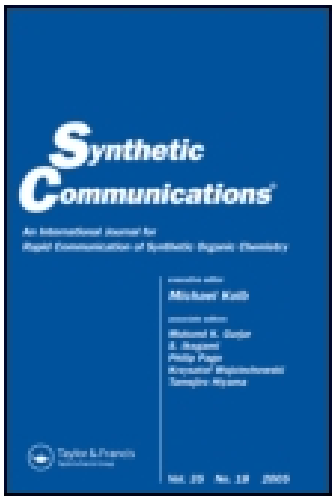

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An Expeditious Synthesis of 6-Alkyl-5-(4′-amino-phenyl)-pyrimidine-2,4-diamines

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An Expeditious Synthesis of 6-Alkyl-5-(4′-amino-phenyl)-pyrimidine-2,4-diamines

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ABSTRACT

A rapid synthesis of a series of 6-alkyl substituted-5-(4′-amino-phenyl)-pyrimidine-2,4-diamines is described. These analogs were produced in good yields on moderate scale (ca. 8 g) without chromatography. Furthermore, the methodology described herein allows the production of 6-[ethyl, propyl, isopropyl, and isobutyl]-5-(4′-amino-phenyl)-pyrimidine-2,4-diamines in a more straightforward manner than previously disclosed.[1d] These novel compounds should aid in the structure-activity relationship analysis of current pyrimidines that possess anti-tumor and anti-malarial activities.

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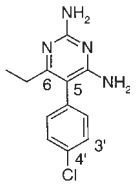
Key Words: 2,4-Diaminopyrimidines; Pyrimidine; Heterocyclic chemistry.

INTRODUCTION

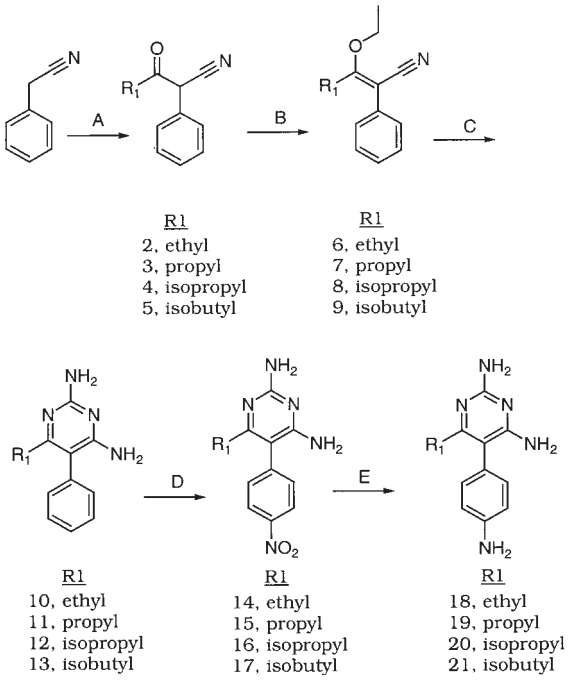
The 6-alkyl-5-phenyl-pyrimidine-2,4-diamine nucleus has received considerable attention as agents for cancer chemotherapy and most notably, as anti-malarials.[1] For instance, Pyrimethamine (**1**) is commonly used for malarial infection by acting as an inhibitor of the dihydrofolate reductase-thymidylate synthase enzyme of *Plasmodium Falciparum*.[2]



(1)

Although many compounds have been disclosed with the 6-ethyl or methyl moiety,[1,3] none have mentioned the synthesis of other alkyl groups in this position, as well as, directly incorporating a nitro group at the 4′ position. Finally, reduction of the nitro moiety yields 6-(alkyl)-5-(4′-aminophenyl)-pyrimidine-2,4-diamino analogs that heretofore, have not been described in the literature. These intermediates are of interest since pyrimidines incorporating secondary and tertiary amine substituents at the 4′-position have demonstrated activity against dihydrofolate reductase.[4] These intermediates serve as templates for further structure-activity relationship investigations of 6-ethyl-5-(3′-azido-4′-chlorophenyl)-pyrimidine-2,4-diamine; an anti-tumor agent that has completed phase I clinical trials.[5,1d] Presently, the approach to 4′ amino analogs employ compound **1** as starting material.[1d] The synthetic protocol of 6-(alkyl)-5-(4′-aminophenyl)-pyrimidine-2,4-diamino analogs is outlined in Sch. 1.

The general route mirrors that of Hitchings[3] with two modifications: (a) The use of triethylorthopropionate with a catalytic amount of sulfuric acid to induce enolization was much easier/safer to use on large scale than diazomethane (**6–9**). Trimethylsilyldiazomethane was tried as a replacement for diazomethane but was not successful in enol formation; (b) Nitration with a mixture of sulfuric acid and nitric acid was higher yielding than with potassium nitrate. Interestingly, Stevens et al.[6] described compound **14** as an inseparable mixture of nitro isomers (3′ and 4′). However, in our hands, nitration of **10** followed by crystallization in hot methanol afforded the 4′ isomer exclusively. Compounds **15**, **16**, and

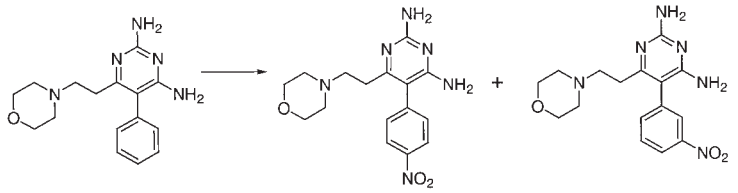


Reaction conditions: (A) NaH, R_1-OMe, THF, 0–85°C, 18 h; (B) Triethylorthopropionate, H_2SO_4 (cat.), 180–200°C, 18 h; (C) Guanidine hydrochloride, NaOEt, EtOH, 130°C, 8 h; (D) H_2SO_4, HNO_3, 0°C-rt, 2 h; (E) Raney-nickel, H_2, MeOH/THF (1:1), 50 psi.

Scheme 1. General route to 6-alkyl-5-(4′-nitrophenyl)-pyrimidine-2,4-diamines.

17 were isolated in this manner. It is important to note, however, that in this situation the separation of nitro regio-isomers is dependent on the substituent at the 6-position of the pyrimidine ring. For example, when an ethylmorpholino group was installed at the 6-position of the pyrimidine ring (Sch. 2), the nitration step yielded an inseparable mixture of nitro regio-isomers. These regio-isomers were detected by ^{1}H NMR, but appeared as a single compound by TLC and HPLC.

An effort to circumvent the regio-isomer problem by commencing with 4-nitrophenylacetonitrile or 4-boc-amino-phenylacetonitrile and employing the route described herein or that of Yuthanvong et al.[1a] was unsuccessful. Although this methodology will not apply to all 6-position analogs where nitration can cause side reactions or produce inseparable nitro regio-isomers, the production of a series of 6-alkyl



Scheme 2. Nitration of 6-ethylmorpholino-5-phenyl-pyrimidine-2,4-diamine produces an inseparable mixture of regio-isomers.

substituted-5-(4′-nitrophenyl) pyrimidine-2,4-diamines were produced in good yields on moderate scale (ca. 8 g) without chromatography. These novel compounds should aid in the structure activity relationship analysis of current pyrimidines that possess anti-tumor and anti-malarial activities.

EXPERIMENTAL SECTION

All reagents were purchased from Aldrich and used without further purification. Solvents used were of HPLC grade and used without further purification. NMR spectra were recorded on a Varian 400 MHz spectrometer and referenced to the solvent. Melting point values are uncorrected.

General Synthesis of Compounds 2–5

Sodium hydride (8.2 g, (60% in mineral oil), 0.204 mol) in THF (100 mL) was cooled to 0°C. Benzyl cyanide (20 g, 0.17 mol) was added via syringe and allowed to stir at 0°C for 30 min. Methyl propionate (17.97 g, 0.20 mol) previously dissolved in THF (50 mL) was added slowly [*CAUTION! Reaction can become exothermic*] via syringe and allowed to warm to rt (3 h) and then heated to 85°C for 18 h. The reaction mixture was cooled to rt and water (120 mL) and diethyl ether (400 mL) were added. The organic and aqueous layers were separated. The aqueous layer was extracted with diethyl ether (3×50 mL) and the etheral layer combined with the previous organic layer. The pH of the aqueous layer was adjusted to pH 6 with acetic acid and extracted with diethyl ether (2×50 mL). The diethyl ether fraction was added to the previous organic fractions, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude compound **2**. Compounds **3–6** were

synthesized in the exact same manner and scale. All crude compounds were used directly in the next step.

3-Oxo-2-phenyl-pentanenitrile (**2**)

25.30 g (86%)

3-Oxo-2-phenyl-hexaenitrile (**3**)

31.49 g (99%)

4-Methyl-3-oxo-2-phenyl-pentanenitrile (**4**)

15.90 g (50%)

5-Methyl-3-oxo-2-phenyl-hexanenitrile (**5**)

22.22 g (65%)

General Synthesis of Compounds 6–9

Compound **2** (25.36 g, 0.146 mol) and molecular sieves (10 g) were added to a round-bottom flask equipped with a Dean-Stark trap. Triethylorthopropionate (58 mL, 0.29 mol) and conc. H_2SO_4 (1 mL) were added and the mixture heated to 180–200°C for 18 h. The reaction mixture was cooled to rt, and filtered. Compound **6**, (black oil) was used immediately without further purification in the next step (assume yield 100%). The same procedure and scale was conducted for the production of compounds **7–9**. All samples were used immediately in the next step without further purification.

General Synthesis of Compounds 10–13

Crude compound **6** (29 g, 0.145 mol, containing residual sulfuric acid, and triethylorthopropionate) was dissolved in EtOH (70 mL), and 21% NaOEt (12.72 mL, 0.159 mol). Guanidine hydrochloride (15.30 g, 0.159 mol) was added in solid portions. The resultant mixture was heated to 130°C for 8 h. The reaction mixture was cooled to rt and poured into ice-water (300 mL). The mixture was stirred for 30 min at

which time a precipitate formed. The oily solid was filtered and washed three times with diethyl ether to afford compound **10** (14.08 g, 45%) as a white solid. The same procedure and scale was conducted for the production of compounds **13–15**.

6-Ethyl-5-phenyl-pyrimidine-2,4-diamine (10). Yield: 45%: M.p. = 244–246°C (Lit,[3] m.p. = 237–240°C): ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.39 (m, 2H), 7.32–7.15 (m, 1H), 7.16–7.10 (m, 2H), 5.79 (s, 2H), 5.33 (brs, 2H), 2.01 (q, $J = 7.6$, 2H), 0.92 (t, $J = 7.2$, 3H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 167.1, 162.7, 162.6, 136.7, 131.2, 129.6, 127.8, 107.2, 28.1, 13.8. MS (APCI) m/z 215.0 (M + 1): Anal. cald. for $C_{12}H_{12}N_4$(%): C, 67.26; H, 6.58; N, 26.15. Found: C, 66.98; H, 6.58; N, 26.25.

5-Phenyl-6-propyl-pyrimidine-2,4-diamine (11). Yield: 28%: M.p. = 174–175°C (Lit,[7] m.p. = 171–173°C): ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.41 (m, 2H), 7.32 (m, 1H), 7.15 (m, 2H), 5.80 (s, 2H), 5.35 (brs, 2H), 2.05 (m, 2H), 1.42 (m, 2H), 0.68 (t, $J = 7.32$, 3H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 165.8, 162.7, 162.0, 136.8, 131.3, 129.5, 127.8, 107.8, 36.8, 22.1, 14.6. MS (APCI) m/z 229.1 (M + 1): Anal. calcd. for $C_{13}H_{16}N_4$ (%): C, 68.39; H, 7.06; N, 24.54. Found: C, 68.07; H, 7.18; N, 24.61.

6-Isopropyl-5-phenyl-pyrimidine-2,4-diamine (12). Yield: 20%: M.p. = 185–187°C (Lit,[8] m.p. = 184–186°C): ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.40 (m, 2H), 7.32 (m, 1H), 7.15 (m, 2H), 5.78 (s, 2H), 5.36 (brs, 2H), 2.47 (hept, $J = 2$, 1H), 0.95 (d, $J = 7.2$, 6H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 170.4, 162.9, 162.7, 136.8, 131.2, 129.6, 127.8, 106.7, 31.3, 22.17. MS (APCI) m/z 229.15 (M + 1).

6-Isobutyl-5-phenyl-pyrimidine-2,4-diamine (13). Yield: 25%: M.p. = 144–145°C (Lit,[8] m.p. = 141–143°C): ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.40 (m, 2H), 7.31 (m, 1H), 7.11 (m, 2H), 5.85 (s, 2H), 5.48 (brs, 2H), 1.98 (m, 2H), 1.92 (m, 1H), 0.66 (d, $J = 7.6$, 6H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 165.14, 162.7, 162.5, 136.8, 131.5, 129.5, 127.7, 108.4, 43.5, 27.8, 23.1. MS (APCI) m/z 243.12 (M + 1).

General Synthesis of Compounds 14–17

Compound **10** (14 g, 0.065 mol) was added to concentrated sulfuric acid (60 mL) at rt. Once the compound was dissolved, the mixture was cooled to 0°C. Concentrated nitric acid (13.79 mL, 3 equiv.) was added dropwise via an addition funnel. [*CAUTION! Do not allow reaction mixture to warm above 15°C*]. The mixture was stirred at 0°C for 1 h and then at rt for an additional hour. The reaction mixture was poured into ice-water (400 mL) and the pH of the mixture adjusted to 12 with 50% NaOH. The resultant yellow precipitate was collected, added to hot

MeOH and filtered. Washings with hot MeOH (two or three times) were continued until all para isomer was isolated (monitored by ^{1}H NMR). 8.65 g (51%) of compound **14** was isolated as a yellow solid. The same procedure and scale was conducted for the production of compounds **15–17**.

6-Ethyl-5-(4′-nitrophenyl)-pyrimidine-2,4-diamine (14). Yield: 51%: M.p. = 345–347°C (dec): ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.22 (*d*, $J = 8.78$, 2H), 7.44 (d, $J = 8.78$, 2H), 5.92 (s, 2H), 5.66 (brs, 2H), 2.46 (q, $J = 3.6$, 2H), 0.93 (t, $J = 7.3$, 3H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 165.4, 161.75, 161.70, 146.5, 143.8, 132.2, 123.9, 104.9, 27.2, 13.0. MS (APCI) m/z 260.1 (M + 1): Anal. calcd. for $C_{12}H_{13}N_5O_2$ (%): C, 55.39; H, 5.05; N, 27.01. Found: C, 55.50; H, 4.87; N, 26.95.

5-(4′-Nitrophenyl)-6-propyl-pyrimidine-2,4-diamine (15). Yield: 48%: M.p. = 282–284°C: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.24 (d, $J = 8.78$, 2H), 7.43 (d, $J = 8.54$, 2H), 5.93 (s, 2H), 5.67 (brs, 2H), 2.06 (t, $J = 7.6$, 2H), 1.44 (q, $J = 7.6$, 2H), 0.70 (t, $J = 7.2$, 3H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 165.7, 163.0, 162.3, 147.1, 145.0, 132.9, 124.6, 106.0, 36.8, 22.0, 14.5. MS (APCI) m/z 274.1 (M + 1): Anal. calcd. for $C_{13}H_{15}N_50_5$ (%): C, 57.13; H, 5.53; N, 25.63. Found: C, 56.82; H, 5.31; N, 25.63.

6-Isopropyl-5-(4′-nitrophenyl)-pyrimidine-2,4-diamine (16). Yield: 40%: M.p. = > 300°C: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.23 (d, $J = 8.8$, 2H), 7.42 (d, $J = 8.8$, 2H), 5.87 (s, 2H), 5.65 (brs, 2H), 2.43 (m, 1H), 0.98 (d, $J = 6.4$, 6H): ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.3, 163.3, 162.2, 147.2, 145.1, 132.9, 124.6, 31.6, 22.1; MS (APCI) m/z 274.01 (M + 1): Anal. calcd. for $C_{13}H_{15}N_50_2 \cdot 0.3\ H_2O$ (%): C, 57.13; H, 5.53; N, 25.63. Found: C, 56.03; H, 5.64; N, 25.13. Found: C, 56.0; H, 5.52; N, 25.24.

6-Isobutyl-5-(4′-nitrophenyl)-pyrimidine-2,4-diamine (17). Yield: 35%: M.p. = 259–261°C: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.24 (d, $J = 8.0$, 2H), 7.41 (d, $J = 8.0$, 2H), 5.93 (s, 2H), 5.68 (brs, 2H), 1.98 (s, 2H), 1.93 (m, 1H), 0.67 (d, $J = 6$, 6H): ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.0, 162.9, 162.3, 147.1, 145.1, 133.2, 124.5, 106.6, 43.6, 27.9, 23.0. MS (APCI) m/z 288.21 (M + 1): Anal. calcd. for $C_{14}H_{17}N_50_2 \cdot 0.9\ H_20$ (%): C, 55.40; H, 6.24; N, 23.07. Found: C, 55.44; H, 5.57; N, 22.65.

General Synthesis of Compounds 18–21

Compound **14** (8.0 g, 0.030 mol) was dissolved in a mixture of MeOH and THF (1:1, 200 mL). Raney nickel (9.3 g) was added and placed under an atmosphere of hydrogen at 50 psi for 18 h. The solution was filtered and concentrated under reduced pressure. The resultant solid was washed

with ethyl acetate/hexanes (1:1), filtered, and dried to obtain compound **18** as a white solid. The same procedure and scale was conducted for the production of compounds **19–21**.

5-(4′-Amino-phenyl)-6-ethyl-pyrimidine-2,4-diamine (18). Yield: 98%: M.p. = 183–185°C: ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.76 (d, $J = 8.8$, 2H), 6.57 (d, $J = 8.4$, 2H), 5.67 (brs, 2H), 5.05 (brs, 2H), 2.09 (q, $J = 8$, 2H), 0.93 (t, $J = 3.6$, 3H): ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.4, 163.3, 162.3, 148.3, 131.5, 123.0, 115.1, 107.6, 28.1, 13.9. MS (APCI) m/z 230.1 (M + 1): Anal. calcd. for $C_{12}H_{15}N_5 \cdot 0.9\ H_2O$ (%): C, 58.71; H, 6.90; N, 28.53. Found: C, 58.51; H, 6.66; N, 28.47.

5-(4′-Amino-phenyl)-6-propyl-pyrimidine-2,4-diamine (19). Yield: 93%: M.p. = 103–105°C: ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.76 (d, $J = 8.3$, 2H), 6.59 (d, $J = 8.3$, 2H), 5.69 (s, 2H), 5.30 (brs, 2H), 5.06 (s, 2H), 2.07 (m, 2H), 1.41 (m, 2H), 0.73 (m, 3H): ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.1, 163.3, 162.2, 148.2, 131.6, 123.1, 115.0, 108.1, 36.9, 22.2, 14.7; MS (APCI) m/z 244.1 (M + 1): Anal. calcd. for $C_{13}H_{17}N_5 \cdot 1.0\ H_2O$ (%): C, 59.75; H, 7.33; N, 26.80. Found: C, 60.00; H, 7.49; N, 26.46.

5-(4′-Amino-phenyl)-6-isopropyl-pyrimidine-2,4-diamine (20). Yield: 85%: M.p. = 218–219°C: ^{1}H NMR (400 MHz, d_6-DMSO): δ 6.76 (d, $J = 8.4$, 2H), 6.59 (d, $J = 8.4$, 2H), 5.64 (brs, 2H), 5.06 (brs, 2H), 2.58 (hept, $J = 6.8$, 1H), 0.93 (d, $J = 6.4$, 6H): ^{13}C NMR (100 MHz, d_6-DMSO): δ 170.7, 163.3, 162.5, 148.3, 131.5, 123.1, 115.1, 107.1, 31.1, 22.2; MS (APCI) m/z 244.1 (M + 1): Anal. calcd. for $C_{13}H_{17}N_5 \cdot 0.6\ H_20$ (%): C, 61.44; H, 7.22; N, 27.56. Found: C, 61.36; H, 7.14; N, 27.48.

5-(4′-Amino-phenyl)-6-isobutyl-pyrimidine-2,4-diamine (21). Yield: 99%: M.p. = 65–67°C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, $J = 8.5$, 2H), 6.74 (d, $J = 8.8$, 2H), 4.97 (brs, 2H), 4.60 (brs, 2H), 3.76 (brs, 2H), 2.20 (d, $J = 7.2$, 2H), 2.06 (hept, $J = 6.8$, 1H), 0.78 (d, $J = 6.8$, 6H): ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 163.8, 161.9, 146.1, 131.9, 124.5, 115.8, 109.9, 68.0, 42.9, 28.3, 22.6; MS (APCI) m/z 258.2 (M + 1): Anal. calcd. for $C_{14}H_{19}N_5 \cdot 0.2\ C_4H_8O_2$ (%): C, 64.34; H, 7.55; N, 25.47. Found: C, 64.24; H, 7.80; N, 25.36.

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