

Original Research Article

One-pot, four component synthesis of pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines derivatives

Ramin Javahershenas* , Jabbar Khalafy

Faculty of Chemistry, Urmia University, 5756151818, Urmia, Iran

ARTICLE INFORMATION

Received: 6 March 2018

Received in revised: 7 April 2018

Accepted: 7 April 2018

Available online: 19 May 2018

DOI: [10.22034/ajgc.2018.62714](https://doi.org/10.22034/ajgc.2018.62714)

KEYWORDS

β -Aminocrotonitrile

Arylglyoxal

1,3-Dimethylbarbituric acid

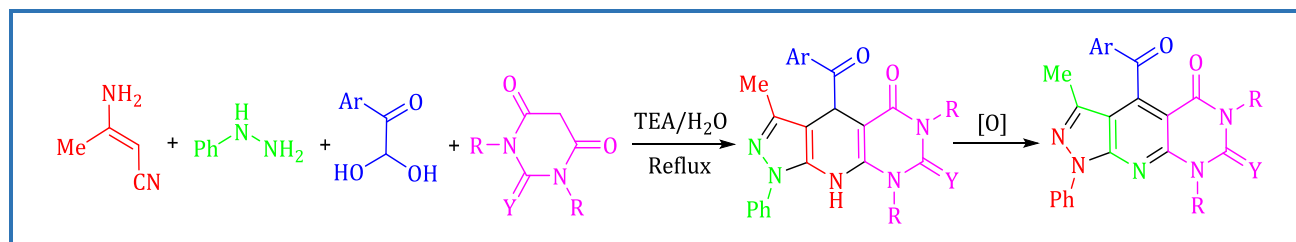
Thiobarbituric acid

TEA (triethylamine)

ABSTRACT

A green approach to synthesis of the polyfunctionalized pyrazole [4',3':5,6]pyrido[2,3-d] pyrimidines derivatives was successfully achieved *via* one-pot, four component reactions of β -aminocrotonitrile, phenylhydrazine, arylglyoxals, barbituric acid derivatives in the presence of TEA (Triethylamine) as a catalyst in water under the reflux conditions. This protocol provided mild reaction conditions, short reaction times, high yields, low cost, easy isolation of products and possible biological, and pharmaceutical activities.

Graphical Abstract



Introduction

One-pot, multicomponent reactions (MCRs) has attracted a great deal of attention from the researchers working on synthesis of the polycyclic heterocyclic compounds with biological and pharmaceutical activities [1–2]. Analysis of drugs on the market shows that more than 70% of them are heterocyclic compounds [3–4].

The pyrazole derivatives have attracted more attention than the other derivatives by synthetic as well as medicinal and pharmaceutical chemists. The pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidines derivatives have wide range of medicinal and biological applications such as antitumor [5–6], antiviral [7], antioxidant [8], antibacterial and antifungal [9], antiasthmatics and antiallergic [10], antihypertensive [11] and antibronchitic [12] activities.

In continuation of our interests in the synthesis of new heterocyclic compounds by one-pot, multicomponent reactions [13–20], herein, we report a one-pot, four component reaction of β -aminocrotonitrile, phenylhydrazine, arylglyoxals and barbituric acid derivatives in the presence of TEA as a catalyst in water under reflux conditions to afforded the corresponding pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine derivatives in high yields.

Experimental

Materials and methods

The chemicals used in this study were purchased from Acros and Merck companies and used without conducting any purification. Freshly distilled solvents were used throughout and anhydrous solvents were dried according to the Perrin and Armarego [21]. Melting points were measured using an Electrothermal 9200 apparatus. FT-IR (KBr) spectra were recorded by a Thermo Nicolet (Nexus 670) spectrometer using KBr discs. ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer in $\text{DMSO-}d_6$ with TMS as the internal reference. Elemental analyses were performed using a Leco Analyzer 932. The arylglyoxals were prepared as their hydrates by oxidation of the corresponding acetophenones with SeO_2 [18].

*General procedure for synthesis of the pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*)-dione derivatives*

A mixture of β -aminocrotonitrile (1 mmol), phenyl hydrazine (1.2 mmol), barbituric acid derivatives (1 mmol) and various arylglyoxals (1 mmol), in the presence of TEA (0.1 mL) was heated under reflux in water (5 mL). The progress of reaction was monitored by TLC (Ethyl acetate/*n*-hexan, 7:3). Upon the completion of reaction, the mixture was cooled and HCl (0.05 mL) was added to neutralize the triethylamine. Upon this neutralization, the final product was precipitated and the

product was easily isolated by simple filtration. The pure products were obtained by recrystallization from dichloromethane. All the products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples. The physical and spectral data for the all new products as well as their elemental analyses were reported.

The selected spectral data

3,6,8-Trimethyl-4-(4-methylbenzoyl)-1-phenyl-1,8-dihydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione (5f)

Pale yellow crystals, yield 0.37 g (85%), mp 236–237 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3062, 2927, 2860, 1715, 1667, 1584, 1505, 1420, 1375, 1267, 1138, 1070, 1025, 756, 577, and 498. ^1H NMR (300 MHz, DMSO- d_6): δ 8.27 (d, $J = 8.1$ Hz, 2H, Ar), 7.86 (d, $J = 7.5$ Hz, 2H, Ar), 7.69 (t, $J = 7.2$ Hz, 1H, Ar), 7.63–7.55 (m, 4H, Ar), 3.81 (3H, s, CH₃), 3.54 (3H, s, CH₃), 3.39 (3H, s, CH₃), 2.25 (3H, s, CH₃). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 193.4, 161.6, 151.6, 151.0, 150.5, 145.1, 143.1, 138.9, 133.1, 130.8, 129.8, 129.8, 129.1, 129.1, 126.5, 114.4, 106.1, 30.1, 28.6, 21.8, 12.5. Anal. Calcd. For C₂₁H₁₃N₃O₅: C, 68.33; H, 4.82; N, 15.94; Found: C, 68.40; H, 4.72; N, 15.12.

4-(4-Chlorobenzoyl)-3,6,8-trimethyl-1-phenyl-1,8-dihydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-dione (5g)

Pale yellow crystals, yield 0.38 g (82%), mp 242–243 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3072, 2932, 2860, 1710, 1670, 1580, 1515, 1425, 1375, 1272, 1145, 1065, 1020, 755, 578, and 498. ^1H NMR (300 MHz, DMSO- d_6): δ 8.27 (d, $J = 8.1$ Hz, 2H, Ar), 8.24 (d, $J = 8.4$ Hz, 2H, Ar), 7.80 (t, $J = 8.1$ Hz, 1H, Ar), 7.60–7.40 (m, 4H, Ar), 3.86 (3H, s, CH₃), 3.34 (3H, s, CH₃), 2.26 (3H, s, CH₃). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 191.9, 160.6, 151.2, 150.7, 150.1, 147.2, 144.3, 138.6, 132.7, 132.7, 131.5, 131.4, 129.2, 126.5, 120.9, 11.7, 103.4, 30.4, 28.6, 13.7. Anal. Calcd. For C₂₅H₂₁N₃O₃ C, 62.68; H, 3.95; N, 15.23; Found: C, 62.60; H, 3.12; N, 15.30.

4-Benzoyl-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5h)

White crystals, yield 0.31 g (79%), mp 273–274 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3374, 3203, 3066, 2930, 2857, 1707, 1667, 1584, 1505, 1419, 1377, 1269, 1140, 1068, 1021, 756, 576, and 492. ^1H NMR (300 MHz, DMSO- d_6): δ 13.41 (s, 1H, exchanged by D₂O addition, NH), 12.62 (s, 1H, exchanged by D₂O addition, NH), 8.31 (d, $J = 7.8$ Hz, 2H, Ar), 7.86 (d, $J = 7.5$ Hz, 2H, Ar), 7.69 (t, $J = 7.2$ Hz, 1H, Ar), 7.63–7.55 (m, 4H, Ar), 7.37 (t, $J = 7.2$ Hz, 1H, Ar), 2.10 (3H, s, CH₃). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 193.4,

176.7, 159.7, 151.7, 151.2, 146.1, 144.0, 138.8, 136.2, 134.7, 129.7, 129.5, 129.3, 126.7, 120.8, 112.1, 106.0, 13.8. Anal. Calcd. For C₂₂H₁₅N₅O₂S: C, 65.29; H, 4.34; N, 15.86; Found: C, 65.19; H, 4.42; N, 15.90.

4-(4-Fluorobenzoyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5i)

White crystals, yield 0.59 g (81%), mp 268–269 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3365, 3198, 3066, 2922, 1667, 1491, 1359, 1312, 1232, 1191, 1098, 1031, 907, 876, 752, 614, and 573. ¹H NMR (300 MHz, DMSO-d₆): δ 13.44 (s, 1H, exchanged by D₂O addition, NH), 12.65 (s, 1H, exchanged by D₂O addition, NH), 8.74–8.69 (2H, m, Ar), 8.00–7.90 (1H, m, Ar), 7.70–7.50 (2 H, m, Ar), 7.41 (1H, t, $J = 7.5$ Hz, Ar), 7.40–7.20 (2H, m, Ar), 7.21 (1H, t, $J = 8.4$ Hz, Ar), 2.31 (3H, s, CH₃). ¹³C NMR (75.5 MHz, DMSO-d₆): δ 192.0, 170.4, 154.9, 152.7, 145.1, 132.1, 129.5, 129.1, 129.1, 129.1, 127.2, 126.5, 121.1, 117.6, 116.3, 115.6, 115.1, 13.8. Anal. Calcd. For C₂₂H₁₄FN₅O₂S: C, 62.73; H, 3.95; N, 15.24; Found: C, 62.62; H, 3.82; N, 15.30.

3-Methyl-4-(4-nitrobenzoyl)-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5j)

Pale yellow crystals, yield 0.38 g (85%), mp 284–285 °C; IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3419, 3312, 3070, 2940, 2881, 1715, 1670, 1591, 1524, 1421, 1362, 1276, 1241, 1152, 1119, 1079, 1025, 977, 875, 830, 794, 756, 692, and 587. ¹H NMR (300 MHz, DMSO-d₆): δ 13.40 (s, 1H, exchanged by D₂O addition, NH), 12.61 (s, 1H, exchanged by D₂O addition, NH), 8.33 (2H, d, $J = 8.1$ Hz, Ar), 8.21 (2H, d, $J = 7.5$ Hz, Ar), 8.00 (2H, d, $J = 8.1$ Hz, Ar), 7.55 (2H, t, $J = 7.5$ Hz, Ar), 7.35 (1H, t, $J = 7.5$ Hz, Ar), 2.26 (3H, s, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆): δ 192.2, 171.2, 152.1, 151.1, 150.8, 150.2, 146.1, 144.2, 141.1, 138.1, 129.8, 129.2, 126.8, 125.1, 122.0, 112.1, 104.5, 13.8. Anal. Calcd. For C₂₂H₁₄N₆O₄S: C, 59.25; H, 3.73; N, 17.27; Found: C, 59.18; H, 3.82; N, 17.33.

4-(4-Methoxybenzoyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5k)

White crystals, yield 0.32 g (76%), mp 290–291 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3432, 3347, 3065, 2938, 2872, 1670, 1585, 1493, 1422, 1363, 1259, 1165, 1067, 1020, 977, 896, 841, 757, 675, 588, and 493. ¹H NMR (300 MHz, DMSO-d₆): δ 13.46 (s, 1H, exchanged by D₂O addition, NH), 12.63 (s, 1H, exchanged by D₂O addition, NH), 8.24 (2H, d, $J = 8.1$ Hz, Ar), 7.88 (2H, d, $J = 7.5$ Hz, Ar), 7.57 (2H, t, $J = 8.1$ Hz, Ar), 7.35 (1H, t, $J = 7.5$ Hz, Ar), 7.18 (2H, d, $J = 8.1$ Hz, Ar), 3.89 (3H, s, OCH₃), 2.26 (3H, s, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆): δ 192.7, 172.3, 151.2, 150.7, 150.6, 146.3, 140.8, 138.5, 134.5, 130.0, 129.5, 129.2, 126.6, 120.9, 114.6, 111.7, 103.4, 55.9, 13.8. Anal. Calcd. For C₂₃H₁₇N₅O₃S: C, 63.68; H, 4.49; N, 14.85; Found: C, 63.75; H, 4.56; N, 14.76.

4-(3,4-Dimethoxybenzoyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5l)

White crystals, yield 0.40 g (88%), mp 264–265 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3526, 3416, 3070, 2927, 2855, 1711, 1671, 1587, 1509, 1422, 1381, 1273, 1145, 1070, 1025, 761, 582, and 499. ^1H NMR (300 MHz, DMSO- d_6): δ 13.45 (s, 1H, exchanged by D₂O addition, NH), 12.66 (s, 1H, exchanged by D₂O addition, NH), 8.27 (2H, d, J = 7.8 Hz, Ar), 7.80 (1H, bs, Ar), 7.57 (2H, t, J = 7.8 Hz, Ar), 7.37 (1H, t, J = 7.5 Hz, Ar), 7.06 (1H, d, J = 7.2 Hz, Ar), 6.79 (1H, d, J = 8.4 Hz, Ar), 3.92 (3 H, s, OCH₃), 3.84 (3 H, s, OCH₃), 2.25 (3 H, s, CH₃). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 182.1, 170.1, 155.1, 151.8, 151.1, 149.6, 148.2, 144.9, 143.9, 130.1, 129.5, 126.8, 121.8, 118.8, 119.1, 114.5, 112.0, 111.0, 110.0, 64.7, 58.1, 13.7. Anal. Calcd. For C₂₄H₁₉N₅O₄S: C, 62.26; H, 4.62; N, 13.96; Found: C, 62.21; H, 3.69; N, 14.13.

3-Methyl-4-(4-methylbenzoyl)-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5m)

Pale yellow crystals, yield 0.35 g (81%), mp 260–261 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3365, 3207, 3070, 2935, 2878, 1716, 1670, 1581, 1515, 1421, 1362, 1273, 1233, 1167, 1121, 1073, 1020, 979, 871, 830, 790, 751, 695, and 582. ^1H NMR (300 MHz, DMSO- d_6): δ 13.42 (s, 1H, exchanged by D₂O addition, NH), 12.64 (s, 1H, exchanged by D₂O addition, NH), 8.40 (2H, d, J = 7.5 Hz, Ar), 8.27 (1H, d, J = 7.5 Hz, Ar), 7.70 (2H, d, J = 7.2 Hz, Ar), 7.60–7.40 (4H, m, Ar), 3.35 (3H, s, CH₃), 2.30 (3H, s, CH₃). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 192.1, 171.8, 152.5, 151.2, 151.0, 151.2, 144.9, 144.2, 141.1, 139.1, 129.2, 129.0, 125.9, 125.1, 121.2, 111.9, 103.8, 21.9, 13.5. Anal. Calcd. For C₂₃H₁₇N₅O₂S: C, 65.92; H, 4.65; N, 15.37; Found: C, 66.11; H, 3.52; N, 15.42.

4-(4-Chlorobenzoyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidin-5-one (5n)

Pale yellow crystals, yield 0.34 g (79%), mp 276–277 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3405, 3271, 3068, 2926, 1729, 1669, 1584, 1491, 1440, 1359, 13232, 1093, 1019, 861, 755, 650, and 564. ^1H NMR (300 MHz, DMSO- d_6): δ 13.44 (s, 1H, exchanged by D₂O addition, NH), 12.65 (s, 1H, exchanged by D₂O addition, NH), 8.39 (d, J = 8.4 Hz, 2H, Ar), 8.25 (d, J = 8.4 Hz, 1H, Ar), 7.83 (t, J = 8.1 Hz, 1H, Ar), 7.70–7.60 (m, 3H, Ar), 7.37 (t, J = 7.2 Hz, 2H, Ar), 2.23 (3H, s, CH₃). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 192.7, 175.8, 160.17, 152.1, 151.4, 146.2, 144.0, 139.0, 136.71, 134.9, 129.8, 129.5, 128.9, 125.9, 121.0, 112.1, 106.1, 13.8. Anal. Calcd. For C₂₂H₁₄ClN₅O₂S: C, 60.57; H, 3.81; N, 14.71; Found: C, 60.48; H, 3.92; N, 14.80.

Results and discussion

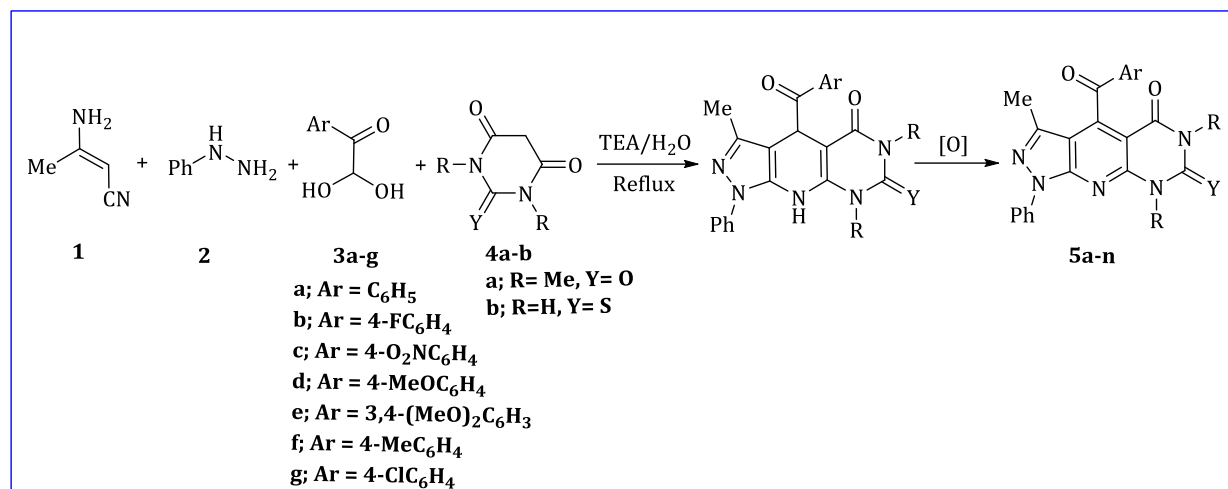
The results revealed that the reaction of the β -aminocrotonitrile **1** and phenylhydrazine hydrate **2** arylglyoxals **3a–g** with barbituric acid derivatives **4a–b** using trimethylamine (TEA) as a catalyst under reflux in water as solvent provide the corresponding pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine derivatives **5a–n** in high yields (Scheme 1).

Water plays a vital role as a green solvent and it is also the best alternative to organic solvents in this protocol. This is due to the fact that the water is inexpensive, nontoxic, non-flammable, highly polar, and environmentally benign without any carcinogenic effects. In addition, we used triethylamine as a commercially available weak basic catalyst, which has been successfully used in catalyzed Knoevenagel condensation and Michael addition reaction.

In our initial studies, the reaction of β -aminocrotonitrile **1**, phenylhydrazine **2**, arylglyoxal **3a** and 1,3-dimethylbarbituric acid **4a** was chosen as a model reaction (Table 1). First we carried out this model reaction in the absence of catalyst, and we did not observe any product even after 24 h of stirring at room temperature (Table 1, entry 1) or refluxing the reaction mixture in water without any catalyst for 2 h (Table 1, entry 2). When we added 5 and 10 mol% of TEA as catalyst, the yield was improved (Table 1, entry 9 and 10). By using 15 mol% of TEA and refluxing the reaction mixture for 2 h, the yield of reaction was decreased to 72% (Table 1, entry 13). The best result was obtained in terms of yield 83% and reaction time 2 h when 10 mol% of TEA (Table 1, entry 10). The products were fully characterized by their FT-IR and ^1H NMR and ^{13}C NMR spectral data.

To find the best solvent for this reaction, we repeated the same model reaction by using various solvents such as acetonitrile (MeCN), dichloromethane (DCM), tetrahydrofuran (THF), and water. Among all these solvents, water was proved to be the best solvent for this reaction in terms of yield and reaction time (Table 2, entry 6). In conclusion, when the reaction was performed in the presence of the TEA in different solvents under reflux conditions, including water, delightfully, we observed the smooth progress of reaction in water, monitored by TLC. Upon completion of the reaction (indicated also by TLC) and conventional work up the corresponding pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-dione, was obtained within 2h in high yield. The generality of this method was established by using various substituted arylglyoxals under the optimal conditions (TEA as catalyst, refluxing in water as green solvent). The results are shown in Table 2.

The reaction conditions were then applied to a range of different arylglyoxals to synthesize a series of products. The reaction times, melting points, and yields of the synthesized pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidines derivatives **5a–n** are shown in Table 3.



Scheme 1. Synthesis of pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines derivatives

Table 1. The effect of several catalyst and mol% of TEA on synthesis of **5a**

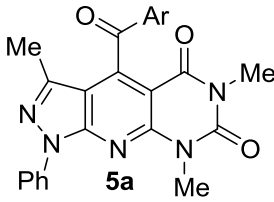
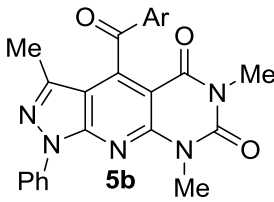
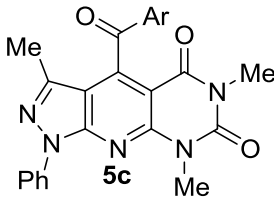
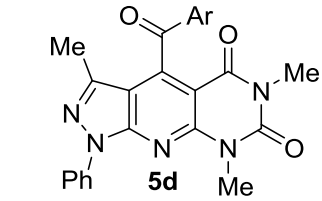
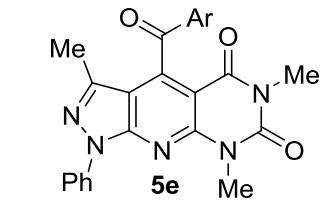
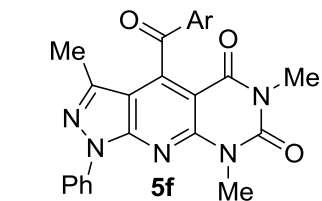
Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	No Catalyst	H ₂ O	24	Trace
2	No Catalyst	H ₂ O	2	Trace
3	DMAP (10)	H ₂ O	2	73
4	Sulfamic acid (10)	H ₂ O	2	65
5	H ₆ P ₂ W ₁₈ O ₆₂ .18H ₂ O (10)	H ₂ O	2	60
6	L-Proline	H ₂ O	2	70
7	Pipridine (10)	H ₂ O	2	74
8	DABCO (10)	H ₂ O	2	76
9	TEA (5)	H ₂ O	2	71
10	TEA (10)	H ₂ O	2	83
11	TEA (15)	H ₂ O	2	72

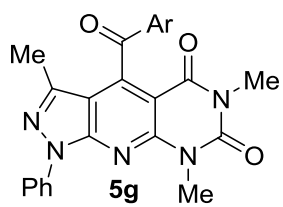
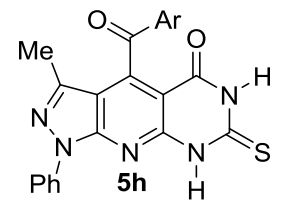
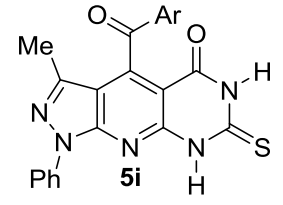
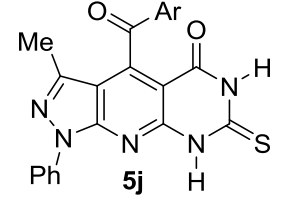
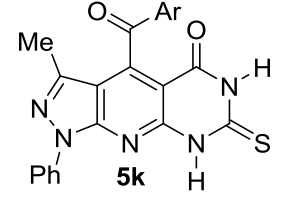
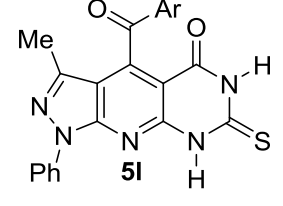
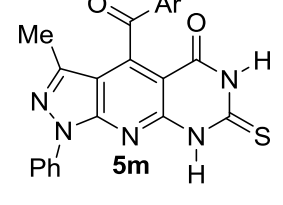
Table 2. The effect of several solvents on synthesis of **5a**

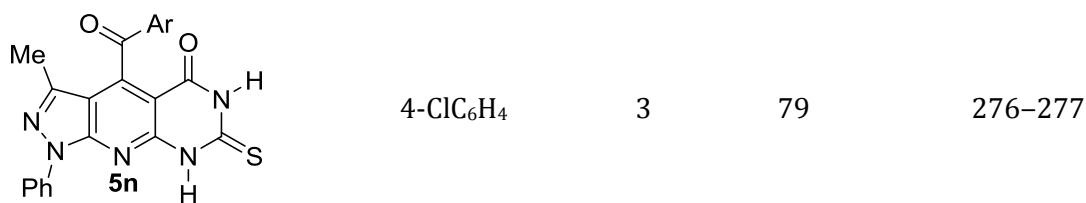
Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	TEA (10)	EtOH:H ₂ O (1:1)	2	76
2	TEA (10)	EtOH	2	75
3	TEA (10)	CH ₂ Cl ₂	2	67
4	TEA (10)	CH ₃ CN	2	65
5	TEA (10)	THF	2	65

6	TEA (10)	H ₂ O	2	83
7	TEA (10)	AcOH	2	70

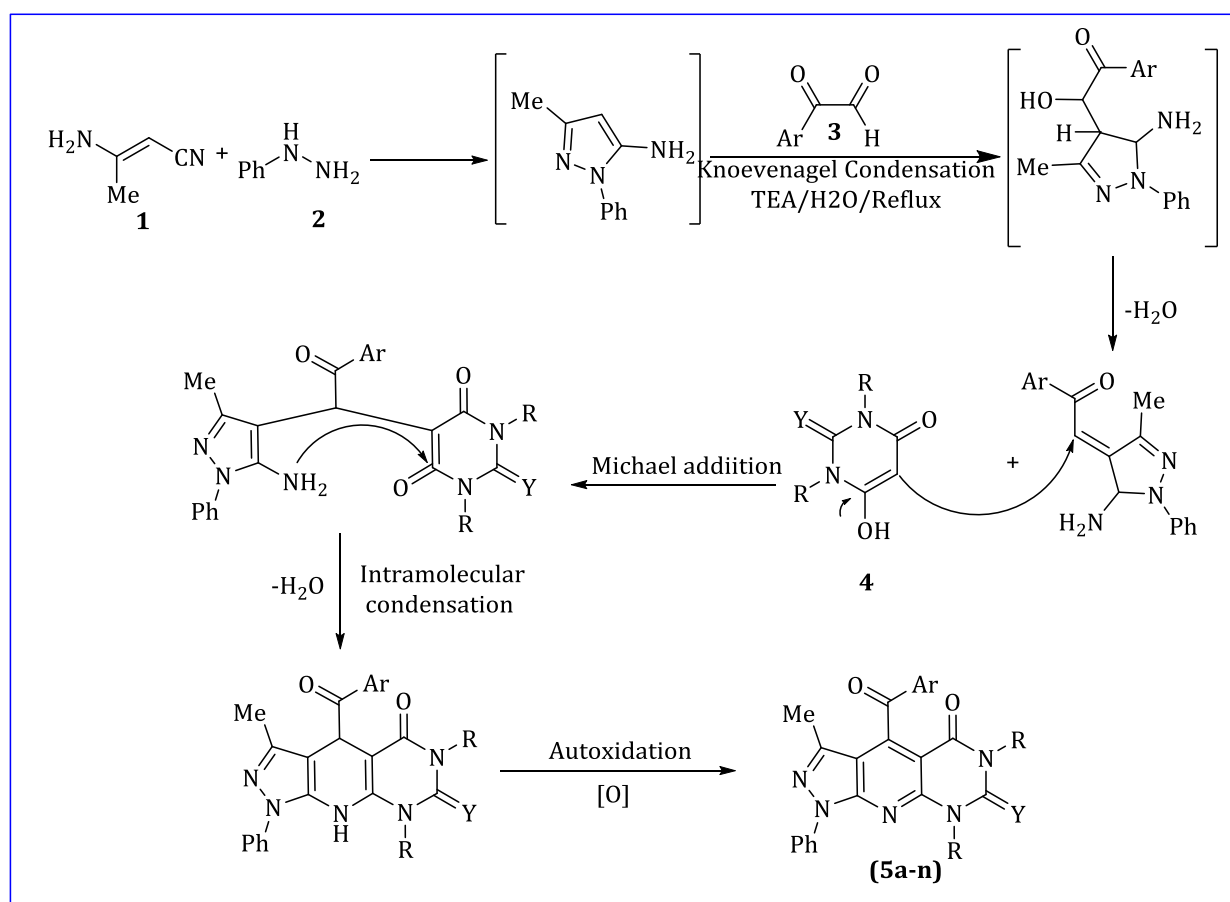
Table 3. The yields, reaction times and melting points of compounds **5a-n**

Product	Ar	Time (h)	Yield (%)	M.p. (°C) (Lit.)
 5a	C ₆ H ₅	2	83	240–241 241 [13]
 5b	4-FC ₆ H ₄	3	86	231–232 230 [13]
 5c	4-NO ₂ C ₆ H ₄	2.5	87	256–257 256 [13]
 5d	4-MeOC ₆ H ₄	3	78	264–265 263 [13]
 5e	3,4-(MeO) ₂ C ₆ H ₃	3	91	232–233 233 [13]
 5f	4-MeC ₆ H ₄	1.5	85	236–237

 <p>5g</p>	4-ClC ₆ H ₄	2	82	242–244
 <p>5h</p>	C ₆ H ₅	2	79	273–274
 <p>5i</p>	4-FC ₆ H ₄	2.5	81	278–279
 <p>5j</p>	4-NO ₂ C ₆ H ₄	1.5	85	284–285
 <p>5k</p>	4-MeOC ₆ H ₄	2	76	290–291
 <p>5l</p>	3,4-(MeO) ₂ C ₆ H ₃	3	88	264–265
 <p>5m</p>	4-MeC ₆ H ₄	3	81	261–262



A proposed mechanism for this reaction is shown in [Scheme 2](#). The formation of the products **5a-n** involve *Knoevenagel* condensation of 3-methyl-1-phenyl-1H-pyrazol-5-amine, which was formed of β -aminocrotonitrile and phenylhydrazine hydrate, with arglyoxal by loss of water molecule, then intermediate component undergoes *Michael* addition followed of 1,3-dimethylbarbituric acid or thiobarbituric acid to provide the corresponding leads to the synthesis of tri-substituted methane derivatives. The intramolecular heterocyclization followed by autoxidation leads to the formation of annulated pyrido[4',3:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*)-dione derivatives **5a-n**.



Scheme 2. The proposed mechanism for the one-pot four component reaction

In the ^1H NMR spectra of the products **5a-n**, the singlets at around $\delta = 13.45\text{-}12.60$, $\delta = 3.86\text{-}3.87$, $3.34\text{-}3.54$, and $2.26\text{-}2.27$ ppm are attributed to two N-H of thiobarbituric acid, the 3-methyl, 1-methyl and the methyl of pyrazole ring respectively and were present in all products. In the ^{13}C NMR spectra of products **5a-n**, signals located around $\delta = 180.6\text{-}193.4$, $170.1\text{-}176.7$ and $151.2\text{-}173.5$ ppm were due to aroyl, C=S and C-4 carbonyl groups respectively. In the FT-IR spectra, the characteristic absorption bands at $1665\text{-}1729\text{ cm}^{-1}$ could be assigned to the vibrations of three different carbonyl groups.

Conclusion

We have successfully synthesized a new series of the pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*)-dione derivatives **5a-n** by one-pot four component reaction of the mixture β -aminocrotonitrile **1**, phenylhydrazine **2** and arylglyoxals **3a-g** with 1,3-dimethylbarbituric acid **4a** or thiobarbituric acid **4b** using 10 mol% TEA as a catalyst by refluxing in water. Simplicity of the method, ease of product isolation, green reaction condition, high yields, and short reaction times are the most important advantages of this procedure. The synthesized pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine derivatives may have biological and pharmacological activities.

Acknowledgment

The authors gratefully acknowledge the financial assistance from the Urmia University.

Disclosure statement

No potential conflict of interest was reported by the authors.

Orcid

Ramin Javahershenas  0000-0001-5751-7203

References

- [1]. Domling A., Wang W., Wang K. *Chem. Rev.*, 2012, **112**:3083
- [2]. Jorissen W.P. *Chem. Rev.*, 2006, **6**:17
- [3]. Rewcastle G.W., Bridges A.J., Fry D.W., Rubin J.R., Denny W.A. *J. Med. Chem.*, 1997, **40**:1820
- [4]. Fry D.W., Becker M.A. Switzer R.L. *Mol. Pharm.*, 1995, **47**:810
- [5]. Sanghvi Y.S., Larson S.B., Matsumoto S.S., Nord L.D., Smee D.F. Willis R.C., Avery T.H., Robins R.K., Revankar G.R.J. *Med. Chem.*, 1989, **32**:629
- [6]. Armstrong R.W., Combs A.P., Tempst P.A., Brown S.D., Keating T.A. *Acc Chem. Res.*, 1996, **29**:123

- [7]. Tenser R.B., Gaydos A., Hay K.A. *Antimicrob. Agents Chemother.*, 2001, **45**:3657
- [8]. Nizamuddin-Mishra M., Srivastava M.K., Khan M.H. *Indian J. Chem.*, 2001, **40**:49
- [9]. Ajmal R.B., Rajendra S.D., Rupali S.S. *Int. J. Pharma. Bio. Sci.* 2014, **5**:422
- [10]. Balme G., Bossharth E. Monteiro N. *Eur. J. Org. Chem.*, 2003, **21**:4101
- [11]. Dmytro H., Borys Z., Olexandr V., Lucjusz Z., Andrzej G., Roman L. *Eur. J. Med. Chem.*, 2009, **44**:1396
- [12]. Sakuma Y., Hasegawa M., Kataoka K., Hoshina K., Yamazaki N., Kadota T. *Chem. Abstr.*, 1991, **115**:71646
- [13]. Ezzati M., Khalafy J., Poursattar Marjani A., Prager R.H. *Tetrahedron*, 2017, **73**:6587
- [14]. Poursattar Marjani A., Khalafy J., Chitan M., Mahmoodi S. *Iran. J. Chem. Chem. Eng.*, 2017, **36**:1
- [15]. Khalafy J., Majidi Arlan F., Soleimani Chalanchi Sh. *J. Heterocycl. Chem.*, 2018, **55**:149
- [16]. Poursattar Marjani A., Khalafy J. Rostampoor A. *J. Heterocycl. Chem.*, 2017, **54**:648
- [17]. Majidi Arlan F., Khalafy J., Maleki R. *Chem. Heterocycl. Comp.*, 2018, **54**:51
- [18]. Javahershenas R., Khalafy J. *J. Heterocycl. Chem.*, 2017, **54**:3163
- [19]. Javahershenas R., Khalafy J. *Heterocycl Commun.*, 2018, **24**:37
- [20]. Javahershenas R., Khalafy J. *J. Mex. Chem. Soc.*, 2018 <http://dx.doi.org/10.29356/jmcs.v62i3.340>
- [21]. Perrin D.D., Armarego W.L.F., Purification of Laboratory Chemicals, Pergamon Press: Oxford, U.K., 1988, 15

How to cite this manuscript: Ramin Javahershenas*, Jabbar Khalafy. One-pot, four component synthesis of pyrazolo [4',3':5,6]pyrido[2,3-d]pyrimidines derivatives. *Asian Journal of Green Chemistry*, 2018, 2, 318-329. DOI: [10.22034/ajgc.2018.62714](https://doi.org/10.22034/ajgc.2018.62714)