Synthesis of 4,4′-(1,4-Phenylene)di-pyridine and -pyrimidine Derivatives†

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The preparation and structural characterization of 4,4′-(1,4-phenylene)di-pyridine and -pyrimidine derivatives are described.

The biological importance of a variety of pyridine and pyrimidine derivatives has resulted in a lot of interest in their syntheses.[1–5] As a part of our program directed towards the synthesis of heterocyclic derivatives with possible biological activity,[6–11] the present work is aimed at synthesizing 4,4′-(1,4-phenylene)di-pyridine and -pyrimidine derivatives in high yields by a one-pot method from basic laboratory reagents.

Thus, reacting a mixture of benzene-1,4-dicarbaldehyde (**1**), malononitrile (**2**) and 2-acetylthiophene (**3a**) in ethanol containing a catalytic amount of ammonium acetate (1:2.2) under reflux for 3 h afforded 4,4′-(1,4-phenylene)di[2-amino-3-cyano-6-(2-thienyl)pyridine] (**7a**) (see Scheme 1). The structure of **7a** was established by analytical and spectral data (see Experimental). The formation of **7a** was rationalized in terms of the initial formation of **4** or **5a** followed by the addition of **3** or **2** to the ylidenic bond forming an acyclic intermediate **6**. Amination of **6** in the presence of ammonium acetate[12] followed by cyclization of the enamine and partial dehydrogenation under the reaction conditions afforded the final product (see Scheme 1).

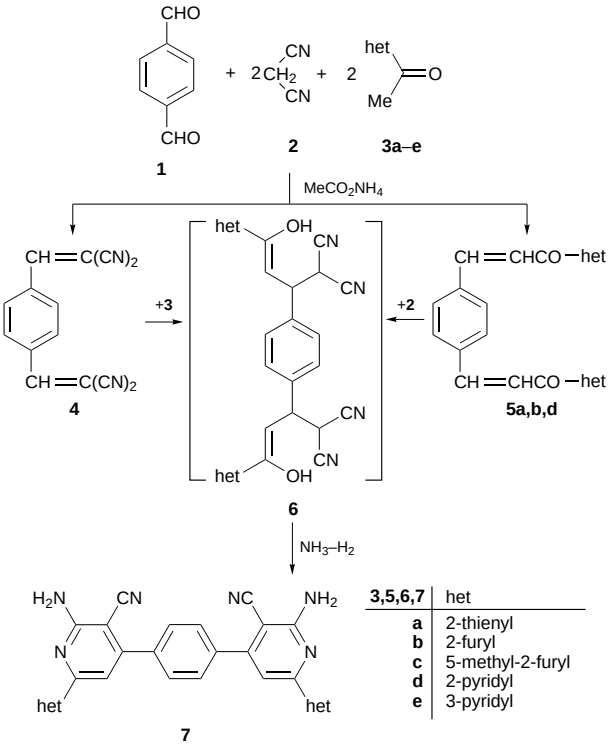
Structural proof was obtained through a two-component condensation of 2,2′-(1,4-phenylene)di(1,1-dicyanoethylene) (**4**)[13] and/or **5a**[14,15] with **3a** or **2** (1:2) under the previous conditions. Compound **7a** was also afforded (see Experimental). Compounds **7b–e** were prepared in similar way (see Scheme 1).

We extended the previous reaction to a wide range of active methylene carbonyl reagents. Thus, treatment of **1** with **2** and cycloalkanones **8a–c** under the reaction conditions mentioned above afforded **9a–c** (see Scheme 2).

Meanwhile, the ternary condensation of **1**, **2** and cyclohexanone (**8b**) in refluxing alcoholic sodium ethoxide gave 4,4′-(1,4-phenylene)di[3-cyano-2-ethoxy-5,6,7,8-tetrahydroquinoline] (**10**) (see Scheme 2).

Alternatively, compounds **9a–c** and **10** could also be prepared by treating **4** with cycloalkanones **8a–c** under the same reaction conditions (see Scheme 2). The structures of **9a–c** and **10** were confirmed by analytical and spectral data (see Experimental).

To extend the scope of this reaction to the synthesis of pyrimidine derivatives, we studied another model system that contained thiourea and/or urea. Thus, treatment of **1** with **11a**,**b** and thiourea (**12a**) or urea (**12b**) (1:2.2) in ethanol containing catalytic amounts of hydrochloric acid yielded the corresponding 4,4′-(1,4-phenylene)di(1,2,3,4-tetrahydropyrimidines) **13a–c**. The structure of **13** was deduced on the basis of analytical and spectral data (see Scheme 3 and Experimental).



Scheme 1

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Shimadzu 480 spectrophotometer. ^{1}H NMR Spectra were recorded in [$^2H_6$]Me_2SO on Varian EM-390 and Varian XL 200 (90 and 200 MHz) spectrometers with Me_4Si as internal standard; chemical shifts δ expressed in ppm. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. Compounds **4** and **5** were prepared by literature procedures.[13–16]

General Procedure for the Synthesis of Compounds **7** *and* **9**. *Method A.*—A mixture of **1** (0.01 mol), **2** (0.02 mol), ammonium acetate (0.08 mol) and the appropriate ketone (0.02 mol) of either **3a–e** or **8a–e** in absolute ethanol (50 ml) was heated under reflux for 3 h. The solid product formed was collected by filtration and recrystallized from the appropriate solvent.

Method B.—A mixture of **4** (0.01 mol), ammonium acetate (0.08 mol) and the appropriate ketone (0.02 mol) of either **3a**,**c**,**e** or **8a–c** in absolute ethanol (50 ml) was heated under reflux for 3 h. The solid product formed was collected and purified as in method A.

Alternative Synthesis of **7a**,**b**,**d**.—A solution of **5a**,**b**,**d** (0.01 mol), ammonium acetate (0.08 mol) and **2** (0.02 mol) in absolute ethanol (50 ml) was heated under reflux for 3 h. The solid product was collected by filtration and recrystallized from the appropriate solvent.

4,4′-(1,4-*Phenylene*)*di*[2-*amino*-3-*cyano*-6-(2-*thienyl*)*pyridine*] (**7a**).—Obtained in 76% yield, mp >300 °C (from DMF); (Found: C, 65.4; H, 3.3; N, 17.5; S, 13.3. $C_{26}H_{16}N_6S_2$ requires C, 65.54; H, 3.38; N, 17.63; S, 13.43%); ν_{max}/cm^{-1} 3400, 3300 (NH_2) and 2210 (CN). δ_H 6.2 (s, 4 H, 2 NH_2), 7.2 (m, 2 H, 2 thiophene 4-H), 7.3 (d, *J* 6.0 Hz, 2 H, 2 thiophene 3-H), 7.4 (d, *J* 6.0 Hz, 2 H, 2, thiophene 5-H), 7.6–7.8 (m, 4 H, Ar-H), 8.1 (s, 2 H, 2 pyridyl 5-H).

4,4′-(1,4-*Phenylene*)*di*[2-*amino*-3-*cyano*-6-(2-*furyl*)*pyridine*] (**7b**).—Obtained in 71% yield; mp >300 °C (from DMF); (Found: C, 70.3; H, 3.5; N, 19.0. $C_{26}H_{16}N_6O_2$ requires C, 70.26; H, 3.62; N, 18.91%); ν_{max}/cm^{-1} 3400, 3200 (NH_2) and 2200 (CN). δ_H 6.3 (s, 4 H, 2 NH_2), 6.5–7.5 (m, 6 H, 2 furan protons), 7.6–7.8 (m, 4 H, Ar-H) and 8.0 (s, 2 H, 2 pyridyl 5-H).

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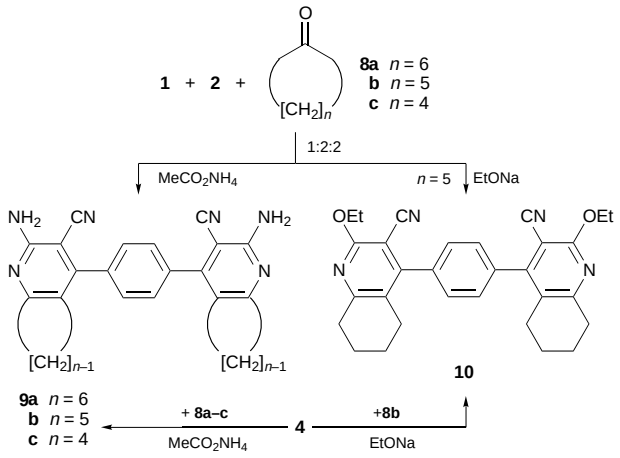
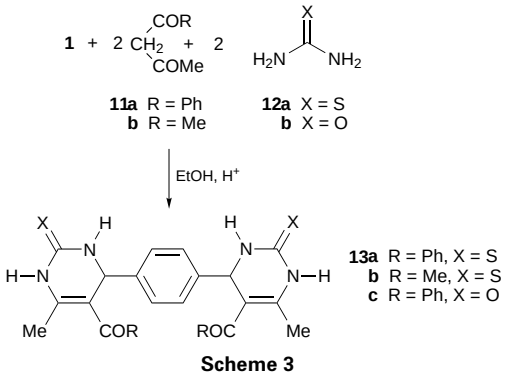
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2



Scheme 3

4,4′-(1,4-*Phenylene*)*di*[2-*amino*-3-*cyano*-6-(5-*methyl*-2-*furyl*)*pyridine*] (**7c**).—Obtained in 75% yield; mp >300 °C (from DMF); (Found: C, 71.3; H, 4.2; N, 17.8. $C_{28}H_{20}N_6O_2$ requires C, 71.17; H, 4.26; N, 17.78%); ν_{max}/cm^{-1} 3400, 3200 (NH_2) and 2200 (CN). δ_H 2.1 (s, 6 H, 2 CH_3), 6.2 (s, 4 H, 2 NH_2), 6.5 (d, *J* 3.5 Hz, 2 H, 2 furan 4-H), 7.5 (d, *J* 3.5 Hz, 2 H, 2 furan 3-H), 7.6–7.8 (m, 4 H, Ar-H), 8.0 (s, 2 H, 2 pyridyl 5-H).

4,4′-(1,4-*Phenylene*)*di*[2-*amino*-3-*cyano*-6-(2-*pyridyl*)*pyridine*] (**7d**).—Obtained in 68% yield; mp >300 °C (from DMF); (Found: C, 72.0; H, 3.7; N, 24.2. $C_{28}H_{18}N_8$ requires C, 72.09; H, 3.88; N, 24.02%); ν_{max}/cm^{-1} 3400, 3200 (NH_2) and 2200 (CN). δ_H 6.3 (s, 4 H, 2 NH_2), 7.6–7.8 (m, 4 H, Ar-H) and 8.1–8.4 (m, 10 H, pyridyl H).

4,4′-(1,4-*Phenylene*)*di*[2-*amino*-3-*cyano*-6-(3-*pyridyl*)*pyridine*] (**7e**).—Obtained in 74% yield; mp >300 °C (from DMF); (Found: C, 72.1; H, 3.9; N, 23.9. $C_{18}H_{18}N_8$ requires C, 72.09; H, 3.88; N, 24.02%); ν_{max}/cm^{-1} 3400, 3200 (NH_2) and 2200 (CN).

4,4′-(1,4-*Phenylene*)*di*(2-*amino*-3-*cyano*-6,7,8,9-*tetrahydro*-5H-*cyclohepta*[b]*pyridine*) (**9a**).—Obtained in 81% yield; mp >300 °C (from DMF–EtOH); (Found: C, 74.8; H, 6.3; N, 18.8. $C_{28}H_{28}N_6$ requires C, 74.97; H, 6.29; N, 18.73%); ν_{max}/cm^{-1} 3400, 3300 (NH_2) and 2200 (CH). δ_H 1.1–3.0 (m, 20 H, 2 $[CH_2]_5$), 6.5 (s, br, 4 H, 2 NH_2), 7.3–7.6 (m, 4 H, Ar-H); *m*/*z* 449 (M^+ +1, 100%).

4,4′-(1,4-*Phenylene*)*di*(2-*amino*-3-*cyano*-5,6,7,8-*tetrahydroquinoline*) (**9b**).—Obtained in 86% yield; mp >300 °C (from DMF–EtOH); (Found: C, 74.1; H, 54.7; N, 20.1. $C_{26}H_{24}N_6$ requires C, 74.26; H, 5.75; N, 19.98%); ν_{max}/cm^{-1} 3400, 3300 (NH_2) and 2200 (CN). δ_H 1.3–3.2 (m, 16 H, 2 $[CH_2]_4$), 6.4 (s, 4 H, 2 NH_2) and 7.2–7.5 (m, 4 H, Ar-H).

4,4′-(1,4-*Phenylene*)*di*(2-*amino*-3-*cyano*-6,7-*dihydro*-5H-*cyclopenta*[b]*pyridine*) (**9c**).—Obtained in 73% yield; mp >300 °C (from DMF–EtOH); (Found: C, 73.5; H, 5.2; N, 21.2. $C_{24}H_{20}N_6$ requires C, 73.45; H, 5.13; N, 21.41%); ν_{max}/cm^{-1} 3400, 3300 (NH_2) and 2200 (CN). δ_H 1.5–2.2 (m, 12 H, 2 $[CH_2]_3$), 6.4 (s, 4 H, 2 NH_2) and 7.3–7.5 (m, 4 H, Ar-H).

Synthesis of 4,4′-(1,4-*Phenylene*)*di*(3-*cyano*-2-*ethoxy*-5,6,7,8-*tetrahydroquinoline*) (**10**). *Method A*.—A solution of sodium (0.02 mol) in absolute ethanol (30 ml), was added to a stirred solution of **1** (0.01 mol), **2** (0.02 mol) and **8b** (0.02 mol) in absolute ethanol (20 ml). The resulting solution was refluxed for 2 h and then, after cooling to room temperature, the precipitate was separated and collected by filtration, washed with ethanol and recrystallized from DMF–EtOH.

Method B.—Sodium (0.02 mol) was dissolved in absolute ethanol (30 ml), and **8b** (0.02 mol) was added. The mixture was stirred for 15 min and then added to a stirred suspension of **4** (0.01 mol) in absolute ethanol (20 ml). The resulting mixture was then refluxed for 2 h. The resulting product was worked-up as described for method A. Compound **10** was obtained in 80% yield; mp >300 °C; (Found: C, 75.1; H, 6.5; N, 11.8. $C_{30}H_{30}N_4O_2$ requires C, 75.29; H, 6.32; N, 11.7%); ν_{max}/cm^{-1} 2220 (CN). δ_H 1.05 (t, 6 H, 2 OEt), 1.2–2.8 (m, 16 H, 2 $[CH_2]_4$), 4.1 (q, 4 H, 2 OEt) and 7.3 (s, 4 H, Ar-H).

General Procedure for the Synthesis of Pyrimidine Derivatives **13a–c**.—A mixture of **1** (0.01 mol), **11a**,**b** (0.02 mol) and **12a**,**b** (0.02 mol) in absolute ethanol (50 ml) containing 10 drops of concentrated hydrochloric acid was refluxed for 5 h. The solid product formed was collected by filtration and recrystallized from the appropriate solvent.

4,4′(1,4-*Phenylene*)*di*(5-*benzoyl*-6-*methyl*-2-*thioxo*-1,2,3,4-*tetrahydropyrimidine*) (**13a**).—Obtained in 88% yield; mp 231–233 °C (from DMF–EtOH); (Found: C, 66.8; H, 4.9; N, 10.3; S, 11.9. $C_{30}H_{26}N_4O_2S_2$ requires C, 66.90; H, 4.86; N, 10.40; S, 11.88%); ν_{max}/cm^{-1} 3400 (NH) and 1660 (CO). δ_H 1.72 (s, 6 H, 2 CH_3), 5.25 (d, *J* 4.6 Hz, 2 H, 2 H-4), 7.16 (s, 4 H, Ar-H), 7.48 (m, 10 H, Ar-H), 9.68 (s, 2 H, 2 NH), 10.35 (d, *J* 4.6 Hz, 2 H, 2 NH). *m*/*z* 538 (M^+, 8%).

4,4′-(1,4-*Phenylene*)*di*(5-*acetyl*-6-*methyl*-2-*thioxo*-1,3,4,5-*tetrahydropyrimidine*) (**13b**).—Obtained in 78% yield; mp >300 °C (from DMF–EtOH); (Found: C, 58.1; H, 5.4; N, 13.4; S, 15.5. $C_{20}H_{22}N_4O_2S_2$ requires C, 57.96; H, 5.35; N, 13.52; S, 15.44%); ν_{max}/cm^{-1} 3400 (NH) and 1660 (CO).

4,4′-(1,4-*Phenylene*)*di*(5-*benzoyl*-6-*methyl*-2-*oxo*-1,2,3,4-*tetrahydropyrimidine*) (**13c**).—Obtained in 71% yield; mp >300 °C (from DMF–etOH); (Found: C, 71.2; H, 5.3; N, 11.2. $C_{30}H_{26}N_4O_4$ requires C, 71.13; H, 5.17; N, 11.06%); ν_{max}/cm^{-1} 3400 (NH), 1660 and 1640 (CO). δ_H 1.7 (s, 6 H, 2 CH_3), 5.3 (d, *J* 3 Hz, 2 H, 2 H-4), 7.3 (s, 4 H, Ar-H), 7.6 (m, 10 H, Ar-H), 9.7 (s, 2 H, 2 NH) and 10.3 (d, *J* 3 Hz, 2 H, 2 NH).

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