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AN IMPROVED APPROACH TO *meso*-SUBSTITUTED 1,9-DICYANODIPYRROLYLMETHANES

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Abstract: A series of *meso*-substituted 1,9-dicyanodipyrrolylmethanes and phenylene-bridges bis-dipyrrolylmethanes containing one / and two phenyl bridges have been prepared from condensation of 2-cyano-3,4-dialkylpyrrole 1 with various aromatic aldehydes.

The synthesis of tetrapyrrolic imine containing pigments named "porphocyanines" have recently received considerable attention due to their biomedical applications, specially as photosensitizers for use in photodynamic therapy (PDT).[1,2] These porphyrin-like molecules are prepared by *in situ* oxidation of the lithium aluminum hydride reduction product of 1,9-dicyano substituted dipyrrolylmethanes.[3,4] Two approaches have just been developed by our group to make the symmetrical 1,9-dicyano-5-unsubstituted dipyrrolylmethanes.[5] A general and rather simple procedure has been introduced[6] for synthesis of the 1,9-dicyanodipyrrolylmethanes from 1,9-dicarboxy- or 1,9-diunsubstituted dipyrrolylmethanes by decarboxylation (of the acids) and treatment with a large excess of chlorosulfurylisocyanate (CSI) at

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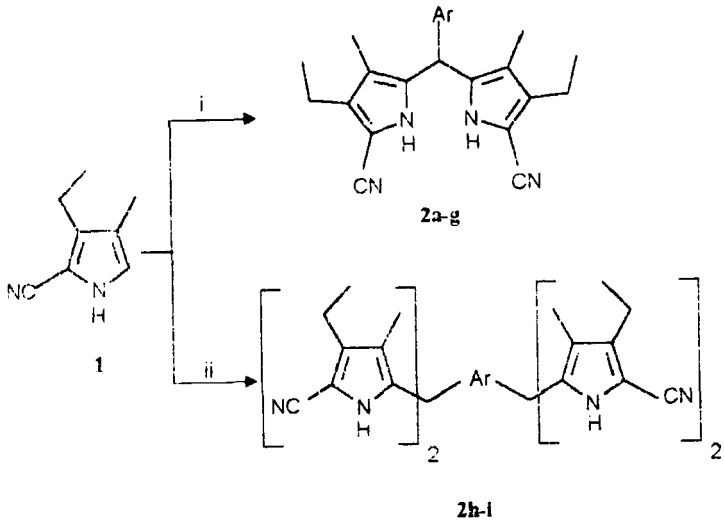
-78°C. While the above methods remain popular, our continued interest on this class of compound has resulted in the synthesis of novel 1,9-dicyanodipyrrolylmethanes by a simple method. Herein, we report an improved and facile one-step route to prepare a series of *meso*-substituted 1,9-dicyanodipyrrolylmethanes, and bis-dipyrrolylmethanes which are connected by one and two phenylene linkers. The synthetic route used to obtain these dipyrrolylmethanes **2a-i** is given in Scheme 1.

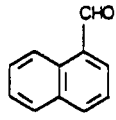
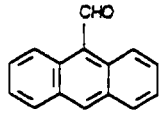
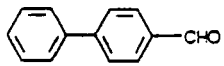
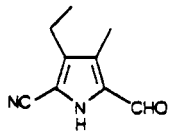
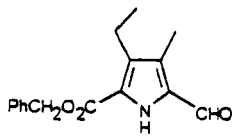
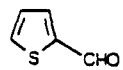
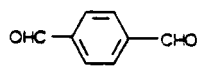
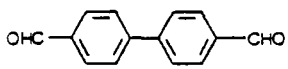


i: ArCHO ; ii: $Ar(CHO)_2$

Scheme **1**

The key starting material pyrrole **1** used to prepare all products was made according to a simple method outlined by Adamczyk et al.[7] Some aldehydes were made in our laboratory (Table 1, entries 3 , 5 , 6 , and 9) according to literature

Table 1: Condensation of pyrrole 1 with various aromatic aldehydes

Entry	Aldehyde	Reaction Time (h)		Product m.p. (°C)	Product Yield (%)[a]
1	PhCHO	2	2a	113-115	71
2		1.5	2b	184-186	41
3		11	2c	257-258	34
4		3.5	2d	184-185	55
5		4	2e	203-206	58
6		5	2f	201-202	70
7		4	2g	156-158	62
8		1.5	2h	301-303	74
9		1.5	2i	299-301	76

[a] all yields refer to pure isolated products.

procedures.[8-10] 5-Cyano-4-ethyl-2-formyl-3-methylpyrrole (Table 1, entry 5) was prepared by formylation of the parent pyrrole **1**. *meso*-Substituted 1,9-dicyanodipyrrolylmethanes **2a-g** and bis-dipyrrolylmethane analogues **2h-i** were synthesized according to the procedure of Chang and Abdalmuhdi[11] (see Experimental Section) in good yields (Table 1). An important feature of this method is seen with α-thienyl carboxaldehyde which is condensed with the α-free pyrrole **1** in good yield (Table 1, entry 7). Condensation of the α-free pyrrole **1** with the 5-cyano-2-pyrrolecarboxaldehyde (Table 1, entry 5) and 2-benzyloxycarbonyl-5-pyrrolecarboxaldehyde (Table 1, entry 6) gave symmetrical 2,2′,2″-tripyrrolylmethanes (**2e** and **2f**). Also, treatment of 1,4-diformylbenzene (Table 1, entry 8), and 4,4′-diformyl-1,1′-biphenyl (Table 1, entry 9) with four molar equivalents of pyrrole **1** gave, in high yields, the corresponding symmetrical bis-dipyrrolylmethanes, **2h** and **2i** respectively.

In conclusion, we have achieved a relatively high-yielding one-pot procedure for preparation of *meso*-substituted 1,9-dicyanodipyrrolylmethanes. This synthetic route is superior to that reported by Dolphin et al.[6] in which 1,9-dicarboxydipyrrolylmethanes were decarboxylated followed by cyanation using CSI at low temperature.

EXPERIMENTAL SECTION: Melting points were determined in open capillaries with a Gallenkamp electrothermal apparatus and were all corrected. Progress of reactions was followed by TLC using Silica gel polygram G / UV_{254}

plates. ^{1}H NMR spectra were recorded at 60, 90, and 250 MHz in $CDCl_3$ or Acetone-d_6 solutions using TMS as an internal standard. The chemical shifts reported are in ppm downfield from TMS. IR spectra were obtained using a Shimadzu IR 470 instrument. Low resolution mass spectra (LRMS) were run by Finnigan Mat. 8430 GC-MS instrument. Elemental analyses were performed by NIOC research institute of petroleum industry of Tehran.

General procedure for preparation of *meso*-substituted 1,9-dicyanodipyrrolylmethanes (2a-i): 2-Cyano-3-ethyl-4-methylpyrrole 1 (1.1 mmol), and monoaldehyde (0.55 mmol) or dialdehyde (0.28 mmol) were dissolved in absolute ethanol (6 ml); concentrated hydrochloric acid (0.093 ml) or *p*-toluenesulfonic (0.14 g) was added to the solution and heated to reflux under a stream of dry nitrogen for the time specified in Table 1. During the course of reaction the color of the solution turns red. After evaporation of ethanol, the residue was dissolved in dichloromethane and washed sequentially with saturated aqueous solution of sodium bicarbonate, and with water. Separation of the organic phase and removal of the solvent followed by crystallization from benzene, petroleum ether, or benzene/n-hexane gave pure compounds in 34-76% yields.

The products are easily characterized by their spectral and analytical data. The spectral and analytical data of the products are as follows :

2a: IR (KBr) 3294,2208 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.18 (6H, t, J=7.5 Hz), 1.83 (6H, s), 2.56 (4H, q, J=7.5 Hz), 5.5 (1H, s) 6.93-7.50 (5H, m), 8.35 (2H, br

s); LRMS calcd. For $C_{23}H_{24}N_4$ 356.47, found 357. (Calcd.: C,77.5; H,6.79 ; N, 15.7. Found: C, 77.8; H, 6.69; N, 15.6).

2b: IR (KBr) 3300, 3250, 2200 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.19 (6H, t, J=7.5 Hz), 1.83 (6H, s), 2.59 (4H, q, J= 7.5 Hz), 6.17 (1H, s), 6.86-8.03 (7H, m), 8.2 (2H, br s). LRMS calcd. for $C_{27}H_{26}N_4$ 406.53, found 407. (Calcd.: C, 79.8; H, 6.45; N, 13.8. Found: C, 79.6; H, 6.34; N, 13.6).

2c: IR (KBr) 3384, 3240, 2200 cm^{-1}; ^1H NMR (Acetone-d_6, 90 MHz) δ 1.12 (3H, t, J= 7.5 Hz), 1.3 (3H, t, J= 7.5 Hz), 1.73 (3H, s), 2.09 (3H, s), 2.50 (2H, q, J= 7.5 Hz), 2.74 (2H, q, J= 7.5 Hz), 4.97 (1H, s), 7.27-8.40 (9H, m),9.07 (1H, br s), 9.76 (1H, br s). LRMS calcd. for $C_{31}H_{28}N_4$ 456.60, found 457. (Calcd.: C, 81.5; H, 6.18; N, 12.3. Found: C, 81.7; H, 6.32; N, 12.4).

2d: IR (KBr) 3292, 2200 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.18 (6H, t, J= 7.6 Hz), 1.82 (6H, s), 2.57 (4H, q, J= 7.6 Hz), 5.47 (1H, s), 6.93-7.70 (9H, m), 8.23 (2H, br s). LRMS calcd. for $C_{29}H_{28}N_4$ 432.57, found 433. (Calcd.: C, 80.5; H, 6.52; N, 12.95. Found: C, 80.8; H, 6.67; N, 12.7).

2e: IR (KBr) 3273, 2200 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.15 (9H, t, J= 7.6 Hz), 1.82 (9H, s), 2.52 (6H, q, J= 7.6 Hz), 5.50 (1H, s), 8.93 (3H, br s). LRMS calcd. for $C_{25}H_{28}N_6$ 412.54, found 413. (Calcd.: C, 72.8; H, 6.84; N, 20.4. Found: C, 72.6; H, 6.66; N, 20.1).

2f: IR (KBr) 3328, 2208, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.07 (3H, t, J= 7.5 Hz), 1.15 (6H, t, J= 7.5 Hz),1.8 (6H, s), 1.85 (3H, s), 2.53 (4H, q, J= 7.5 Hz), 2.72 (2H, q, J= 7.5 Hz), 5.2 (2H, s), 5.62 (1H, s), 7.30 (5H, s), 9.27 (1H,br

s),10.17 (2H, br s). LRMS calcd. for $C_{32}H_{35}N_5O_2$ 521.67, found 522. (Calcd.: C, 73.7; H, 6.76; N, 13.4. Found: C, 73.9; H, 6.84; N, 13.5).

2g: IR (KBr) 3376, 3312, 2200 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.17 (6H, t, J= 7.8 Hz), 1.85 (6H, s), 2.55 (4H, q, J= 7.8 Hz), 5.63 (1H, s), 6.60-7.30 (3H, m), 8.58 (2H, br s). LRMS calcd. for $C_{21}H_{22}N_4S$ 362.50, found 363. (Calcd.: C, 69.6; H, 6.12; N,15.5; S, 8.8. Found: C, 69.3; H, 5.90; N, 15.3; S, 8.7).

2h: IR (KBr) 3294, 3264, 2208 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (12H, t, J= 7.8 Hz), 1.88 (12H, s), 2.55 (8H, q, J= 7.8 Hz), 5.48 (2H, s), 6.93 (4H, s), 10.73 (4H, s). LRMS calcd. for $C_{40}H_{42}N_8$ 634.83, found 635. (Calcd.: C, 75.7; H, 6.67; N,17.6. Found: C, 75.9; H, 6.85; N, 17.3).

2i: IR (KBr) 3300, 2200 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (12H, t, J= 7.6 Hz), 1.97 (12H, s), 2.56 (8H, q, J= 7.6 Hz), 5.53 (2H, s), 6.97 (4H, d, J= 9.0 Hz), 7.44 (4H, d, J= 9.0 Hz), 10.72 (4H, s). LRMS calcd. for $C_{46}H_{46}N_8$ 710.93, found 711. (Calcd.: C, 77.7; H, 6.52; N, 15.8. Found: C, 77.9; H, 6.81; N, 15.5).

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