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Pseudo four-component synthesis of benzopyranopyrimidines

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ABSTRACT

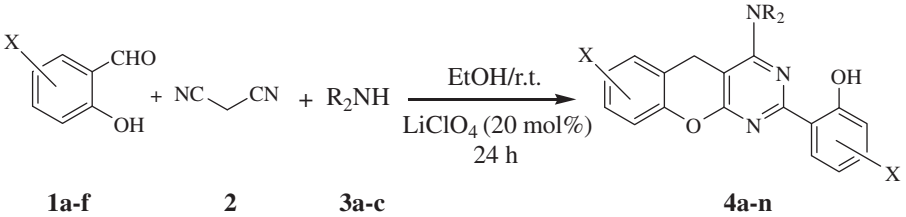
An efficient and simple method for the synthesis of new benzopyranopyrimidines via a pseudo four-component reaction of salicylic aldehydes, malononitrile and various amines in the presence of a catalytic amount of $LiClO_4$ is reported. The advantages of this procedure are mild reaction conditions, high yields of products and operational simplicity.

Multicomponent reactions (MCRs) in which several reactions are combined into one synthetic operation have been used extensively to form carbon–carbon bonds.[1–4] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single step, thus avoiding complicated purification operations and allowing savings of both solvents and reagents. There has been tremendous development in multicomponent reactions, and significant efforts continue to be made to develop new MCRs.[5–8] In this context, benzopyranopyrimidines show interesting features which make them attractive targets for the synthesis via MCRs.

Benzopyranopyrimidines demonstrate antiinflammatory, analgesic and, importantly, in vitro anti-aggregating activities.[9–13] Several benzopyrano[2,3-*d*]pyrimidines were tested for their cytotoxic activity against a panel of cancer cell lines, and a number were shown to cause significant perturbation in cell cycle kinetics.[14] Therefore, numerous methods have been reported for the preparation of benzopyranopyrimidine derivatives.[9–13,15–17]

As part of our research aimed at developing new methods for the preparation of heterocyclic compounds,[18–37] we report herein an efficient and simple synthesis of new benzopyranopyrimidines in high yields via a one-pot, pseudo four-component reaction of salicylic aldehydes **1a–f**, malononitrile (**2**) and amines **3a–c** in the presence of $LiClO_4$ as a catalyst, in EtOH at room temperature (Scheme 1).[38]

To achieve suitable conditions for the synthesis of the benzopyranopyrimidines **4**, various Lewis and protic acid catalysts, namely, $ZnCl_2$, $FeCl_3$, $SnCl_2$, $Bi(NO_3)_2$, NH_2SO_3H, *p*-TSA, HOAc and $LiClO_4$ and different solvents were investigated in the model reaction of 2-hydroxybenzaldehyde (**1a**), malononitrile (**2**) and dimethylamine (**3a**). The best overall yield (93%) was obtained using



Scheme 1.

E-mail address: a_bazgir@sbu.ac.ir (A. Bazgir).

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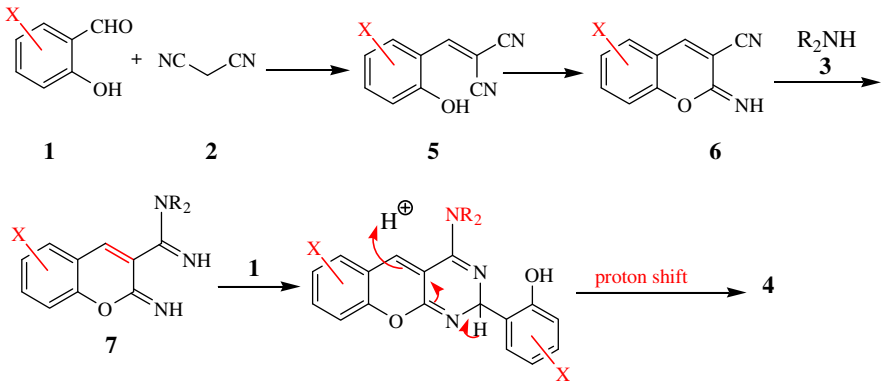
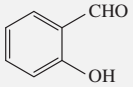
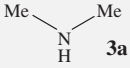
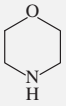
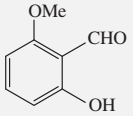
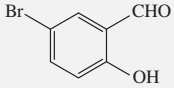
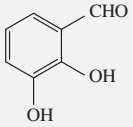
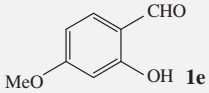
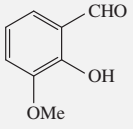


Scheme 2.

Table 1
Synthesis of benzopyrano[2,3-*d*]pyrimidines **4**

Aldehyde	Amine	Product	Yield (%)
 **1a**	 **3a**	**4a**	93
1a	 **3b**	**4b**	84
1a	 **3c**	**4c**	95
 **1b**	**3b**	**4d**	96
1b	**3c**	**4e**	91
 **1c**	**3a**	**4f**	70
1c	**3b**	**4g**	80
1c	**3c**	**4h**	88
 **1d**	**3b**	**4i**	82
1d	**3c**	**4j**	79
 **1e**	**3a**	**4k**	73
1e	**3b**	**4l**	80
1e	**3c**	**4m**	81
 **1f**	**3b**	**4n**	92

$LiClO_4$ in EtOH at room temperature. Similarly, the molar ratio of $LiClO_4$ was studied with the optimum amount being 20 mol %.

Encouraged by this success, we investigated the use of a wide range of amines **3** and salicylic aldehydes **1** in this pseudo four-component reaction and have prepared a library of (5*H*-benzopyrano[2,3-*d*]pyrimidin-2-yl)phenols **4**. The results are shown in Table 1. These reactions proceeded very cleanly under mild conditions at room temperature, and no side reactions were observed. To the best of our knowledge, this new procedure provides the first example of an efficient and pseudo four-component reaction for the synthesis of (5*H*-benzopyrano[2,3-*d*]pyrimidin-2-yl)phenols.

The work-up involved filtration and washing with EtOH to provide the products in high purity. The nature of these compounds as 2:1:1 adducts was apparent from their mass spectra, which displayed, in each case, a molecular ion peak at the appropriate *m*/*z* value. Compounds **4a–n** are stable solids whose structures were established by IR, ^1H and ^{13}C NMR spectroscopy and by elemental analysis.

It is reasonable to assume that products **4** result from initial Knoevenagel condensation of salicylic aldehyde (**1**) and malononitrile (**2**) followed by subsequent Pinner reaction (**5**→**6**). Next, the cyano group of intermediate **6** can be attacked by the amine **3** to produce intermediate **7**. Finally, amine **7** reacts with another molecule of salicylic aldehyde **1** followed by proton transfer to afford the product **4** (Scheme 2).

In conclusion, we have developed a new, simple, pseudo four-component method for the synthesis of (5*H*-benzopyrano[2,3-*d*]pyrimidin-2-yl)phenols via the reaction of salicylic aldehydes, malononitrile and amines at room temperature. We believe that this method will find useful applications in the growth of benzopyranopyrimidine chemistry.

Acknowledgements

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38. *Typical procedure for the preparation of 2{4-(dimethylamino)-5H-benzopyrano[2,3-d]pyrimidin-2-yl)}phenol* (**4a**): A mixture of 2-hydroxybenzaldehyde (**1a**) (2 mmol), malononitrile (**2**) (1 mmol), dimethylamine (**3a**) (1 mmol) and $LiClO_4$ (20 mol %) in EtOH (5 ml) was stirred at rt for 24 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with H_2O (5 ml) and EtOH (5 ml) to afford pure **4a**. White powder (93%); mp: 177–179 °C. IR (KBr) (ν_{max}/cm^{-1}): 3427, 3048, 1608. MS (EI, 70 eV) *m*/*z*: 319 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.18 (6H, s, $N(CH_3)_2$), 4.15 (2H, s, CH_2), 6.88 (2H, br s, H-Ar), 7.12 (2H, br s, H-Ar), 7.27 (3H, br s, H-Ar), 8.22 (1H, br s, H-Ar), 13.36 (1H, s, OH). Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.57; H, 5.29; N, 13.05. (Due to the very low solubility of product **4a**, we were unable to obtain the ^{13}C NMR spectrum). *2-{4-(Piperidin-1-yl)-5H-benzopyrano[2,3-d]pyrimidin-2-yl)phenol}* (**4b**): white powder (84%); mp: 168–170 °C. IR (KBr) (ν_{max}/cm^{-1}): 3416, 3064, 2933, 1608. MS (EI, 70 eV) *m*/*z*: 359 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.69 (6H, s, $3CH_2$), 3.48 (4H, s, $2CH_2$), 3.99 (2H, s, CH_2), 6.89–6.95 (2H, m, H-Ar), 7.13–7.20 (2H, m, H-Ar), 7.26–7.39 (3H, m, H-Ar), 8.26 (1H, d, $^3J_{HH}$ = 6.0 Hz, H-Ar), 13.28 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 24.3, 25.3, 26.0, 49.2, 97.8, 116.8, 117.8, 118.6, 119.3, 120.6, 125.0, 128.6, 129.1, 129.5, 133.3, 150.4, 160.3, 161.0, 163.8, 146.8. Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.43; H, 5.81; N, 11.76. *4-Bromo-2-{7-bromo-4-(dimethylamino)-5H-benzopyrano[2,3-d]pyrimidin-2-yl)phenol}* (**4f**): white powder (70%); mp: 196–198 °C. IR (KBr) (ν_{max}/cm^{-1}): 3453, 2917, 1596. MS (EI, 70 eV) *m*/*z*: 477 (M^++2), 475 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.16 (6H, s, $2CH_3$), 4.12 (2H, s, CH_2), 6.80–7.08 (2H, m, H-Ar), 7.40–7.50 (3H, m, H-Ar), 8.20–8.27 (1H, br s, H-Ar), 13.30 (1H, s, OH). Anal. Calcd for $C_{19}H_{15}Br_2N_3O_2$: C, 47.83; H, 3.17; N, 8.81. Found: C, 47.71; H, 3.11; N, 8.72. (Due to the very low solubility of product **4f**, we were unable to obtain the ^{13}C NMR spectrum). *2-Methoxy-6-{9-methoxy-4-(piperidin-1-yl)-5H-benzopyrano[2,3-d]pyrimidin-2-yl}phenol* (**4n**): white powder (92%); mp: 181–183 °C. IR (KBr) (ν_{max}/cm^{-1}): 3442 2933, 1572. MS (EI, 70 eV) *m*/*z*: 419 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.66 (6H, s, $3CH_2$), 3.43 (4H, s, $2CH_2$), 3.78 (3H, s, CH_3), 3.84 (3H, s, CH_3), 3.91 (2H, s, CH_2), 6.80–6.85 (2H, m, H-Ar), 6.92–6.99 (1H, m, H-Ar), 7.01–7.03 (2H, m, H-Ar), 7.82 (1H, d, $^3J_{HH}$ = 6.0 Hz, H-Ar), 13.47 (1H, s, OH). Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.81; H, 5.93; N, 10.10. (Due to the very low solubility of product **4n**, we were unable to obtain the ^{13}C NMR spectrum).