Chromeno[2,3-*d*]pyrimidine-triones Synthesis by a Three-Component Coupling Reaction

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A simple and one-pot synthesis of new chromeno[2,3-*d*]pyrimidine-triones by a three-component condensation reaction of barbituric acids, aldehydes and cyclohexane-1,3-diones in refluxing ethanol in the presence of *p*-toluenesulfonic acid (*p*-TSA) for 3—10 h is reported. Two cyclohexane-1,3-diones, four barbituric acids and six substituted aldehydes were chosen for the library validation. Prominent among the advantages of this new method are operational simplicity, good yields and easy work-up procedures employed.

Key words chromeno[2,3-*d*]pyrimidine; cyclohexane-1,3-dione; barbituric acid; aldehyde

Multicomponent reactions (MCRs), an important subclass of tandem reactions, are one-pot processes in which three or more easily accessible components react to form a single product that incorporates essentially most or all atoms in starting materials.[1)] MCRs are highly flexible, (chemo) selective, convergent, and atom-efficient processes of high exploratory power.[2—5)] As such they closely approach the concept of ideal synthesis. Heterocyclic systems are common structural elements in many natural products and pharmacologically active substances. Accordingly, the development of efficient methods for the synthesis of (combinatorial libraries of) heterocyclic compounds has been posing a real challenge to organic chemists for over a century. In the course of time, MCRs have proved to be a convenient tool for the construction of many heterocyclic compound classes.[1—5)]

The chromene moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols, and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[6—9)]

Pyrimidine derivatives are well-known[10—16)] for their biological activity. Numerous pyrimidine and uracil based compounds have found application in medicine and therapeutics *e.g.* some are used in the chemotherapy of cancer[17)] and some are used against HIV and viral diseases.[18—21)] Usually functionalization of uracil at the C-5 and C-6 positions leads to biologically interesting molecules. A number of heterocyclic compounds fused with pyrimidines are known for their varied biological acivities.[22—26)] For example, the chromeno [2,3-*d*]pyrimidine-2,4(3*H*)-diones (oxadeazaflavines), which are biomimetic models of the 5-deazaflavin coenzyme, have been shown to possess strong redox properties in the conversion of alcohols to aldehydes or ketones.[27—29)] Novel methods for preparing heterocycle containing pyrimidine moiety have attracted much interest in recent years.[30—35)] Despite the available synthetic methods, there still exists a need for developing more efficient procedures, which allow the ready synthesis of pyrimidine polycyclic systems.

As part of our continuing efforts on the development of new routes for the synthesis of biologically active small heterocyclic compounds,[36—42)] we have already reported some procedures for the synthesis of fused-pyrimidine heterocycles.[43—51)] Herein, we report a simple and efficient synthesis of chromeno[2,3-*d*]pyrimidine-triones by a new three-component coupling reaction.

Experimental

General Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical Procedure for Preparation of 8,8-Dimethyl-5-phenyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4a A mixture of 5,5-dimethyl-cyclohexane-dione (0.14 g, 1 mmol), barbituric acid (0.13 g, 1 mmol), benzaldehyde (0.13 g, 1 mmol) and *p*-toluenesulfonic acid (*p*-TSA) (0.1 g) in refluxing ethanol (5 ml) was stirred for 4 h. After completion of the reaction confirmed by TLC (eluent: EtOAc/*n*-hexane, 1 : 3), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water (10 ml) and ethanol (5 ml) to afford the pure **4a** as a white powder (yield 84%). mp 160 °C (dec.). IR (KBr) cm^{-1}: 3180, 2938, 2870, 1719, 1676, 1654. MS *m*/*z*: 338 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.07—2.57 (4H, m, $2CH_2$), 4.52 (1H, s, CH), 7.11—7.22 (5H, m, H-Ar), 11.03 (1H, s, NH), 12.04 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.0, 28.9, 32.2, 32.3, 50.4, 90.8, 115.2, 126.0, 126.8, 128.3, 128.5, 128.6, 144.3, 149.8, 153.1, 162.8, 163.3, 170.4, 196.3. *Anal.* Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.53; H, 5.30; N, 8.21.

5-(4-Chlorophenyl)-8,8-dimethyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*, 5*H*,7*H*)-trione 4b 79% yield. Yellow powder. mp 170 °C (dec.). IR (KBr) cm^{-1}: 2954, 2870, 2807, 1719, 1698. MS *m*/*z*: 372 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.12, 2.26 (2H, ABq, $^3J_{HH}$=15.6 Hz, CH_2), 2.56 (2H, s, CH_2), 4.49 (1H, s, CH), 7.16—7.29 (4H, m, H-Ar), 11.02 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 26.9, 28.8, 31.9, 32.3, 50.4, 90.3, 114.4, 125.9, 128.3, 128.5, 130.5, 143.3, 149.8, 153.2, 162.9, 163.3, 163.5, 196.3. *Anal.* Calcd for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51. Found: C, 61.11; H, 4.65; N, 7.57.

8,8-Dimethyl-5-(4-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*, 5*H*,7*H*)-trione 4c 85% yield. Yellow powder. mp 200 °C (dec.). IR (KBr) cm^{-1}: 3259, 3201, 2938, 1722, 1685. MS *m*/*z*: 383 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.11, 2.27 (2H, ABq, $^3J_{HH}$=16.1 Hz, CH_2), 2.64 (2H, s, CH_2), 4.62 (1H, s, CH), 7.10—8.10 (4H, m, H-Ar), 11.11 (1H, s, NH), 12.16 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.1, 28.7, 32.3, 32.8, 50.3, 89.7, 114.0, 123.5, 130.1, 146.5, 149.8, 151.8, 153.4, 163.3, 163.4, 196.4. *Anal.* Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.62; H, 4.40; N, 10.88.

8,8-Dimethyl-5-(3-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*, 5*H*,7*H*)-trione 4d 83% yield. White powder. mp 180 °C (dec.). IR (KBr) cm^{-1}: 3180, 2959, 2812, 1729, 1694. MS *m*/*z*: 383 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.13,

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2.29 (2H, ABq, $^3J_{HH}$=15.9 Hz, CH_2), 2.61 (2H, s, CH_2), 4.64 (1H, s, CH), 7.51—8.04 (4H, m, H-Ar), 11.10 (1H, s, NH), 12.16 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.0, 28.8, 32.4, 32.6, 50.3, 89.7, 114.1, 122.0, 123.3, 125.9, 129.9, 135.4, 146.4, 147.8, 149.8, 153.4, 163.3, 196.4. *Anal.* Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.45; H, 4.41; N, 10.90.

8,8-Dimethyl-5-*p*-tolyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4e 73% yield. Yellow powder. mp 185 °C (dec.). IR (KBr) cm^{-1}: 3243, 3190, 2933, 1719, 1679. MS *m/z*: 352 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.07—2.29 (5H, m, CH_2, CH_3), 2.56 (2H, s, CH_2), 4.46 (1H, s, CH), 7.00—7.09 (4H, m, H-Ar), 11.02 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 21.0, 27.0, 28.9, 31.8, 32.3, 50.4, 90.9, 115.3, 128.4, 128.9, 135.8, 141.4, 149.8, 153.0, 162.6, 163.2, 196.3. *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.26; H, 5.67; N, 7.49.

5-Phenyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4f 77% yield. Light yellow powder. mp >300 °C. IR (KBr) cm^{-1}: 3190, 2938, 2817, 1723, 1682. MS *m/z*: 310 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.86—2.00 (2H, m, CH_2), 2.22—2.23 (2H, m, CH_2), 2.26—2.73 (2H, m, CH_2), 4.55 (1H, s, CH), 7.11—7.23 (5H, m, H-Ar), 11.03 (1H, s, NH), 12.02 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.2, 26.8, 32.1, 36.8, 90.8, 116.2, 126.8, 128.4, 128.5, 144.4, 149.8, 153.1, 163.3, 164.8, 196.5. *Anal.* Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.71; H, 4.48; N, 8.95.

5-(4-Chlorophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4g 74% yield. Light yellow powder. mp >300 °C. IR (KBr) cm^{-1}: 3195, 3064, 2922, 1719, 1651. MS *m/z*: 344 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.94 (2H, br s, CH_2), 1.28 (2H, br s, CH_2), 2.65 (2H, br s, CH_2), 4.51 (1H, s, CH), 7.25 (4H, br s, H-Ar), 11.04 (1H, s, NH), 12.03 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.1, 26.8, 31.8, 36.7, 90.2, 115.7, 128.2, 130.5, 131.3, 143.4, 149.8, 153.1, 163.3, 164.9, 196.5. *Anal.* Calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; N, 8.13. Found: C, 59.31; H, 3.84; N, 8.04.

5-(4-Nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4h 72% yield. Orange powder. mp 275 °C. IR (KBr) cm^{-1}: 1719, 1692, 1653. MS *m/z*: 355 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.27 (2H, br s, CH_2), 1.95 (2H, br s, CH_2), 2.28 (2H, br s, CH_2), 4.63 (1H, s, CH), 7.53—8.07 (4H, m, H-Ar), 11.10 (1H, s, NH), 12.15 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.1, 26.8, 32.7, 36.7, 89.6, 115.1, 123.5, 130.1, 146.5, 149.8, 151.9, 153.3, 163.3, 165.4, 196.5. *Anal.* Calcd for $C_{17}H_{13}N_3O_6$: C, 57.47; H, 3.69; N, 11.83%. Found: C, 57.33; H, 3.61; N, 11.90%.

5-(3-Nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4i 81% yield. White powder. mp 210 °C (dec.). IR (KBr) cm^{-1}: 3285, 3216, 3074, 1729, 1693. MS *m/z*: 355 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.90—1.98 (2H, m, CH_2), 2.28—2.34 (2H, m, CH_2), 2.69—2.71 (2H, m, CH_2), 4.66 (1H, s, CH), 7.50—8.07 (4H, m, H-Ar), 11.07 (1H, s, NH), 12.11 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.1, 26.8, 32.5, 36.7, 89.7, 115.1, 121.9, 123.4, 126.0, 129.9, 135.4, 146.5, 147.8, 149.8, 153.3, 163.3, 165.4, 196.6. *Anal.* Calcd for $C_{17}H_{13}N_3O_6$: C, 57.47; H, 3.69; N, 11.83. Found: C, 57.41; H, 3.75; N, 11.89.

Due to very low solubility of the products **4j**, we can not report the ^{13}C-NMR data for this product.

1,3,8,8-Tetramethyl-5-phenyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4j 74% yield. Light yellow powder. mp 197 °C. IR (KBr) cm^{-1}: 2964, 2870, 1703, 1635. MS *m/z*: 366 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.93 (6H, br s, $2CH_3$), 2.17—2.71 (4H, m, $2CH_2$), 2.97 (3H, s, NCH_3), 3.11 (3H, s, NCH_3), 4.64 (1H, s, CH), 7.00—7.47 (5H, m, H-Ar). *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.94; H, 6.01; N, 7.72.

1,3,8,8-Tetramethyl-5-(4-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4k 79% yield. White powder. mp >300 °C. IR (KBr) cm^{-1}: 2959, 2870, 1707, 1645. MS *m/z*: 411 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.16, 2.30 (2H, ABq, $^3J_{HH}$=16.2 Hz, CH_2), 2.68 (2H, s, CH_2), 3.07 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 4.73 (1H, s, CH), 7.56 (2H, d, $^3J_{HH}$=8.6 Hz, H-Ar), 8.09 (2H, d, $^3J_{HH}$=8.6 Hz, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 27.2, 28.2, 28.7, 29.6, 32.4, 33.6, 50.3, 89.9, 114.1, 123.5, 130.2, 146.6, 150.4, 151.6, 152.3, 161.3, 163.3, 196.3. *Anal.* Calcd for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.42; H, 5.08; N, 10.29

1,3,8,8-Tetramethyl-5-(3-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4l 81% yield. Light yellow powder. mp 185 °C. IR (KBr) cm^{-1}: 2962, 2933, 2864, 1696, 1642. MS *m/z*: 411 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.16, 2.30 (2H, ABq, $^3J_{HH}$=16.1 Hz, CH_2), 2.69 (2H, s, CH_2), 3.07 (3H, s, NCH_3), 4.73 (1H, s, CH), 7.51—8.08 (4H, m, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 27.0, 28.2, 28.8, 29.6, 32.5, 33.5, 50.3, 89.9, 114.1, 122.1, 123.4, 129.9, 135.5, 146.2, 147.8, 150.4, 152.3, 161.4, 163.4, 196.4. *Anal.* Calcd for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.39; H, 5.19; N, 10.16.

5-(4-Bromophenyl)-1,3,8,8-tetramethyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4m 78% yield. White powder. mp 203 °C. IR (KBr) cm^{-1}: 1711, 1684, 1653. MS *m/z*: 446 (M^++2), 444 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.17—2.25 (2H, m, CH_2), 2.64 (2H, br s, CH_2), 3.07 (3H, s, NCH_3), 4.58 (1H, s, CH), 7.21 (2H, br s, H-Ar), 7.39 (2H, br s, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 27.1, 28.2, 28.8, 29.5, 32.4, 32.8, 50.4, 90.4, 114.6, 120.0, 131.0, 131.1, 143.5, 150.4, 152.1, 161.3, 162.9, 163.1, 196.3. *Anal.* Calcd for $C_{21}H_{21}BrN_2O_4$: C, 56.64; H, 4.75; N, 6.29%. Found: C, 56.72; H, 4.82; N, 6.23%.

5-(4-Chlorophenyl)-1,3-dimethyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4n 65% yield. Yellow powder. mp 170 °C. IR (KBr) cm^{-1}: 1711, 1674, 1637. MS *m/z*: 372 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.92—1.97 (2H, m, CH_2), 2.30—2.31 (2H, m, CH_2), 2.73—2.75 (2H, m, CH_2), 3.09 (3H, s, NCH_3), 3.35 (3H, s, NCH_3), 4.62 (1H, s, CH), 7.27 (4H, br s, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 20.2, 26.7, 28.2, 29.5, 32.6, 36.8, 90.5, 115.8, 128.2, 130.6, 131.4, 143.2, 150.4, 152.1, 161.3, 164.8, 196.5. *Anal.* Calcd for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51%. Found: C, 61.11; H, 4.55; N, 7.43%.

1,3-Dimethyl-5-(4-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4o 70% yield. Light yellow powder. mp 222 °C (dec.). IR (KBr) cm^{-1}: 3069, 2959, 2938, 2870, 1724, 1635. MS *m/z*: 383 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.93—2.00 (2H, m, CH_2), 2.31—2.33 (2H, m, CH_2), 2.49—2.50 (2H, m, CH_2), 3.07 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 4.74 (1H, s, CH), 7.55—8.09 (4H, m, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 20.2, 26.8, 28.2, 29.6, 33.5, 36.7, 89.9, 115.1, 123.5, 130.2, 146.6, 150.4, 151.7, 152.3, 161.3, 165.2, 196.5. *Anal.* Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.64; H, 4.42; N, 11.04.

Due to very low solubility of the products **4p** we can not report the ^{13}C-NMR data for this product.

1,3-Dimethyl-5-(3-nitrophenyl)-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione 4p 68% yield. White powder. mp >300 °C (dec.). IR (KBr) cm^{-1}: 2959, 2927, 2864, 1712, 1688, 1669. MS *m/z*: 383 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.18—1.37 (2H, m, CH_2), 1.93—2.00 (2H, m, CH_2), 2.32—2.41 (2H, m, CH_2), 3.08 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 4.75 (1H, s, CH), 7.50—8.10 (4H, m, H-Ar). *Anal.* Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.46; H, 4.41; N, 10.89.

8,8-Dimethyl-5-phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4q 73% yield. Light brown powder. mp 180 °C. IR (KBr) cm^{-1}: 3495, 3190, 2958, 1715, 1692. MS *m/z*: 354 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.12, 2.26 (2H, ABq, $^3J_{HH}$=13.3 Hz, CH_2), 2.57 (2H, s, CH_2), 4.53 (1H, s, CH), 7.13—7.22 (5H, m, H-Ar), 12.46 (1H, s, NH), 13.54 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.1, 28.8, 32.3, 32.4, 50.4, 95.8, 114.8, 127.0, 128.4, 128.6, 143.6, 152.5, 161.0, 162.7, 174.1, 196.2. *Anal.* Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90. Found: C, 64.31; H, 5.08; N, 7.82.

5-Phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4r 70% yield. Yellow powder. mp >300 °C (dec.). IR (KBr) cm^{-1}: 3106, 3027, 2885, 1691, 1658. MS *m/z*: 326 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.88—1.98 (2H, m, CH_2), 2.23—2.29 (2H, m, CH_2), 2.67—2.75 (2H, m, CH_2), 4.56 (1H, s, CH), 6.99—7.24 (5H, m, H-Ar), 12.39 (1H, s, NH), 13.51 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.2, 26.8, 32.1, 36.8, 95.8, 115.9, 127.0, 128.4, 128.6, 143.7, 152.5, 161.0, 164.7, 174.1, 196.4. *Anal.* Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.61; H, 4.28; N, 8.51.

8,8-Dimethyl-5-(4-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4s 80% yield. Orange powder. mp 265 °C. IR (KBr) cm^{-1}: 1686, 1627, 1570. MS *m/z*: 399 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.13, 2.27 (2H, ABq, $^3J_{HH}$=16.1 Hz, CH_2), 2.59 (2H, s, CH_2), 4.64 (1H, s, CH), 7.55 (2H, d, $^3J_{HH}$=8.7 Hz, H-Ar), 8.10 (2H, d, $^3J_{HH}$=8.7 Hz, H-Ar), 12.48 (1H, s, NH), 13.65 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.2, 28.6, 32.4, 32.8, 50.3, 56.5, 94.6, 113.8, 123.5, 130.2, 146.6, 151.1, 152.7, 161.0, 163.3, 174.3, 196.2. *Anal.* Calcd for $C_{19}H_{17}N_3O_5S$: C, 57.13; H, 4.29; N, 10.52%. Found: C, 57.04; H, 4.21; N, 10.44%.

5-(4-Nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4t 82% yield. Brown powder. mp 270 °C (dec.). IR (KBr) cm^{-1}: 1713, 1669, 1635. MS *m/z*: 371 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.90—1.99 (2H, m, CH_2), 2.23—2.35 (2H, m, CH_2), 2.73 (2H, br s, CH_2), 4.77 (1H, s, CH), 7.52 (2H, d, $^3J_{HH}$=8.4 Hz, H-Ar), 8.09

(2H, d, $^3J_{HH}$=8.3 Hz, H-Ar), 12.94 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 14.8, 20.2, 24.8, 27.2, 33.5, 36.7, 114.2, 123.6, 130.0, 146.5, 151.8, 166.7, 196.6. *Anal.* Calcd for $C_{17}H_{13}N_3O_5S$: C, 54.98; H, 3.53; N, 11.31%. Found: C, 54.99; H, 3.46; N, 11.39%.

8,8-Dimethyl-5-(3-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4u 81% yield. Light orange powder. mp 190 °C. IR (KBr) cm^{-1}: 2959, 2870, 1691, 1624. MS *m*/*z*: 399 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.14, 2.28 (2H, ABq, $^3J_{HH}$=15.7 Hz, CH_2), 2.61 (2H, s, CH_2), 4.65 (1H, s, CH), 7.54—8.04 (4H, m, H-Ar), 12.46 (1H, s, NH), 13.60 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 15.6, 27.1, 28.7, 32.4, 50.3, 65.4, 94.6, 113.8, 122.1, 123.4, 129.9, 135.5, 145.7, 147.9, 152.8, 161.1, 163.4, 174.3, 196.3 *Anal.* Calcd for $C_{19}H_{17}N_3O_5S$: C, 57.13; H, 4.29; N, 10.52. Found: C, 57.22; H, 4.22; N, 10.46.

5-(3-Nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4v 81% yield. Yellow powder. mp >300 °C (dec.). IR (KBr) cm^{-1}: 3101, 2864, 1703, 1671, 1650. MS *m*/*z*: 371 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.95 (2H, br s, CH_2), 2.29 (2H, br s, CH_2), 2.70 (2H, br s, CH_2), 4.66 (1H, s, CH), 7.52—8.08 (4H, m, H-Ar), 12.48 (1H, s, NH), 13.61 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.1, 26.9, 32.6, 36.6, 94.6, 114.8, 122.1, 123.5, 130.0, 135.5, 145.7, 147.8, 152.7, 161.1, 165.4, 174.3, 196.5. *Anal.* Calcd for $C_{17}H_{13}N_3O_5S$: C, 54.98; H, 3.53; N, 11.31. Found: C, 54.90; H, 3.59; N, 11.26.

Due to very low solubility of the products **4w**, we can not report the ^{13}C-NMR data for this product.

5-(4-Bromophenyl)-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4w 78% yield. White powder. mp 180 °C. IR (KBr) cm^{-1}: 2960, 2854, 1708, 1663. MS *m*/*z*: 432 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.03—2.28 (2H, m, CH_2), 2.55 (2H, s, CH_2), 4.46 (1H, s, CH), 7.10—7.42 (4H, m, H-Ar), 11.06 (1H, s, NH), 12.07 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 13.7, 28.8, 29.1, 32.4, 50.4, 90.2, 95.2, 114.3, 120.1, 124.1, 131.0, 143.0, 149.1, 162.9, 196.3. *Anal.* Calcd for $C_{19}H_{17}BrN_2O_3S$: C, 52.66; H, 3.95; N, 6.46. Found: C, 52.72; H, 3.89; N, 6.51.

1,3-Diethyl-8,8-dimethyl-5-phenyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4x 72% yield. White powder. mp 180 °C. IR (KBr) cm^{-1}: 2962, 2933, 2870, 1683, 1625. MS *m*/*z*: 410 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, s, CH_3), 1.06—1.11 (6H, m, 2CH_3), 1.29—1.33 (3H, m, CH_3), 4.24—4.56 (4H, m, 2NCH_2), 4.67 (1H, s, CH), 7.13—7.26 (5H, m, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 11.7, 12.9, 27.1, 28.9, 32.4, 33.1, 43.3, 45.3, 50.4, 96.3, 115.0, 127.1, 128.5, 128.7, 143.3, 152.1, 159.1, 162.9, 174.7, 196.0. *Anal.* Calcd for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82. Found: C, 67.20; H, 6.33; N, 6.89.

5-(4-Chlorophenyl)-1,3-diethyl-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4y 70% yield. Light yellow powder. mp 133 °C. IR (KBr) cm^{-1}: 2959, 2933, 2870, 1694, 1635. MS *m*/*z*: 444 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, s, CH_3), 1.07 (6H, br s, 2CH_3), 1.31 (3H, s, CH_3), 2.17, 2.27 (2H, ABq, $^3J_{HH}$=15.7 Hz, CH_2), 2.67 (2H, s, CH_2), 3.77—4.65 (5H, m, 2NCH_2, CH), 7.29 (4H, br s, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 11.7, 12.9, 27.2, 28.8, 32.4, 32.9, 43.3, 45.3, 50.4, 95.8, 114.5, 128.4, 130.6, 131.7, 142.3, 152.1, 159.1, 162.9, 174.8, 196.1. *Anal.* Calcd for $C_{23}H_{25}ClN_2O_3S$: C, 62.08; H, 5.66; N, 6.30. Found: C, 62.17; H, 5.72; N, 6.39.

1,3-Diethyl-8,8-dimethyl-5-(4-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4z 74% yield. Light orange powder. mp 190 °C. IR (KBr) cm^{-1}: 2964, 2927, 2875, 1692, 1650. MS *m*/*z*: 455 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, s, CH_3), 1.07 (6H, br s, 2CH_3), 1.30—1.34 (3H, m, CH_3), 2.17, 2.29 (2H, ABq, $^3J_{HH}$=16.1 Hz, CH_2), 2.69 (2H, s, CH_2), 4.24—4.66 (4H, m, 2NCH_2), 4.77 (1H, s, CH), 7.57—8.12 (4H, m, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 11.7, 12.9, 27.3, 28.7, 32.4, 33.7, 43.3, 45.4, 50.3, 95.1, 113.9, 123.6, 130.3, 146.7, 150.7, 152.3, 159.1, 163.3, 174.9, 196.2. *Anal.* Calcd for $C_{23}H_{25}N_3O_5S$: C, 60.64; H, 5.53; N, 9.22. Found: C, 60.58; H, 5.49; N, 9.14.

Due to very low solubility of the products **4a′** we can not report the ^{13}C-NMR data for this product.

5-(4-Chlorophenyl)-1,3-diethyl-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4a′ 72% yield. White powder. mp 214 °C. IR (KBr) cm^{-1}: 3448, 3064, 2927, 1609. MS *m*/*z*: 416 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.34 (8H, br s, 2CH_3, CH_2), 1.87 (2H, br s, CH_2), 2.50 (2H, br s, CH_2), 4.05—4.39 (5H, m, 2NCH_2, CH), 6.99—7.23 (4H, m, H-Ar). *Anal.* Calcd for $C_{21}H_{21}ClN_2O_3S$: C, 60.50; H, 5.08; N, 6.72. Found: C, 6.59; H, 5.02; N, 6.64.

Due to very low solubility of the products **4b′** we can not report the ^{13}C-NMR data for this product.

1,3-Diethyl-5-(4-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4b′ 73% yield. Light yellow powder. mp 207 °C. IR (KBr) cm^{-1}: 3106, 2985, 2927, 1614. MS *m*/*z*: 427 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.08 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.99 (2H, br s, CH_2), 2.33 (2H, br s, CH_2), 2.79 (2H, br s, CH_2), 4.27—4.68 (4H, m, 2NCH_2), 4.79 (1H, s, CH), 7.47—8.13 (4H, m, H-Ar). *Anal.* Calcd for $C_{21}H_{21}N_3O_5S$: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.08; H, 4.99; N, 10.03.

1,3-Diethyl-8,8-dimethyl-5-(3-nitrophenyl)-2-thioxo-2,3,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione 4c′ 71% yield. White powder. mp 154 °C. IR (KBr) cm^{-1}: 2975, 2915, 2868, 1690, 1670. MS *m*/*z*: 455 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.96 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.14—1.18 (3H, m, CH_3), 1.30—1.34 (3H, s, CH_3), 4.25—4.53 (4H, m, 2NCH_2), 4.78 (1H, s, CH), 7.48—8.12 (4H, m, H-Ar). ^{13}C-NMR (DMSO-d_6) δ: 11.7, 12.7, 12.9, 27.1, 28.8, 32.4, 33.6, 43.3, 45.4, 50.3, 95.2, 95.8, 113.9, 121.3, 122.3, 123.6, 130.0, 135.5, 145.4, 148.0, 152.3, 159.2, 161.6, 163.4, 174.9, 196.2. *Anal.* Calcd for $C_{23}H_{25}N_3O_5S$: C, 60.64; H, 5.53; N, 9.22. Found: C, 60.71; H, 5.58; N, 9.17.

Due to very low solubility of the product **6** we can not report the ^{13}C-NMR data for this product.

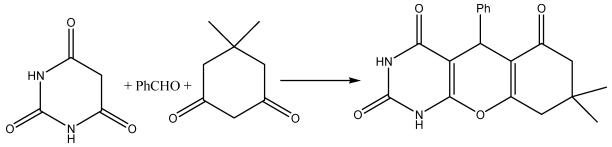
5-Phenyl-9,10-dihydropyrido[2,3-*d*:6,5-*d*]dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone 6 White powder. mp >300 °C. IR (KBr) cm^{-1}: 3230, 3089, 1691, 1668. MS *m*/*z*: 325 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 4.64 (1H, s, CH), 7.04—7.25 (5H, m, H-Ar), 9.95 (2H, s, 2NH), 10.81 (2H, s, 2NH). *Anal.* Calcd for $C_{15}H_{11}N_5O_4$: C, 55.39; H, 3.41, N, 21.53. Found: C, 55.40; H, 3.35; N, 21.42.

Results and Discussion

The choice of an appropriate reaction media is of crucial importance for successful synthesis. Initially, the three-component reaction of barbituric acid **1a**, benzaldehyde **2a** and dimedone **3a** as a simple model substrate was investigated to establish the feasibility of the strategy and optimize the reaction conditions (Table 1). Different solvents in the presence of *p*-TSA as an inexpensive and available catalyst and various Lewis acids were screened in the model reaction. As can be seen from Table 1, in the presence of *p*-TSA, ethanol is the solvent of choice for the reaction and the desired product, 8,8-dimethyl-5-phenyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione **4a**, was obtained in good yield (Entry 5), while without *p*-TSA and over long period of time (20 h) the yield of product was trace (Entry 7).

Encouraged by this success, in regard to library construction and evaluation the substrate scope of this reaction, different barbituric acids **1a**—**d**, cyclohexane-1,3-diones **3a**, **b**

Table 1. Model Reaction, Conditions, and Yields[a)]



1a **2a** **3a** **4a**

Entry	Conditions	Catalyst	Time (h)	Yield (%)
1	$CHCl_3$ (reflux)	*p*-TSA (0.3 mmol)	4	Trace
2	Water (reflux)	*p*-TSA (0.3 mmol)	4	Trace
3	CH_3CN (reflux)	*p*-TSA (0.3 mmol)	4	64
4	EtOH (reflux)	*p*-TSA (0.2 mmol)	4	63
5	EtOH (reflux)	*p*-TSA (0.3 mmol)	4	84
6	EtOH (reflux)	*p*-TSA (0.4 mmol)	4	82
7	EtOH (reflux)	—	20	Trace
8	EtOH (reflux)	LiCl (0.3 mmol)	4	Trace
9	EtOH (reflux)	$ZnCl_2$ (0.3 mmol)	4	Trace
10	EtOH (reflux)	$AlCl_3$ (0.3 mmol)	4	54

[a)] Barbituric acid (1 mmol), benzaldehyde (1 mmol), dimedone (1 mmol).

and aromatic aldehydes **2a**—**f** were employed under similar circumstances (Chart 1). Corresponding chromeno[2,3-*d*]pyrimidine-trione **4** were selectively synthesized by the three-component condensation reaction of barbituric acids **1**, aldehydes **2** and cyclohexane-1,3-diones **3** in good yields at refluxing ethanol in the presence of *p*-TSA for 3—10 h. The reaction can be represented as in Table 2. Aromatic aldehydes carrying different functional groups work satisfactorily in the reaction (Table 2). All compounds described in the paper were synthesized for the first time. Prominent among the advantages of this new method are operational simplicity, good yields, and an easy workup procedure without using any chromatographic methods.

When this reaction was carried out with an aliphatic aldehyde such as propionaldehyde or butanaldehyde in same conditions (EtOH/*p*-TSA), TLC and ^{1}H-NMR spectra of the reaction mixture showed a combination of starting materials and numerous by-products, the yield of the expected product was very poor. This can be attributed to the aldol condensation side reaction.

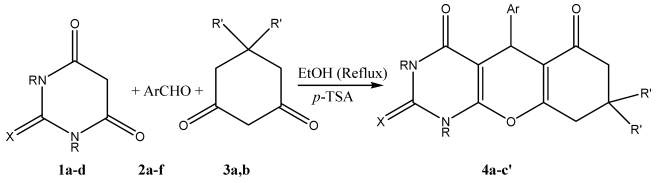


Chart 1. Synthesis of Chromeno[2,3-*d*]pyrimidinones **4**

Table 2. Chromeno[2,3-*d*]pyrimidinones **4**

Product **4**	R	R′	X	Ar	Time (h)	Yield (%)[a]
a	H	Me	O	C_6H_5	4	84
b	H	Me	O	4-Cl-C_6H_4	6	79
c	H	Me	O	4-NO_2-C_6H_4	3	85
d	H	Me	O	3-NO_2-C_6H_4	3	83
e	H	Me	O	4-Me-C_6H_4	10	73
f	H	H	O	C_6H_5	8	77
g	H	H	O	4-Cl-C_6H_4	7	74
h	H	H	O	4-NO_2-C_6H_4	6	72
i	H	H	O	3-NO_2-C_6H_4	6	81
j	Me	Me	O	C_6H_5	6	74
k	Me	Me	O	4-NO_2-C_6H_4	6	79
l	Me	Me	O	3-NO_2-C_6H_4	6	81
m	Me	Me	O	4-Br-C_6H_4	6	78
n	Me	H	O	4-Cl-C_6H_4	8	65
o	Me	H	O	4-NO_2-C_6H_4	7	70
p	Me	H	O	3-NO_2-C_6H_4	8	68
q	H	Me	S	C_6H_5	8	73
r	H	H	S	C_6H_5	8	70
s	H	Me	S	4-NO_2-C_6H_4	6	80
t	H	H	S	4-NO_2-C_6H_4	6	81
u	H	Me	S	3-NO_2-C_6H_4	6	81
v	H	H	S	3-NO_2-C_6H_4	6	81
w	H	Me	S	4-Br-C_6H_4	8	78
x	Et	Me	S	C_6H_5	8	72
y	Et	Me	S	4-Cl-C_6H_4	8	70
z	Et	Me	S	4-NO_2-C_6H_4	7	74
a′	Et	H	S	4-Cl-C_6H_4	8	72
b′	Et	H	S	4-NO_2-C_6H_4	7	73
c′	Et	Me	S	3-NO_2-C_6H_4	7	71

[a] Isolated yields.

Compounds **4** are stable solids whose structures were established by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and elemental analysis.

Finally, in order to investigate the formation of by-products in the reaction, we examined the reaction of barbituric acid **1a**, benzaldehyde **2a** and dimedone **3a** in the optimized conditions. Besides chromeno[2,3-*d*]pyrimidine-trione **4a** (84%) as the main product, by-product **6** also identified in 10%. The by-product **6** was thought to be produced from the reaction of heterodienes **5** and barbituric acid **1a**. Although by-product **7** seems to be a reasonable candidate, we did not identify it in the reaction (Chart 2).

Therefore, the formation of products **4** can be rationalized by initial formation of heterodiene **5** by standard Knoevenagel condensation of barbituric acids **1** and aromatic aldehydes **2**. Subsequent Michael-type addition of cyclohexane-1,3-diones **3** to the heterodienes **5**, followed by cyclization afforded the corresponding products **4** and water (Chart 3).[44,52—54]

Conclusion

In conclusion, an efficient, one-pot and simple method for the preparation of chromeno[2,3-*d*]pyrimidinones using readily available starting materials is reported. Prominent among the advantages of this new method are operational simplicity, good yields and easy work-up procedures employed. Further reactivity studies and synthetic application of this methodology are in progress in our laboratory.

Acknowledgements We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

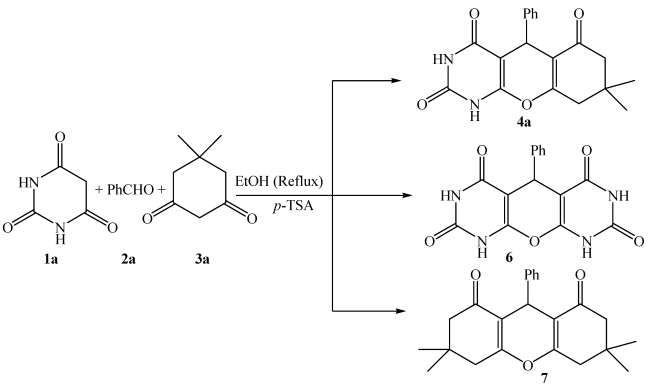


Chart 2. Probable Products of the Reaction

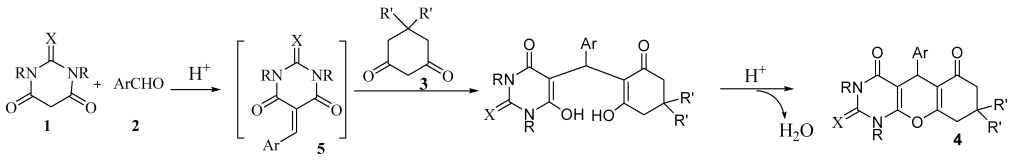


Chart 3. Proposed Mechanism of the Reaction

References and Notes

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