract: A convenient and general method has been developed for directly converting bis-nitriles to cyclic diamidines using reagents derived from diaminoalkanes saturated with hydrogen sulfide. A 1:1 mixture of a diaminoalkane and ethyl alcohol (or without) was effective in most cases (72-88%). The synthetic utility of this methodology in the preparation of 1,3,6,8-tetrakis(cyclic amidino)pyrenes from 1,3,6,8-tetracyanopyrene is described.

In recent years a rapidly growing interest has been focused on diaryl diamidines due to their biological activities. Convenient methods currently available for diamidine synthesis involve the Pinner synthesis or direct salt-fusion reactions.[1] A one-stage preparation of a cyclic diamidine by the direct reaction of a diaminoalkane with the parent bis-nitrile is a desirable transformation.

This work presents a convenient and general procedure for the direct conversion of aromatic bis-nitriles into the corresponding diaryl cyclic diamidines *via* reaction with an excess of diaminoalkane saturated with hydrogen sulfide. The diaminoalkane-H_2S reagents may be generated by passing dry hydrogen sulfide through the reaction medium as needed, or prepared as stock solutions or suspensions which can be stored for longer time. The optimum formation of cyclic diamidines requires the use of high concentrations (1:1 mixture with ethanol or without any solvent) and heating under reflux. The yields obtained are generally high. Lower reagent concentrations resulted in significantly decreased yields and a small amount of mono-substitution product was obtained.[1a] A general preparative procedure has been worked out with certain bis-imidazolines **3** and the results are shown in Table 1.

Scheme 1. Mechanism.



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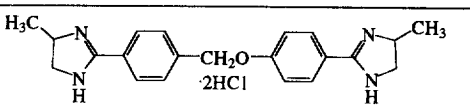
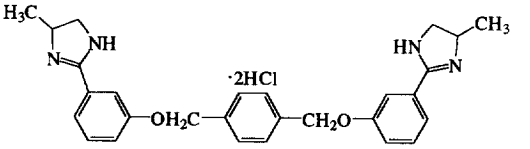
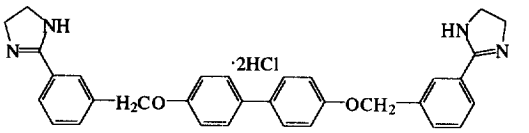
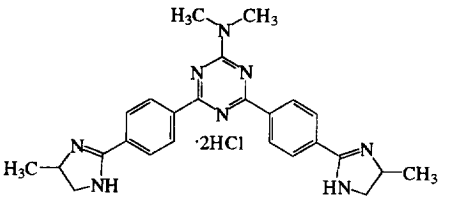
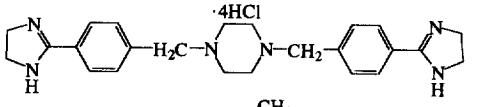
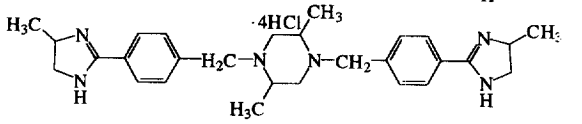
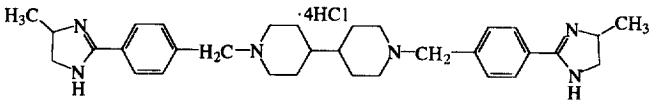
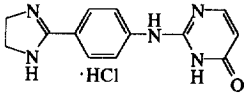
The mechanism probably involves three known reactions: (1) base catalysed addition of H_2S to a cyano group, (2) nucleophilic substitution of the thiocarbamoyl amino group by the diamine with evolution of ammonia, (3) intramolecular cyclisation and removal of hydrogen sulfide leading to the formation of the cyclic diamidine as illustrated in Scheme 1.[2,3]

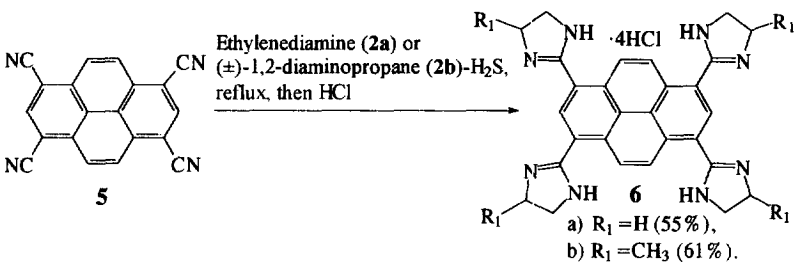
Table 1. Diaryl Cyclic Diamidines.

Compound number	Product	Yield	HR MS, Calculated/Found (m/z)
3a		83	EI, $M^{+\cdot}$, 348.19501/348.19544.
3b		88	EI, $M^{+\cdot}$, 454.23688/454.23518.
3c		77	FAB, $[M+H]^+$, 503.24469/503.24014.
3d		75	EI, $M^{+\cdot}$, 440.24368/440.24735.
3e		84	EI, $M^{+\cdot}$, 402.25320/402.25397.
3f		80	EI, $M^{+\cdot}$, 458.31580/458.31491.
3g		72	FAB, $[M+H]^+$, 513.37054/513.36957.
4		69	EI, $M^{+\cdot}$, 255.11201/255.11140.

All melting points are uncorrected and higher than 300 °C with the exception of **3a** (245-246 °C), **3b** (255-256 °C), **4** (297-299 °C). The free base of **3b** was dissolved in DMF and then acidified with HCl. TLC ($CHCl_3$: CH_3OH: 25% NH_4OH= 44:8:1, 11:4:1, or 7:5:2; v/v/v) showed one component. The spots on silica gel $60F_{254}$ glass plates were detected by UV absorption (254 nm) or visualised with iodine. The following bisnitriles were prepared by the known methods: **1a**, **1b**, **1c** (m.p. 203 °C) by the standard Williamson ether synthesis[4c-g]; **1d**[4b]; **1e** (m.p. 207 °C), **1f** (m.p. 184 °C), **1g** (m.p. 209 °C) by a simple nucleophilic substitution of α-bromo-*p*-tolunitrile with the appropriate piperidine or piperazine compound.[1b,4h-i] The products (**3a**, **3b**, **3d**, **3f**. and **3g**) are mixtures of diastereoisomers.

In a typical experiment, bis-nitrile **1** (0.005 mol) in a 1:1 mixture of the diaminoalkane **2** and anhydrous ethanol (10 ml) saturated with dry hydrogen sulfide was boiled under reflux with stirring after which the substrate dissolved. After some time the mixture became semisolid owing to the separation of the free base. The reaction was practically complete after 18 hours. Most of these products were essentially pure and a little improvement in purity was effected by crystallization from methanol/ 2-propanol. The crude products were treated with aqueous HCl to obtain water soluble hydrochloride salts **3**.[5] Obviously, this method can be widely applied for the preparation of mono-amidines. N^2-(4-Cyanophenyl)isocytosine[4a] was reacted under the conditions used to afford N^2-[4-(2-imidazolinyl)phenyl]isocytosine (**4**) in 69 %.

Scheme 2. 1,3,6,8-Tetrakis(cyclic amidino)pyrenes.



The applicability of the above method for the preparation of tetraamidines was also tested. 1,3,6,8-Tetracyanopyrene[4j,k] (**5**, 0.005 mol) can be transformed to the corresponding 1,3,6,8-tetrakis(4,5-dihydro-1*H*-imidazol-2-yl)pyrene (**6a**) under similar conditions, however before heating, the reaction mixture was kept tightly stoppered for several days under ambient temperature without employing any solvent (in 20 ml of anhydrous $H_2NCH_2CH_2NH_2$ saturated with H_2S). The tetrahydrochlorides **6** [6] were crystallized from methanol/2-propanol and recrystallized from methanol (see Scheme 2 for yields).

In summary, I belive that this method of synthesizing cyclic amidines is generally applicable and more advantageous than the methods used so far, especially in the synthesis of di-and more substituted derivatives.

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3. 2,4-Bis(4-cyanophenyl)-1,3,5-triazine[18] is resistant to cyclisation in reacting with 1,4-diaminobutane under similar conditions and affords the N-substituted thioamide: 2,4-bis{4-[N-(4-aminobutyl)thiocarbamoyl]phenyl}-1,3,5-triazine (m.p. 151-2 °C; anal. ($C_{25}H_{31}N_7S_2$) C, H, N; ^{1}H-NMR (DMSO-d_6), δ, 1.40-2.10 (m, 8H), 2.70 (m., 4H), 3.80 (m, 4H), 5.00 (br.s, 6H), 8.02 (d, 4H), 8.70 (d, 4H), 9.55 (s, 1H); ^{13}C-NMR (DMSO-d_6), δ, 24.7, 30.3, 41.1, 46.3, 127 8, 128.2, 136.3, 145.1, 167.3, 169.9, 195.9; this product gave a positive reaction with 0.2 % ninhydrin ethanolic solution).

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5. ^{13}C-NMR (D_2O, $(CH_3)_3Si(CH_2)_3SO_3Na$) data are consistent with the structures assigned (**3a**: δ, 22.6, 53.8, 54.0, 56.0, 56.2, 71.7, 117.3, 118.4, 124.3, 130.6, 131.1, 133.0, 145.8, 165.4, 166.7, 167.2, **3b** (DMSO-d_6): δ, 20.5, 51.0, 53.0, 69.5, 114.7, 120.9, 121.2, 123.3, 128.0, 130.6, 136.2, 158.5, 163 2, **3c** (DMSO-d_6): δ, 44.4, 68.5, 115.3, 122.5, 127.3, 127.5, 128.1, 129.5, 132.7, 133.6, 138.6, 157.2, 164.7, **3d**: δ, 22.5, 38.1, 53.6, 56.0, 126.0, 130.0, 131.1, 143.3, 165.4, 166.0, 170.0, **3e**: δ, 47.4, 51.2, 62.3, 126.9, 131.7, 134.9, 136.9, 168.7, **3f**: δ, 16.6, 22.6, 54.2, 55.5, 56.4, 58.6, 59.5, 126.8, 131.7, 134.9, 137.3, 167.3, **3g**: δ, 22.5, 28.9, 39.5, 54.1, 55.4, 56.3, 62.4, 126.6, 131.5, 134.8, 137.8, 167.3).

6. 1,3,6,8-Tetrakis(4,5-dihydro-1*H*-imidazol-2-yl)pyrene (**6a**): m.p.> 300 °C; HR MS (FAB), $[M+H]^+$, calc. 475.23587, found 475.23463; ^{1}H-NMR (D_2O, DSS), δ, 4.63 (s, 16H), 8.96 (s, 2H), 9.07 (s, 4H); ^{13}C-NMR (D_2O, DSS), δ, 48.7, 123.2, 126.7, 130.6, 130.7, 134.6, 168.7. 1,3,6,8-Tetrakis(4,5-dihydro-4-methyl-1*H*-imidazol-2-yl)pyrene (**6b**): m.p.> 300 °C; HR MS (FAB), $[M+H]^+$, calc. 531.29846, found 531.30192; ^{1}H-NMR (D_2O, DSS), δ, 1.77 (d, 12H), 4.11 (dd, 4H), 4.62 (t, 4H), 4.94-5.03 (m, 4H), 8.84 (s, 2H), 8.93 (s, 4H); ^{13}C-NMR (D_2O, DSS), δ, 22.9, 55.0, 57.4, 122.9, 126.4, 130.2, 130.5, 134.3, 166.9. DSS: sodium 2,2-dimethyl-2-silapentane-5-sulfonate.