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ORIGINAL PAPER

Synthesis of new derivatives of pyrazol-chromeno[2,3-d] pyrimidine-ones by a one-pot three-component reaction

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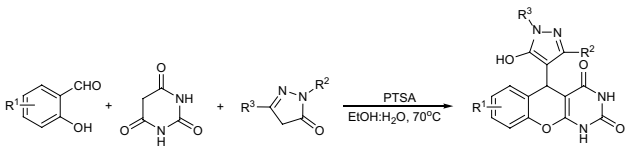
Abstract A new three-component reaction between salicylaldehydes, barbituric acid, pyrazolones, in the presence of para-toluenesulfonic acid, efficiently provides pyrazol-chromeno[2,3-d]pyrimidine-ones derivatives in good yields in ethanol/water at 70 °C. This multicomponent reaction showed high atom economy.

Graphical Abstract



Keywords Chromeno[2,3-d]pyrimidine · Multicomponent reactions · Salicylaldehyde · Barbituric acid · PTSA

Introduction

Multicomponent reactions (MCRs), because of their productivity, simple procedures, time-saving manner, convergence, and facile execution, are one of the best tools in combinatorial chemistry [1–7]. MCRs, particularly those performed in aqueous media, have become increasingly useful tools for the synthesis of chemically and biologically important compounds because of their environmentally friendly atom economy and green characteristics [1–7].

Among the wide variety of heterocycles that have been explored for developing potential pharmacologically active compounds, pyrazoles fused with different heterocycles that are known to contribute to various chemotherapeutic effects have emerged as antimicrobial [8, 9], antifungal [10], and antiviral agents [11]. In addition, some fused pyrazole derivatives were reported to induce various antileukemic [12], antitumor [13, 14], and antiproliferative [15, 16] activities.

The benzopyrano[2,3-d]pyrimidines are organic compounds which are constructed from two fused benzopyran and pyrimidine rings which exhibit extremely diverse biological and pharmaceutical activities [17–28]. The benzopyrans (4H-chromene) have shown a wide range of biological activities such as anti-HBV, cytotoxic [17], antibacterial [18], antioxidant [19], antigenotoxic [20], ATP sensitive potassium channel openers [21], and antiangiogenic activity [22]. On the other hand, pyrimidine scaffold is the base of many bioactive molecules such as antitubercular [23], antibacterial [24], antitumor [25], antiinflammatory [26], antifungal [27], and antileishmanial agent [28]. Consequently, synthetic methodologies for the synthesis of novel benzopyrano[2,3-d]pyrimidine [28] are of particular interests to organic and medicinal chemists.

Recently, we described the synthesis of alkyl-1H-chromeno[2,3-d]pyrimidine-5-carboxamides via a new three-component reaction of isocyanide, barbituric acid, and a salicylaldehyde in the presence of acetic acid in ethanol/water mixture at 75 °C [29]. Herein, we aim to expand the versatility of the reaction using pyrazolones instead of isocyanides. Therefore, we examined the reaction between the salicylaldehydes **1**, barbituric acid **2**, and pyrazolones **3**

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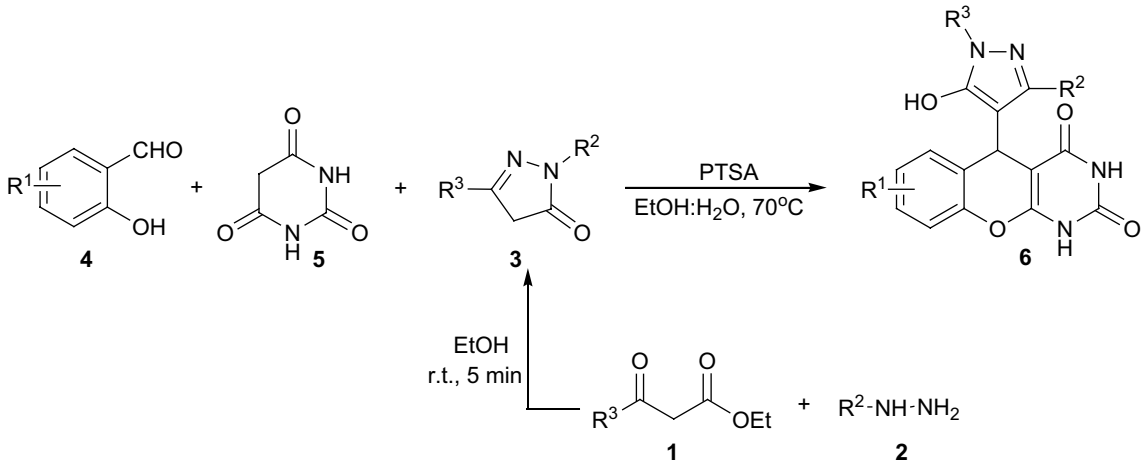
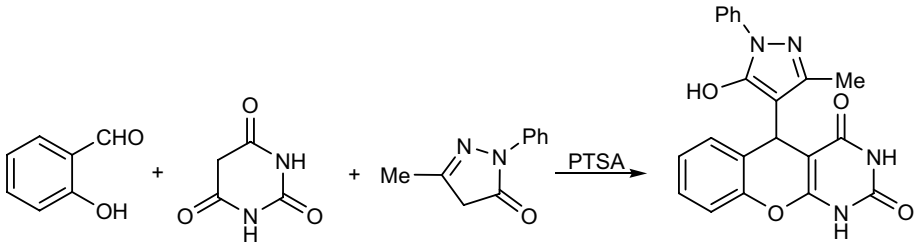


Scheme 1 Synthesis of pyrazol-chromeno[2,3-d]pyrimidine-ones

Table 1 Optimization of the reaction



Entry	Solvent	Temperature	Yield (%)
1	Water	70	80
2	Ethanol	70	30
3	Methanol	70	70
4	Ethyl acetate	70	85
5	Acetonitrile	70	80
6	Toluene	70	Trace
7	Dichloromethane	25	Trace
8	Water/ethanol (4:1)	70	95
9	Water/ethanol (2:1)	70	80
10	Water/Ethanol (1:1)	70	70
11	Water/ethanol (4:1)	25	40
12	Water/ethanol (4:1)	50	75
13	Water/ethanol (4:1)	100	95

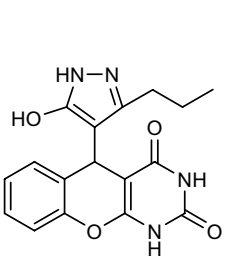
[a] The reaction was carried out by salicylaldehyde (1.0 mmol), barbituric acid (1.0 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one (1.0 mmol) catalyzed by PTSA in different solvents and temperature

[b] Isolatedyiled

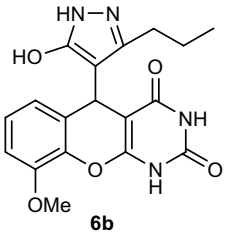
in the presence of PTSA in mixture of water/ethanol (4:1) at 70 °C (Scheme 1). It should be noted that pyrazolone **3** was synthesized by the condensation between β-keto esters **1** and hydrazines **2** in ethanol after 5 min and purified before used in above reaction [30].

For optimization reaction, we achieved effect of solvents and temperature on the yield of the reaction. Therefore, the reaction of salicylaldehyde and barbituric acid with 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one in the presence

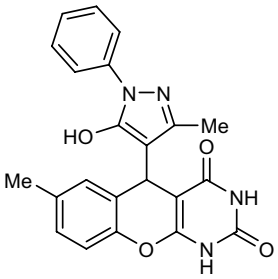
Table 2 Synthesis of pyrazol-chromeno[2,3-d]pyrimidine-ones derivatives



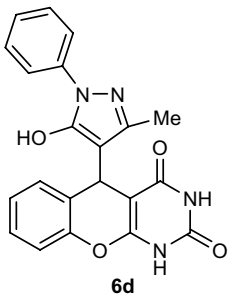
6a



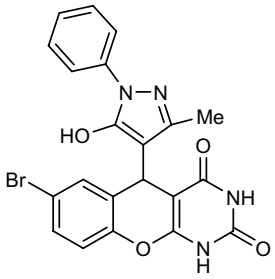
6b



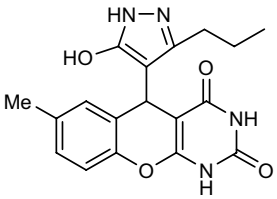
6c



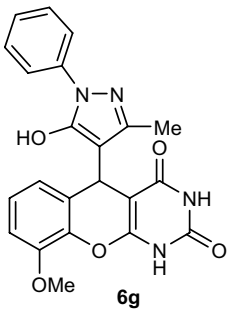
6d



6e



6f

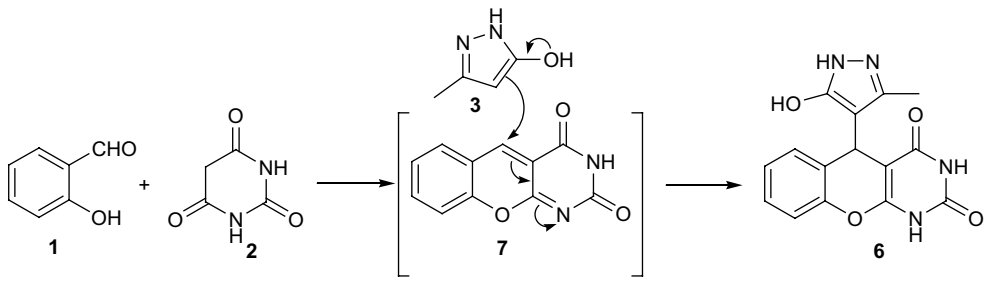


6g

Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	Pr	H	**6a**	83
2	H	Pr	MeO	**6b**	60
3	Ph	Me	Me	**6c**	89
4	Ph	Me	H	**6d**	95
5	Ph	Me	Br	**6e**	91
6	H	Pr	Me	**6f**	87
7	Ph	Me	MeO	**6g**	60

[a] The reaction was carried out by salicylaldehydes (1.0 mmol), barbituric acid (1.0 mmol), and pyrazolones (1.0 mmol) catalyzed by PTSA in water/ethanol (4:1) at 70 °C

[b] Isolatedyiled



Scheme2 Proposed mechanism

and PTSA was selected as a model reaction. We first investigated the model reaction rate in different solvents by measuring the isolated yield using identical amounts of reactants in the presence of 10 % mol of PTSA for a fixed reaction time of 12 h at 70 °C (Table 1, entries 1–8). The desired product was obtained in polar solvents, such as water, ethanol and methanol, ethyl acetate, and acetonitrile but water can afford the product in good yield even better than other solvents (Table 1, entry 8). It was found that addition of ethanol to the water solution can improve the reaction

outcome and interestingly (Table 1, entries 8–10) when the reaction was performed in water/ethanol mixture (4:1) the corresponding product was obtained qualitatively (Table 1, entry 8). The desired product was not obtained in non-polar solvents, such as dichloromethane, toluene (Table 1, entries 6–7). This effect can be explained by a simple acid catalysis mechanism facilitated by the strong hydrogen bond interaction at the organic-water interface, which stabilizes the reaction intermediate. Next, we studied the model reaction in water/ethanol mixture (4:1) at different temperatures (entry 8 and entries 11–13). The reaction rate increased as the temperature was raised. At 70 °C, the maximum yield (93 %) was obtained in a reaction time of 12 h (entry 8).

With the optimized condition established above, we next attempted to extend the process to four different salicylaldehydes (3-methoxy, 5-methyl and 5-bromosalicylaldehyde and salicylaldehyde) and various types of pyrazolones. The results have been summarized in Table 2. The structures of the products were established by different spectroscopic methods (for details see Experimental section). In all cases, good yields were obtained, whatever the nature of the subsistent present on the salicylaldehyde (electron donating or electron withdrawing). The structure of the products was deduced from ^{1}H NMR and ^{13}C NMR spectra (see the experimental section).

To explore the scope and limitations of this process, we further examined the reactions of various withdrawing groups of salicylaldehydes such as 5-nitrosalicylaldehyde, 3-nitrosalicylaldehyde, 5-fluorosalicylaldehyde, and 3,5-difluorosalicylaldehyde under reaction condition. However, in all these cases, the desired products **6** were not formed.

Mechanistically, it is conceivable that the reaction involves the initial formation of the activated alkene (benzopyran ring) **7** through a Knoevenagel condensation of salicylaldehydes 1 and barbituric acid 2. Benzopyran ring **7** undergoes nucleophilic addition with the pyrazolone **3** followed tautomerization to afford 4 (Scheme 2).

In conclusion, we have developed a new pyrazolone-based MCRs for the synthesis of a wide range of pyrazol-chromeno[2,3-d]pyrimidine-ones from salicylaldehydes and barbituric acid with pyrazolones. This high yielding reaction has been shown to display a good functional group tolerance, while the product isolation is very straightforward. We hope that this approach may be valuable to others seeking for novel synthetic fragments with unique properties for medicinal chemistry programs.

General procedure for synthesis of pyrazol-chromeno[2,3-d]pyrimidine-ones (6a–g)

A solution of salicylaldehyde (1 mmol) and barbituric acid (1 mmol) in ethanol/water (1:4) (5 mL) was stirred at 70 °C. After 2 h, PTSA (0.1 mmol) and pyrazolones (1 mmol) were added and stirred for 10 h at 70 °C (pyrazolone derivatives made of hydrazine hydrate and alkyl acetoacetate in ethanol at room temperature in 5 min). After completion of the reaction, as indicated by TLC, the precipitate was washed with ethanol and the products were obtained as a white powder.

5-(5-Hydroxy-3-propyl-4, 5-dihydro-1*H*-pyrazol-4-yl)-1*H*-chromeno[2, 3-d]pyrimidine-2, 4(3H, 5H)-dione (6a)

White powder (0.28 g, yield 83 %); mp 226–228 °C. IR (KBr) (ν_{max}/cm^{-1}): 3398 (NH), 1725 (C=O), 1647, 1597. MS, *m/z*: 340 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 0.9 (3H, t, $^{3}J_{HH} = 7.2$ Hz, CH_3), 1.52 (2H, m, CH_2) 2.50 (2H, t, $^{3}J_{HH} = 7.2$ Hz, CH_2), 3.40 (OH exchanged with water of DMSO-d_6), 4.77 (1H, s, CH), 7.05–7.24 (4H, m, H-Ar), 10.92 (3H, s, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 13.7 (CH_3), 22.0 (CH_2), 25.6 (CH_2), 26.3 (CH), 87.3 (C=C–OH), 115.7 (C=C–O), 124.6, 125.1, 125.3, 127.6, 129.6, 129.7, 142.0, 148.5, 153.6, 158.91, 163.2. Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.96; H, 4.73; N, 16.44.

5-(5-Hydroxy-3-propyl-1*H*-pyrazol-4-yl)-9-methoxy-1*H*-chromeno[2,3-d]pyrimidine-2, 4(3H, 5H)-dione (6b)

White powder (0.22 g, yield 60 %); mp 279 °C. IR (KBr) (ν_{max}/cm^{-1}): 3397 (NH), 1720 (C=O), 1643, 1596. MS, *m/z*: 370 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 0.86 (3H, t, $^{3}J_{HH} = 7.2$ Hz, CH_3), 1.50 (2H, m, CH_2), 2.50 (2H, t, $^{3}J_{HH} = 7.2$ Hz, CH_2), 3.40 (OH exchanged with water of DMSO-d_6), 3.83 (3H, s, OCH_3), 4.74 (1H, s, CH), 6.67–7.06 (3H, m, H-Ar), 10.88, 11.69, 11.78 (3H, 3s, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 13.9 (CH_3), 22.2 (CH_2), 25.7 (CH_2), 26.3 (CH), 55.7 (OCH_3), 87.2 (C=C–OH), 110.2 (C=C–O), 120.7, 123.2, 124.8, 125.4, 129.3, 138.1, 146.9, 149.5, 153.8, 161.2, 163.3. Anal. Calcd for $C_{18}H_{18}N_4O_5$: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.38; H, 4.91; N, 15.16.

5-(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7-methyl-1*H*-chromeno[2,3-d]pyrimidine-2, 4(3H, 5H)-dione (6c)

White powder (0.35 g, yield 89 %); mp 245 °C. IR (KBr) (ν_{max}/cm^{-1}): 3397 (NH), 1727 (C=O), 1641, 1594. MS, *m/z*: 402 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.74 (3H, s, CH_3), 2.22 (3H, s, CH_3), 4.69 (1H, s, CH), 6.93–7.63 (8H, m, H-Ar), 10.70, 10.90, 11.76 (3H, 3s, OH, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 20.2 (CH_3), 26.1 (CH_3), 29.5 (CH), 80.2 (C=C–OH), 114.8

(C=C–O), 115.5, 117.9, 123.0, 124.3, 128.8, 129.5, 135.4, 138.9, 146.9, 149.6, 152.7, 154.4, 154.4, 163.3, 165.1. Anal. Calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.65; H, 4.53; N, 13.94.

5-(5-Hydroxy-3-methoxy-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-chromeno[2,3-d]pyrimidine-2, 4(3H, 5H)-dione (6d)

White powder (0.37 g, yield 95 %); mp 285–288 °C. IR (KBr) (ν_{max}/cm^{-1}): 3389 (NH), 1788 (C=O), 1486, 1644. MS, *m/z*: 388 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.34 (3H, s, CH_3), 3.35 (OH exchanged with water of DMSO-d_6), 4.72 (1H, s, CH), 7.04–7.67 (9H, m, H-Ar), 10.80, 10.93 (2H, 2s, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 12.8 (CH_3), 26.3 (CH), 87.3 (C=C–OH), 109.5 (C=C–O), 115.6, 117.8, 120.6, 123.3, 124.0, 128.1, 125.1, 127.8, 128.7, 129.5, 137.1, 146.9, 149.6, 154.4, 163.2. Anal. Calcd for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43. Found: C, 64.95; H, 4.16; N, 14.44.

7-Bromo-5-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-chromeno[2,3-d]pyrimidine-2, 4(3H, 5H)-dione (6e)

White powder (0.35 g, yield 91 %); mp 282 °C. IR (KBr) (ν_{max}/cm^{-1}): 3389 (NH), 1716 (C=O), 1662, 1075. MS, *m/z*: 467 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.38 (3H, s, CH_3), 4.76 (1H, s, CH), 6.99–7.72 (H-Ar), 10.84, 10.98 (2H, 2s, NH), 11.67 (1H, s, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 10.8 (CH_3), 26.2 (CH), 84.8 (C=C–OH), 107.5 (C=C–O), 115.0, 117.9 108.7, 124.2, 126.3, 128.8, 130.7, 131.8, 140.1, 143.4, 149.5, 154.1, 158.8, 163.4, 168.4. Anal. Calcd for $C_{21}H_{15}BrN_4O_4$: C, 53.98; H, 3.24; N, 11.99. Found: C, 53.94; H, 3.24; N, 11.96.

5-(5-hydroxy-3-propyl-1*H*-pyrazol-4-yl)-7-methyl-1H-chromeno[2,3-d]pyrimidine-2, 4(3H, 5H)-dione (6f)

White powder (0.31 g, yield 87 %); mp 246 °C. IR (KBr) (ν_{max}/cm^{-1}): 3399 (NH), 1721 (C=O), 1643, 1591. MS, *m/z*: 354 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 0.98 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.49 (2H, m, CH_2), 2.20 (3H, s, CH_3), 2.50 (2H, t, $^3J_{HH}$ = 7.2 Hz, CH_2), 3.34 (OH exchanged with water of DMSO-d_6), 4.72 (1H, s, CH), 6.91–7.03 (3H, m, H-Ar), 10.00 (3H, s, 3NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 13.9 (CH_3), 20.3 (CH_3), 22.0 (CH_2), 25.7 (CH), 26.4 (CH_2), 87.3 (C=C–OH), 104.9 (C=C–O), 115.5, 124.3, 128.1, 129.7, 129.8, 134.0, 146.6, 149.6, 153.9, 163.3, 164.0. Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.07; H, 5.10; N, 15.82.

5-(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-9-methoxy-1*H*-chromeno[2,3-d]pyrimidine-2,4(3H,5H)-dione (6g)

White powder (0.25 g, yield 60 %); mp 269 °C. IR (KBr) (ν_{max}/cm^{-1}): 3398 (NH), 1722 (C=O), 1630, 1591. MS, *m/z*: 418 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.32 (3H, s, CH_3), 3.34 (OH exchanged with water of DMSO-d_6), 3.83 (3H, s, OCH_3), 4.73 (1H, s, CH), 6.76–7.63 (8H, m, H-Ar), 10.79, 10.95 (2H, 2s, 2NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 14.3 (CH_3), 26.2 (CH), 55.7 (OCH_3), 87.0 (C=C–OH), 106.0 (C=C–O), 106.5, 110.6, 110.7, 119.0, 120.7, 124.1, 124.4, 124.5, 128.8, 146.9, 149.5, 151.7, 154.3, 163.6, 165.9. Anal. Calcd for $C_{22}H_{18}N_4O_5$: C, 63.15; H, 4.34; N, 13.39. Found: C, 63.14; H, 4.34; N, 13.37.

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