Synthesis of Substituted Furo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines and Furo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines

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Dedicated to the memory of Professor Nicholas Alexandrou

A series of substituted furo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines and furo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines were obtained from reactions of substituted 2-dimethylamino-4-hydrazinofuro[2,3-*d*]pyrimidines with orthoesters or sodium nitrite in acetic acid, respectively.

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Introduction.

Historically, a wide range of biological activities have been attributed to fused triazoles and tetrazoles. For instance, derivatives of the [1,2,4]triazolo[4,3-*c*]quinazoline nucleus **1** [1] are known to possess antiinflammatory [2], anxiolytic [3] and antitumor activity [4] (Figure 1). The analogous thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **2** have been reported [5] and also have been investigated as potential antiinflammatory agents [6]. Treuner and Breuer [7] have prepared the pyrazolo[4,3-*e*][1,2,4]-triazolo[4,3-*c*]pyrimidines **3** for study as antiinflammatory agents while the closely related pyrido[3,2-*e*][1,2,4]-triazolo[4,3-*c*]pyrimidines **4** have been synthesized for their analgesic, CNS depressant and antipyretic properties [8]. The [1,2,4]triazolo[3,4-*i*]purines **5** have been pursued for their bronchodilatory activity [9] and Brown and Shinozuka [10] have used the [1,2,4]triazolo[4,3-*c*]-pteridines **6** to potentiate the activity of antibiotics.

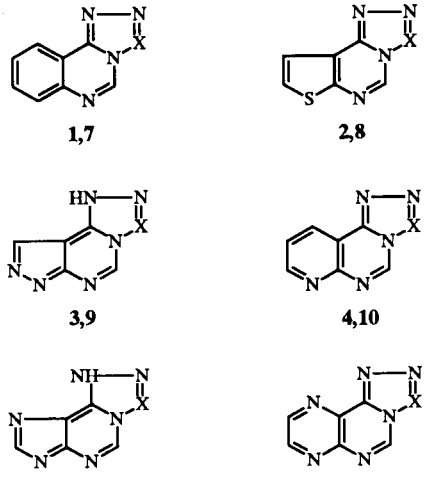
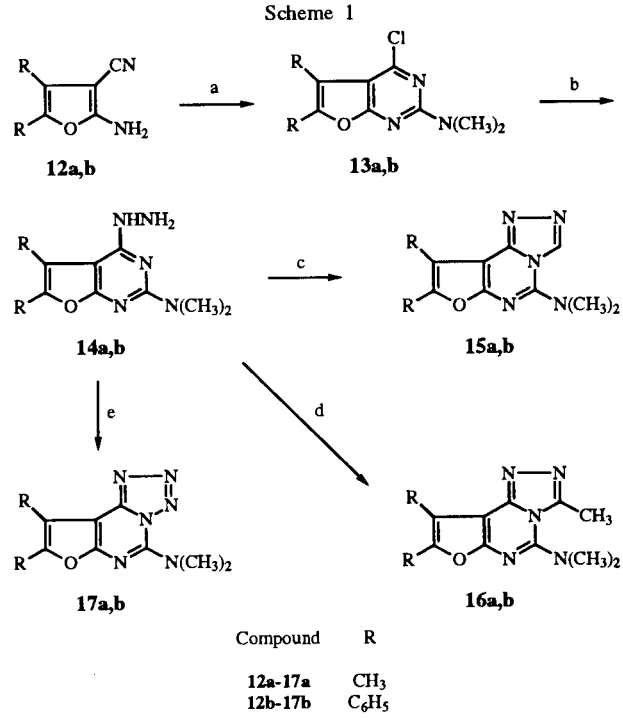


Figure 1.

The fused tetrazoles have been found to exhibit similar biological properties. The tetrazolo[1,5-*c*]quinazolines **7** have been synthesized by Hand and Baker [4] for their antitumor activity (Figure 1) while the tetrazolo[1,5-*c*]-thieno[3,2-*e*]pyrimidines **8** have been reported as potential antifolates [11]. The pyrazolo[4,3-*e*]tetrazolo[1,5-*c*]-pyrimidines **9** have been of interest as antimalarials [12] and the derivatives of pyrido[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines **10** have been associated with anxiolytic activity [13]. Montgomery and coworkers [14] have associated the tetrazolo[5,1-*i*]purines **11** with the inhibition of blood platelet aggregation. We now wish to report a series of novel furo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines and furo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines.

Scheme 1



(a) Phosgene iminium chloride, 1,2-dichloroethane; (b) Hydrazine hydrate, ethanol, reflux; (c) Trimethyl orthoformate; (d) Triethyl orthoacetate; (e) Sodium nitrite, acetic acid.

The previously reported 4,5-disubstituted-2-amino-3-cyanofurans **12a,b** were available by condensation of acetoin or benzoin respectively with malononitrile under basic conditions [15] (Scheme 1). These furans were then converted to the 5,6-disubstituted-4-chloro-2-dimethylaminofuro[2,3-*d*]pyrimidines **13a,b** by reaction with phosgene iminium chloride in 1,2-dichloroethane [16]. Displacement of the halogen by hydrazine [17] in refluxing ethanol yielded the 5,6-disubstituted-2-dimethylamino-4-hydrazinofuro[2,3-*d*]pyrimidines **14a,b**. These compounds served as the immediate precursors for the direct synthesis of all the title compounds.

The compounds **14a,b** were converted to the 8,9-disubstituted-5-dimethylaminofuro[3,2-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines **15a,b** and their 3-methyl analogs **16a,b** by reaction with trimethyl orthoformate and triethyl orthoacetate, respectively [6]. The 8,9-disubstituted-5-dimethylaminofuro[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines **17a,b** were obtained by reaction of **14a,b** with sodium nitrite in acetic acid [17] (Scheme 1).

Structural assignments of all novel compounds were made on the basis of elemental analyses, nmr, infrared, and mass spectra (see Experimental).

EXPERIMENTAL

Melting points were determined on an Electrothermal apparatus (capillary method) and are uncorrected. The infrared spectra were performed on a Beckmann Acculab 4 spectrophotometer using the potassium bromide technique. The tlc were performed with Baker silica plates, type Si250F. Column chromatography was performed with E.M. Science Silica Gel type 60, 40-63 μm. The proton nmr spectra were obtained on a Bruker WH-400 NMR spectrometer using deuteriochloroform as the solvent and mass spectra were obtained by a VG-70 SQ instrument. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.

The procedures given for the syntheses of **13a-17a** were utilized in the preparations of **13b-17b**, respectively.

4-Chloro-2-dimethylamino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**13a**).

Phosgene iminium chloride (0.041 mole, 6.61 g) was added to a solution of 2-amino-3-cyano-4,5-dimethylfuran (**12a**) (0.033 mole, 4.62 g) in 150 ml of 1,2-dichloroethane. The reaction mixture was stirred for two days at 40-50° under a calcium chloride drying tube and then washed twice with sodium bicarbonate. The organic layer was concentrated *in vacuo* to yield a dark red solid. The product was obtained by column chromatography with a dichloromethane mobile phase and recrystallization (methanol) yielded (3.05 g, 41%) a white powder, tlc R_f, hexanes:ethyl acetate (9:1), 0.45, mp 86-88°; ir: ν 2860, 1610, 1530, 1400, 1350, 1290, 1250, 1050, 1000 cm^{-1}; ^{1}H-nmr: δ 2.2 (s, 3H, 5-CH_3), 2.3 (s, 3H, 6-CH_3), 3.2 (s, 6H, $N(CH_3)_2$); ms: ei (m/z) 225 (M^+).

Anal. Calcd. for $C_{10}H_{12}ClN_3O$: C, 53.22; H, 5.36; Cl, 15.71; N, 18.62. Found: C, 53.05; H, 5.39; Cl, 15.60; N, 18.50.

4-Chloro-2-dimethylamino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**13b**).

Recrystallization from methanol:acetone (3:1) yielded (9.52 g, 54%) white needles, tlc R_f, hexanes:ethyl acetate (9:1), 0.57, mp 205-207°; ir: ν 3000, 2910, 1620, 1560, 1540, 1410, 1350, 1290 cm^{-1}; ^{1}H-nmr: δ 3.2 (s, 6H, 2-$N(CH_3)_2$), 7.3 (m, 10H, Ar-H); ms: ei (m/z) 349 (M^+).

Anal. Calcd. for $C_{20}H_{16}ClN_3O$: C, 68.67; H, 4.61; Cl, 10.14; N, 12.01. Found: C, 68.67; H, 4.64; Cl, 10.24; N, 11.91.

2-Dimethylamino-4-hydrazino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**14a**).

A solution of hydrazine hydrate (0.022 mole, 1.10 g) and 4-chloro-2-dimethylamino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**13a**) (0.01 mole, 2.25 g) in 70 ml of absolute ethanol was refluxed for 24 hours. The solvent was removed *in vacuo* and the residue was recrystallized from methanol to yield (1.20 g, 54%) off-white crystals, tlc R_f, hexanes:ethyl acetate:dichloromethane (2:1:1), 0.25, mp 193-195°; ir: ν 3390, 3280, 2900, 2850, 1580, 1550, 1460, 1420, 1380 cm^{-1}; ^{1}H-nmr: δ 2.25 (s, 3H, 6-CH_3), 2.2 (s, 3H, 5-CH_3), 3.2 (s, 6H, 2-$N(CH_3)_2$), 4.4 (s, 2H, 4-NH_2), 5.7 (s, 1H, 4-NH); ms: ei (m/z) 221 (M^+).

Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.66. Found: C, 54.36; H, 6.87; N, 31.58.

2-Dimethylamino-4-hydrazino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**14b**).

Recrystallization from methanol yielded (3.98 g, 89%) white needles, tlc R_f, hexanes:ethyl acetate:dichloromethane (2:1:1), 0.45, mp 215-217°; ir: ν 3120, 3050, 2850, 1590, 1550, 1400, 1340, 1210 cm^{-1}; ^{1}H-nmr: δ 3.2 (s, 6H, 2-$N(CH_3)_2$), 4.4 (s, 2H, 4-NH_2), 5.8 (s, 1H, 4-NH), 7.4 (m, 10H, Ar-H); ms: ei (m\z) 345 (M^+).

Anal. Calcd. for $C_{20}H_{19}N_5O$: C, 69.54; H, 5.54; N, 20.28. Found: C, 69.54; H, 5.56; N, 20.35.

5-Dimethylamino-8,9-dimethylfuro[3,2-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidine (**15a**).

A solution of 2-dimethylamino-4-hydrazino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**14a**) (0.0017 mole, 0.370 g) in trimethyl orthoformate (25 ml) was stirred at 70° for six hours and then cooled overnight. It was concentrated *in vacuo* and recrystallized from ethyl acetate and hexanes (3:1) to yield (0.190 g, 51%) white needles, tlc R_f, ethyl acetate, 0.20, mp 155-157°; ir: ν 2910, 2880, 1620, 1590, 1550, 1470, 1390, 1370 cm^{-1}; ^{1}H-nmr: δ 2.38 (s, 3H, 9-CH_3), 2.42 (s, 3H, 8-CH_3), 3.19 (s, 6H, 5-$N(CH_3)_2$), 8.82 (s, 1H, 3-H); ms: ei (m\z) 231 (M^+).

Anal. Calcd. for $C_{11}H_{13}N_5O \cdot 0.25H_2O$: C, 56.04; H, 5.77; N, 29.71. Found: C, 55.87; H, 5.82; N, 29.61.

5-Dimethylamino-8,9-diphenylfuro[3,2-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidine (**15b**).

After cooling the reaction mixture in the freezer, the precipitate was collected by filtration and recrystallization (methanol) yielded (0.695 g, 66%) a white powder, tlc R_f, ethyl acetate, 0.25, mp 308-310° dec; ir: ν 3090, 3010, 2960, 1620, 1580, 1500, 1480, 1410, 1340 cm^{-1}; ^{1}H-nmr: δ 3.3 (s, 6H, 5-$N(CH_3)_2$), 7.4 (m, 10H, Ar-H), 8.9 (s, 1H, 3-H); ms: ei (m/z) 355 (M^+).

Anal. Calcd. for $C_{21}H_{17}N_5O$: C, 70.97; H, 4.82; N, 19.71. Found: C, 71.04; H, 4.86; N, 19.63.

5-Dimethylamino-3,8,9-trimethylfuro[3,2-*e*][1,2,4]triazolo-[4,3-*c*]pyrimidine (**16a**).

A solution of 2-dimethylamino-4-hydrazino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**14a**) (0.005 mole, 1.21 g) in triethyl orthoacetate (60 ml) was stirred at 70° for twenty-four hours and then concentrated *in vacuo* to yield a brown solid. Recrystallization from ethyl acetate yielded (0.492 g, 40%) white needles, tlc R_f, ethyl acetate, 0.25, mp 235-237°; ir: ν 2900, 2840, 2780, 1620, 1530, 1500, 1350, 1330, 1290 cm^{-1}; ^1H-nmr: δ 2.40 (s, 3H, 9-CH_3), 2.41 (s, 3H, 8-CH_3), 2.88 (s, 3H, 3-CH_3), 2.95 (s, 6H, 5-$N(CH_3)_2$); ms: ei (m/z) 245 (M^+).

Anal. Calcd. for $C_{12}H_{15}N_5O \cdot 0.20H_2O$: C, 57.91; H, 6.24; N, 28.14. Found: C, 58.11; H, 6.24; N, 28.27.

5-Dimethylamino-3-methyl-8,9-diphenylfuro[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (**16b**).

Recrystallization from methanol:chloroform (4:1) yielded (0.566 g, 61%) tan needles, tlc R_f, ethyl acetate, 0.38, mp 224-226°; ir: ν 3110, 3020, 2970, 1610, 1550, 1530, 1440, 1390, 1270, 1230 cm^{-1}; ^1H-nmr: δ 3.0 (s, 3H, 3-CH_3), 3.3 (s, 6H, 5-$N(CH_3)_2$), 7.2 (m, 10H, Ar-H); ms: ei (m/z) 369 (M^+).

Anal. Calcd. for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.36; H, 5.21; N, 18.88.

5-Dimethylamino-8,9-dimethylfuro[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**17a**).

A solution of 2-dimethylamino-4-hydrazino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**14a**) (0.005 mole, 1.10 g) and sodium nitrite (0.005 mole, 0.345 g) in acetic acid (50 ml) was stirred at room temperature for twenty-four hours. Cold distilled water was added and the precipitate was collected by filtration. Recrystallization from methanol yielded (0.495 g, 33%) white needles, tlc R_f, hexanes:ethyl acetate (9:1), 0.50, mp 92-94°; ir: ν 3260, 1620, 1540, 1400, 1360, 1320, 1280, 1230 cm^{-1}; ^1H-nmr: δ 2.1 (s, 3H, 9-CH_3), 2.21 (s, 3H, 8-CH_3), 3.2 (s, 6H, 5-$N(CH_3)_2$); ms: ei (m/z) 232 (M^+).

Anal. Calcd. for $C_{10}H_{12}N_6O$: C, 51.71; H, 5.21; N, 36.19. Found: C, 51.45; H, 5.30; N, 35.93.

5-Dimethylamino-8,9-diphenylfuro[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**17b**).

Recrystallization in methanol:chloroform (3:1) yielded (0.762 g, 71%) yellow needles, tlc R_f, hexanes:ethyl acetate:dichloromethane (2:1:1), 0.80, mp 168-170°; ir: ν 3100, 3070, 2890, 1590, 1560, 1480, 1300, 1240 cm^{-1}; ^1H-nmr: δ 3.1 (s, 6H, 5-$N(CH_3)_2$), 7.1 (m, 10H, Ar-H); ms: ei (m/z) 356 (M^+).

Anal. Calcd. for $C_{20}H_{16}N_6O$: C, 67.40; H, 4.52; N, 23.58. Found: C, 67.17; H, 4.58; N, 23.79.

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