Bis-4-halophenyl-pyrimidines and -1,2,4,5-tetrazines

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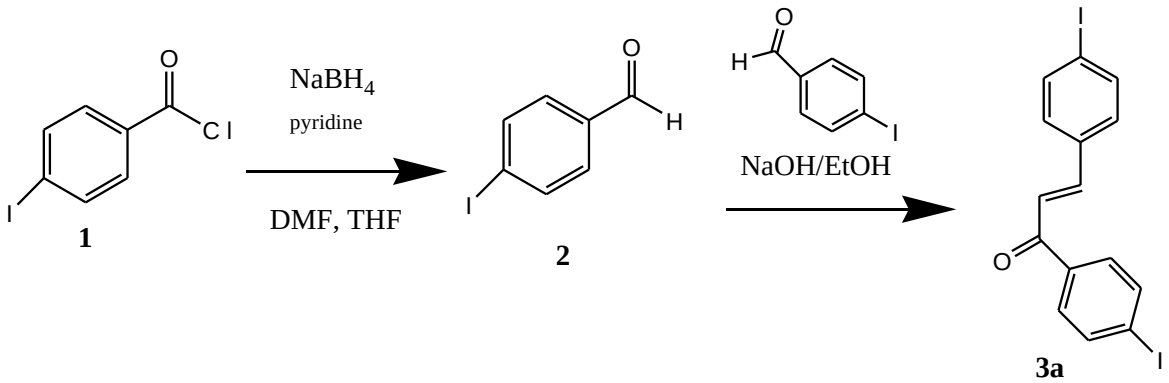
Introduction

For an ongoing project, we required six-membered heterocycles di-substituted with *p*-halophenyl groups. The preparation of such pyrimidines and tetrazines is described in this note.

Results and Discussion

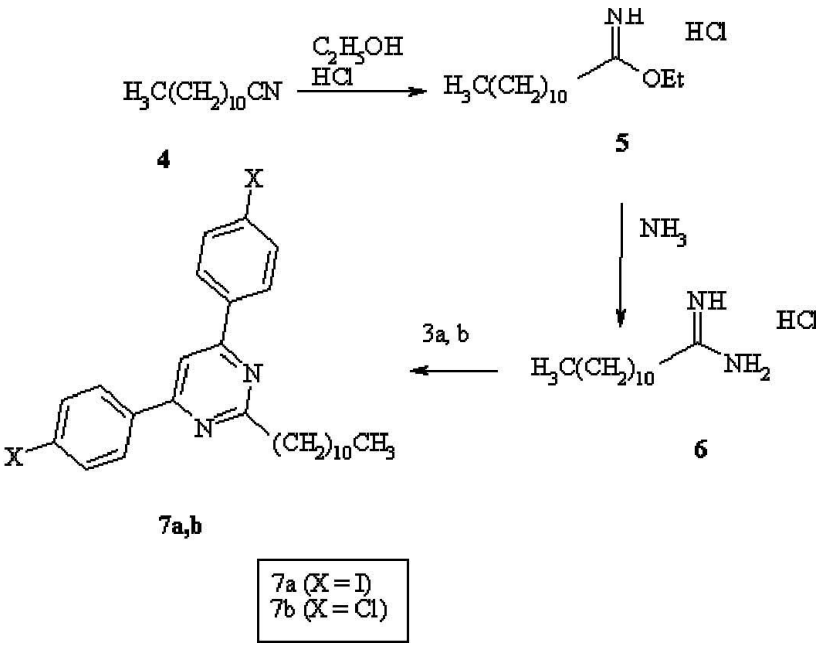
Synthesis of 4,6-bis-(4-halophenyl)-2-undecylpyrimidines 7a,b. Shyrina *et al.*[1] described the preparation of pyrimidines in yields of 20–70 % by the oxidative coupling of chalcones with acetamidine or benzamidine in DMSO or its mixtures with toluene or xylene in the presence of molecular sieves at elevated temperatures. Based on these results, we commenced our preparation of pyrimidines **7a,b** from chalcones **3a,b**. The dichloro- chalcone **3b** is commercially available from Lancaster Synthesis, Inc. The diiodochalcone **3a** was prepared by first reducing the acid chloride **1** with $NaBH_4$ in pyridine, using the general method developed by Babler,[2] to give 4-iodobenzaldehyde **2** in 53% yield (Scheme 1).



Scheme 1

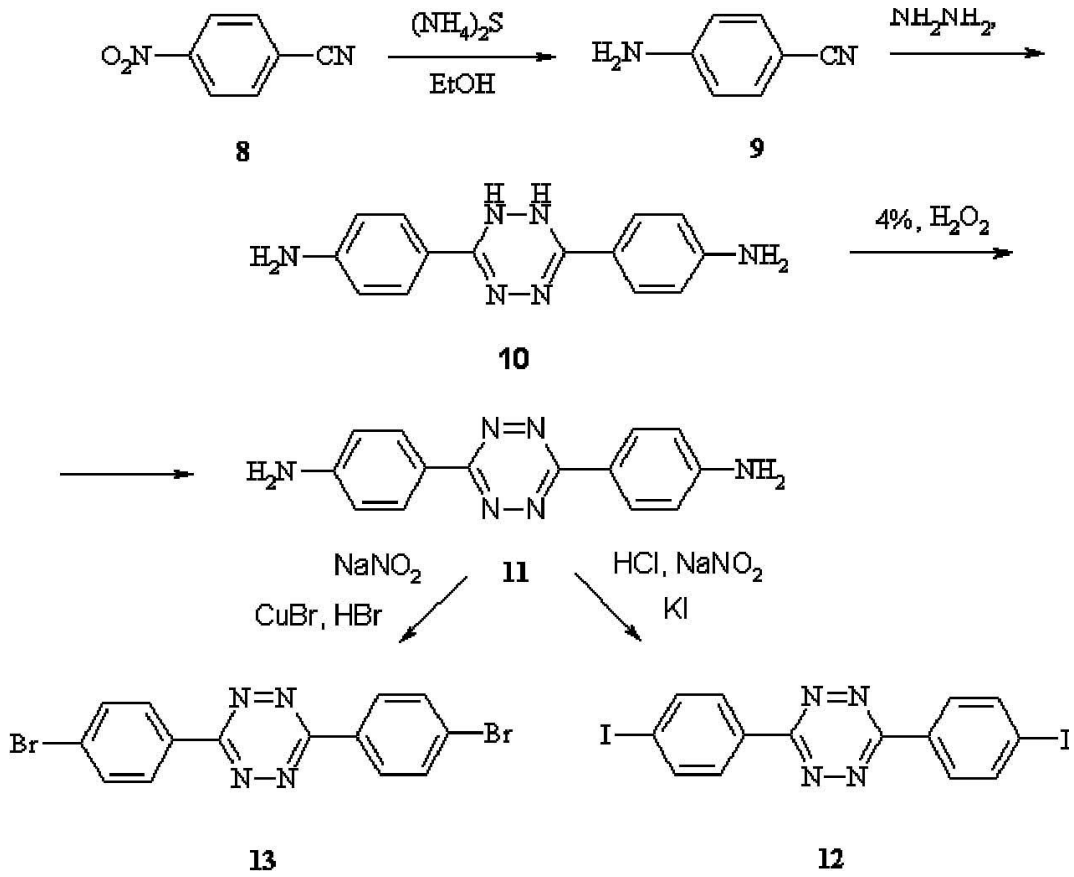
Condensation of **2** with 4-iodoacetophenone in the presence of base gave the chalcone **3a** in

53% yield. The preparation of dodecylamidine hydrochloride **6** (Scheme 2) was achieved by adapting a procedure[3] previously reported for several lower aliphatic amidines. Thus, nitrile **4** was treated with hydrogen chloride in EtOH to afford the imino ester **5** (yield 76%) which was, without further purification, converted into amidine **6** by treatment with ammonia in EtOH at -70 °C. The amidine **6** was isolated as its hydrochloride salt in 79% yield. Condensations of chalcones **3a,b** with amidine hydrochloride **6** in hot (80 °C) DMSO were followed by column chromatography purification which gave the corresponding 4,6-bis-(4-iodophenyl)-2-undecylpyrimidine (**7a)** and 4,6-bis-(4-chlorophenyl)-2-undecylpyrimidine (**7b)** in 72% and 63% yields, respectively.



Scheme 2

Synthesis of 3,6-Bis-(4-halophenyl)-1,2,4,5-tetrazines. The general method of Pinner[4] was modified to develop a practical preparation of the tetrazines **12** and **13**. 4-Aminobenzonitrile (**9**) prepared in 60% yield from 4-nitrobenzonitrile (**8**) as previously reported[5] (Scheme 3), was cyclized by heating with anhydrous hydrazine (98%) into the previously unreported 3,6-bis-(4-aminophenyl)-1,2-dihydro-1,2,4,5-tetrazine (**10)** in 51% yield. Compound **10** was oxidized to the corresponding tetrazine **11** by treatment with hydrogen peroxide (4%) following a literature procedure.[5] 3,6-Bis-(4-aminophenyl)-1,2,4,5-tetrazine (**11)** was isolated by column chromatography in 18% yield. Under the conditions shown in the Scheme 4, diamine **11** was converted by a Sandmeyer reaction, in a procedure similarly to that used for the iodination of 2-bromo-3,6-dimethoxyaniline[6] into 3,6- bis-4-iodophenyl-1,2,4,5-tetrazine (**12)**.



Scheme 3

An analogous Sandmeyer reaction was used to synthesize 3,6-bis-(4-bromophenyl)-1,2,4,5-tetrazine (**13)**. 3,6-Bis-(4-aminophenyl)-1,2,4,5-tetrazine **11** was reacted with $NaNO_2$/HBr/CuBr in methanolic acetic acid at 0 ^oC to give **13** in 47% yield (Scheme 3). Compound **13** was previously reported by Russian workers using a different route. [7]

Experimental Section

General Procedures. Melting points are uncorrected. All NMR spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C) in $CDCl_3$, unless otherwise specified. Column chromatography was carried out on Merck Kiesel gel 60 (5386) silica gel. THF was used immediately after distilling from a solution containing benzophenone/sodium. Other starting materials, reagents and solvents were used as received from suppliers.

4-Iodobenzaldehyde (2). A solution of $NaBH_4$ (129 mg, 3.4 mmol) in dry pyridine (2 mL), dry DMF (5 mL) and dry THF (3 mL) was stirred at 0 ^oC. 4-Iodobenzoyl chloride (1.06 g, 4 mmol) in dry THF (2 mL) was added rapidly to the solution. The mixture was vigorously stirred at 0 ^oC

for 1 min, at which time H_2O (0.5 mL) was added. Stirring was continued at 0 ºC for an additional 1 min, and a mixture of hexane: diethyl ether (50 mL, 4:1 v/v) was quickly added. The globules of pyridine borane which formed at this point were separated by rapid filtration of the reaction mixture through a silica gel bed. Diethyl ether (25 mL) was added to the filtrate, and the organic phase was washed successively with 15% aqueous NaCl (2 x 100 mL), 2 M aqueous hydrochloric acid: brine (100 mL, 1:1 v/v), 1 M aqueous Noah : brine (2 x 100 mL, 4:1 v/v) and saturated brine (100 mL). The organic layer was then dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (eluent - hexane: ethyl acetate, 1:1). Yield 53%, mp 75-78 ºC (lit.[8] mp 77-78 ºC); ^{1}H NMR δ (DMSO-d_6) 7.67 (d, 2H, *J* = 8.2 Hz), 8.02 (d, 2H, *J* = 8.2 Hz), 9.97 (s, 1H); ^{13}C NMR δ (DMSO-d_6) 103.4, 130.9, 135.3, 138.1, 192.6.

1,4-Bis-(4-iodophenyl)-prop-2-enone (3a). 4-Iodoacetophenone (0.1 g, 0.41 mmol) was added under stirring to a solution of NaOH (0.1 g, 2.50 mmol) in EtOH (10 mL) at 20 ºC and stirred for 10 min. A solution of 4-iodobenzaldehyde (0.1 g, 0.43 mmol) in EtOH (5 mL) was added, and the mixture stirred at 20 ºC overnight. The precipitate was collected by filtration and air-dried. Purification by flash chromatography (chloroform) gave **3a**, yield 45%, mp 218-220 ºC (lit.[9] mp 219.5-220 ºC).

Ethyl dodecylimino ester hydrochloride (5). A mixture of dodecanonitrile **4** (1.0 g, 5.5 mmol) and EtOH (5 mL) was treated with hydrogen chloride for 1 h at 0 ºC and then left to stand overnight at 20 ºC. The solvent was evaporated, and the crude product was immediately used in the next step without further purification. Yield 76%, mp 82-84 ºC; ^{1}H NMR δ 0.85-0.88 (m, 3H), 1.25-1.40 (m, 16H), 1.48 (t, 3H, *J* = 6.6 Hz), 1.70-1.80 (m, 2H, *J* = 2.0 Hz), 2.73 (t, 2H, *J* = 7.2 Hz), 4.62 (q, 2H, *J* = 6.7 Hz), 11.45 (br s, 1H), 12.36 (br s, 1H); ^{13}C NMR δ 13.5, 14.0, 22.6, 25.7, 28.7, 28.9, 29.2, 29.4, 29.5, 31.8, 33.0, 70.5, 179.3.

Dodecylamidine hydrochloride (6). A mixture of ethyl dodecylimino ester hydrochloride **5** (1.0 g, 4 mmol) in EtOH (5 mL) was added to a cold (-70 ºC) stirred solution of EtOH (10 mL) saturated with ammonia over a 5 min interval. The mixture was stirred at 0 ºC for 4 h and left stand at 20 ºC overnight. The precipitate was collected by filtration and washed with hexanes. Yield 79%, mp 117-119 ºC; ^{1}H NMR δ 0.89 (t, 3H, *J* = 5.7 Hz), 1.15-1.45 (m, 16 H), 1.71-1.73 (m, 2H), 2.60 (t, 2H, *J* = 7.3 Hz), 8.60 (br s, 2H), 8.72 (br s, 2H); ^{13}C NMR δ 14.1, 22.7, 26.9, 29.0, 29.3, 29.4, 29.6, 29.7, 31.9, 32.6, 172.0; HRMS calcd for $C_{12}H_{27}N_2Cl$ 199.2174 (M+1), found 199.2138.

2-Dodecyl-4,6-bis-(4-iodophenyl)pyrimidine (7a). Sodium hydroxide (0.24 g, 6 mmol) was added to a vigorously stirred solution of dodecane amidine hydrochloride (1.4 g, 6 mmol) in DMSO (20 mL). The mixture was stirred at 20 ºC for 10 min, then diiodochalcone **3a** (1.0 g, 2.2 mmol) and 5Å molecular sieves (5 g) were added. The reaction mixture was heated at 80 ºC for 18 h with an air stream bubbled through. The molecular sieves were removed by filtration of the warm reaction mixture. On cooling, the product precipitated and was collected by filtration. The crude product was purified by column chromatography (hexane : ethyl acetate, 2:1). Yield 72%, mp 113.0-114.5 ºC; ^{1}H NMR δ 0.88 (t, 3H, *J* = 6.5 Hz), 1.15-1.50 (m, 16H), 1.90-1.94 (m,

2H), 3.05 (t, 2H, *J* = 7.5 Hz), 7.75-8.00 (m, 9H); ^{13} C NMR δ 14.1, 22.7, 28.5, 29.3, 29.5, 29.5, 29.6, 29.6, 31.9, 39.7, 97.4, 109.1, 128.8, 136.9, 138.0, 163.8, 172.1. Anal. Calcd for $C_{27}H_{31}N_2$: C, 50.87; H, 4.90, N, 4.39. Found: C, 51.2, H, 5.2, N, 4.33.

2-Undecyl-4,6-bis-(4-chlorophenyl)pyrimidine (7b). Prepared similarly from dichlorochalcone **3b** (1.2 g, 4.4 mmol). Yield 63%, mp 74-75 ºC. ^{1}H NMR δ 0.86 (t, 3H, *J* = 6.67 Hz), 1.25-1.57 (m, 16H), 1.91-2.0 (m, 2H), 3.05 (t, 2H, *J* = 7.69 Hz), 7.48 (d, 4H, *J* = 8.52 Hz), 7.81 (s, 1H), 8.08 (d, 4H, *J* = 8.52 Hz); ^{13}C NMR δ 14.1, 22.7, 28.6, 29.4, 29.5, 29.5, 29.6, 31.9, 39.7, 109.3, 128.5, 129.1, 135.9, 136.9, 163.6, 172.1. Anal. Calcd for $C_{27}H_{31}N_2Cl_2$: C, 71.35; H, 6.87; N, 6.16. Found: C, 71.24, H, 7.47; N, 6.16.

3,6-Bis-(4-aminophenyl)-1,2-dihydro-1,2,4,5-tetrazine (10). A solution of 4-nitrobenzonitrile (2.0 g, 13.5 mmol) and ammonium sulfide in ethanol (20 mL) was heated on a steam bath for 24 h. The precipitate was removed by filtration, and the solvent concentrated under reduced pressure. The residue was recrystallized from water. Yield 60%, mp 84 ºC (lit.[5] mp 85 ºC).

Anhydrous hydrazine (98%, 5 mL) was added to 4-aminobenzonitrile (**9**) (1.0 g, 8.4 mmol). The solution was heated on a steam bath for 18 h. After cooling, the resulting orange-yellow precipitate was filtered, washed with water and immediately used in the next step without purification. Yield 51%, mp 261 ºC; ^{1}H NMR δ (DMSO-d_6) 5.47 (s, 4H, NH_2), 6.53 (d, 4H, *J* = 8.3 Hz, arom H), 7.47 (d, 4H, *J* = 8.3, arom H), 8.51 (s, 2H, NH); ^{13}C NMR δ (DMSO-d_6) 113.0, 117.3, 126.9, 148.6, 150.4. HRMS calcd for $C_{14}H_{14}N_6$ 267. 1371 (M+ 1), found : 267.1371.

3,6-Bis-(4-aminophenyl)-1,2,4,5-tetrazine (11). A solution of 3,6-bis-(4-aminophenyl)-1,2-dihydrotetrazine (0.5 g, 1.8 mmol) and aqueous hydrogen peroxide (4%, 50 mL) was warmed at 60 ºC for 2 h, to yield a red solid, which was collected by filtration and air-dried. The crude product was purified by column chromatography on silica gel using acetone and hexane (2:1) as eluent. Yield 18%, mp 288-289 ºC; ^{1}H NMR δ (DMSO-d_6) 6.01 (s, 4H, NH_2), 6.73 (d, 4H, *J* = 8.7 Hz, arom H), 8.15 (d, 4H, *J* = 8.7 Hz, arom H); ^{13}C NMR δ (DMSO-d_6) 113.8, 118.3, 128.5, 152.8, 162.3; HRMS calcd for $C_{14}H_{12}N_6$ 265.1201 [M +1], found: 265.1207.

3,6-Bis-(4-iodophenyl)-1,2,4,5-tetrazine (12). Sodium nitrite (0.10 g, 4.8 mmol) in water (0.8 mL) was added within 5 min to a solution of 3,6-bis-(4-aminophenyl)-1,2,4,5-tetrazine (0.1 g, 0.37 mmol) in concentrated hydrochloric acid (1 mL) and ice (1.0 g) at 0 ºC while stirring. The mixture was stirred at 0 ºC for a further 20 min, then was placed into a jacketed addition funnel at 0 ºC, and was added over 20 min to a stirred solution of potassium iodide (2.45 g, 0.015 mol) in water (3 mL) at 20 ºC. The mixture was left to stand at 20 ºC overnight and then extracted with ether (2 x 30 mL). The combined organic extracts were washed successively with 10% aqueous NaOH (30 mL), 5% $NaHCO_3$ (30 mL), and H_2O (50 mL) and dried over anhydrous $MgSO_4$. Concentration *in vacuo* and flash chromatography of the residue (hexane: ethyl acetate, 2:1) gave 3,6-bis-(4-iodophenyl)-1,2,4,5-tetrazine (**5**). Yield 30%, mp 278 ºC; ^{1}H NMR δ (DMSO-d_6) 7.84 (d, 4H, *J* = 8.4 Hz, arom H), 7.91 (d, 4H, *J* = 8.1 Hz, arom H); ^{13}C NMR δ (DMSO-d_6) 96.3, 105.9, 127.9, 137.7. Anal. Calcd for $C_{14}H_8N_4$: C, 35.59; H, 1.66. Found: C, 35.58; H, 2.06.

3,6-Bis-(4-bromophenyl)-1,2,4,5-tetrazine (13). Sodium nitrite (3.14 g, 0.045 mol) in water (9.1 mL) was added with stirring over 10 min to a cold (0 ºC) solution of 3,6-bis-(4-aminophenyl)-1,2,4,5-tetrazine (0.5 g, 0.019 mol) in mixture of concentrated sulfuric acid (4.5 mL), methanol (2.3 mL), and water (6.7 mL). The mixture was stirred at 0 ºC for further 30 min and then added over 45 min to a stirred, warm (60 ºC) solution of copper (I) bromide (0.4 g, 2.8 mmol), hydrobromic acid (48%, 1.2 mL), and water (6.7 mL). At the end of the addition the mixture was refluxed for 1 h, cooled, and filtered. The precipitate was washed with water (15 mL), and air-dried. Purification by flash chromatography (hexane : ethyl acetate, 2:1) gave 3,6-bis-(4-bromophenyl)-1,2,4,5-tetrazine (**6**). Yield 47%, mp 198 ºC; (lit.[7] mp 288-289 ºC); ^{1}H NMR δ 7.69 (d, 4H, *J* = 8.3 Hz, arom H), 8.00 (d, 4H, *J* = 8.5 Hz, arom H); ^{13}C NMR δ 122.7, 126.6, 128.3, 132.5, 164.0. Anal. Calcd. for $C_{14}H_8N_4$: C, 42.88; H, 2.05. Found: C, 42.88; H, 2.15.

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