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$ZrOCl_2 \cdot 8H_2O$ as an Efficient Catalyst for the Pseudo Four-Component Synthesis of Benzopyranopyrimidines

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ABSTRACT. An efficient and environmentally benign protocol for the pseudo four-component synthesis of benzopyranopyrimidines via condensation of salicylic aldehydes, malononitrile and various amines catalyzed by $ZrOCl_2 \cdot 8H_2O$ as an inexpensive and eco-friendly catalyst with high catalytic activity under solvent-free conditions is reported. This protocol provides a new and improved method for obtaining benzopyranopyrimidines in terms of good yields, simple experimental procedure and short reaction time.

Key words: Solvent-free, Malononitrile, Benzopyranopyrimidine, Salicylaldehyde

INTRODUCTION

The development of new methods for solvent-free organic synthesis involving multicomponent reactions is an important and attractive area of synthetic research.[1,2] Organic reactions should be fast and facile and the target products should be easily separated and purified in high yields without the isolation of any intermediate.[3] From this point of view, solvent-free multicomponent reactions[4] find application as appealing methods to achieve these goals. Solvent-free multicomponent 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.[5,6]

Functionalized nitrogen-heterocycles play a prominent role in medicinal chemistry and they have been intensively used as scaffolds for drug development. In this context fused pyrimidine derivatives are of particular interest because of their pharmacological profile.[7] Some pyridopyrimidines are known as analgetics[8] and CNS depressants,[9] while pyranopyrimidines exhibits antifungal and antibacterial activity.[10] 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.[11]

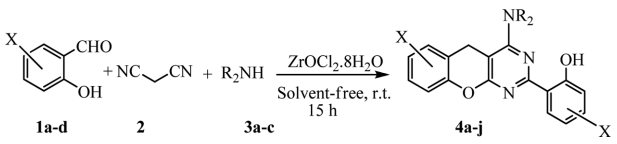
The use of zirconium(IV) salts as an efficient Lewis acid for various transformations, has been well documented in the literature, because of their easy availability, moisture stability and low toxicity.[12–14] Among the various types of Zr(IV) salts, particularly, $ZrOCl_2 \cdot 8H_2O$ has advantages of moisture stability, readily availability and easy handling.[13] Also, the low toxicity of $ZrOCl_2 \cdot 8H_2O$ is evident from their LD50 [LD50 ($ZrOCl_2 \cdot 8H_2O$, oral rat) = 3500 mg/kg].[14] Therefore, the application of $ZrOCl_2 \cdot 8H_2O$ in organic synthesis is of renewed interest.

As part of our research aimed at developing new methods for the preparation of fused pyrimidine derivatives,[15–17] recently, for the first time we have reported synthesis of benzopyrano[2,3-*d*]pyrimidines via pseudo four-component reaction of salicylic aldehyde, malononitrile and amine in the presence of $LiClO_4$ in EtOH at room temperature for 24 h.[18] Very recently, this multicomponent protocol has been developed by ionic liquid, $[Bmim]BF_4$.[19] Due to unique advantages of $ZrOCl_2 \cdot 8H_2O$, the aim of our research described here was to develop the pseudo four-component synthesis of benzopyrano[2,3-*d*]pyrimidines employing $ZrOCl_2 \cdot 8H_2O$ as an efficient and mild Lewis acid catalyst under solvent-free conditions (*Scheme* 1).

EXPERIMENTAL

General Procedure

A mixture of salicylic aldehydes (2 mmol), malononi-



***Scheme* 1.**

trile (1 mmol), amines (1 mmol) and $ZrOCl_2·8H_2O$ (30 mol%) was stirred at room temperature for 15 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was washed with H_2O (5 ml) and EtOH (5 ml) to afford pure product **4**.

All the products are known and were fully characterized by a comparison with authentic samples (melting point) and IR spectra.[18]

2-(4-Morpholino-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4c): White powder (90%); mp 196−198 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3442. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.45 (4H, s, CH_2), 3.77 (4H, s, CH_2), 3.88 (2H, s, CH_2-Ar), 6.84−7.24 (7H, m, H-Ar), 8.18 (1H, bs, H-Ar), 12.99 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 25.1, 48.5, 66.4, 97.8, 116.7, 117.5, 118.5, 119.1, 120.1, 124.9, 128.5, 129.0, 129.4, 133.2, 150.1, 160.2, 160.9, 163.4, 164.3. MS (EI, 70 eV) m/z (%): 361 (M^+).

3-Methoxy-2-(6-methoxy-4-(piperidin-1-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4d): White powder (91%); mp 195−197 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3442. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.69 (6H, s, CH_2), 3.12 (4H, bs, CH_2), 3.76–3.88 (8H, m, 2OCH_3 and CH_2-Ar), 6.53−6.58 (2H, m, H-Ar), 7.71−7.80 (2H, m, H-Ar), 7.17−7.26 (2H, m, H-Ar), 10.93 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.6, 24.4, 26.1, 49.4, 56.5, 56.7, 96.6, 104.2, 106.8, 109.1, 109.5, 110.0, 114.2, 128.6, 130.9, 151.4, 157.6, 158.7, 159.9, 160.7, 156.6. MS (EI, 70 eV) m/z (%): 419 (M^+).

3-Methoxy-2-(6-methoxy-4-morpholino-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4e): White powder (88%); mp 191−193 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3437. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.42 (4H, s, 2CH_2), 3.67–3.73 (7H, m, 2CH_2 and OCH_3), 3.79–3.84 (5H, m, OCH_3 and CH_2-Ar), 6.52 (2H, d, $^3J_{HH}$ = 7.0 Hz, H-Ar), 6.74 (2H, m, $^3J_{HH}$ = 8.0 Hz, H-Ar), 7.14–7.26 (2H, m, H-Ar), 10.15 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.4, 48.7, 56.1, 56.3, 66.5, 56.0, 97.4, 102.8, 106.4, 108.9, 109.0, 109.3, 115.5, 128.8, 130.4, 151.1, 157.2, 157.3, 158.8, 160.8, 164.0, 165.5. MS (EI, 70 eV) m/z (%): 421 (M^+).

4-Bromo-2-(7-bromo-4-(piperidin-1-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4g): White powder (81%); mp 187−189 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3442. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.67 (6H, s, CH_2), 3.41 (4H, s, CH_2), 3.88 (2H, s, CH_2-Ar), 6.81−7.5 (5H, m, H-Ar), 8.19 (1H, bs, H-Ar), 13.2 (1H, bs, OH). MS (EI, 70 eV) m/z (%): 514 (M^+). Due to very low solubility of the product 4h, we unable report the ^{13}C NMR data for this product.

4-Bromo-2-(7-bromo-4-morpholino-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4h): White powder (85%); mp 198−200 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3416. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.47(4H, s, CH_2), 3.78 (4H, s, CH_2), 3.97 (2H, s, CH_2-Ar), 6.84−6.87 (1H, m, H-Ar), 7.12-7.15 (1H, m, H-Ar), 7.42−7.48 (2H, m, H-Ar), 7.54 (1H, bs, H-Ar), 13.07 (1H, bs, OH). MS (EI, 70 eV) m/z (%): 519 (M^+), 474 (38), 353 (30), 127 (90), 86 (100). Due to very low solubility of the product 4i, we unable report the ^{13}C NMR data for this product.

2-(4-(Dimethylamino)-8-methoxy-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)-5-methoxyphenol (4i): White powder (77%); mp 174−176 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3421. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.19 (6H, s, CH_3), 3.77 (6H, s, CH_3), 4.08 (2H, s, CH_2-Ar), 6.43−6.44 (1H, m, H-Ar), 6.50−6.53 (1H, m, H-Ar), 6.71−6.77 (2H, m, H-Ar), 7.2 (1H, d, $^3J_{HH}$ = 8.0 Hz, H-Ar), 8.14 (1H, d, $^3J_{HH}$ = 8.0 Hz, H-Ar), 13.53 (1H, s, OH). MS (EI, 70 eV) m/z (%): 379 (M^+). Due to very low solubility of the product 4j, we unable report the ^{13}C NMR data for this product.

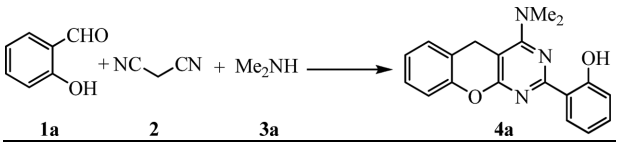
5-Methoxy-2-(8-methoxy-4-(piperidin-1-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4j): White powder (79%); mp 168−170 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3400. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.65 (6H, s, CH_2), 3.28 (2H, s, CH_2), 3.28 (2H, s, CH_2), 3.74 (6H, s, OCH_3), 3.78 (2H, s, CH_2-Ar), 6.39−6.48 (2H, m, H-Ar), 6.66−6.71 (2H, m, H-Ar), 7.51 (1H, d, $^3J_{HH}$ = 6 Hz, H-Ar), 8.11 (1H, d, $^3J_{HH}$ = 6 Hz, H-Ar), 13.33 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 24.3, 24.5, 25.9, 49.1, 55.6, 55.8, 96.9, 101.5, 101.9, 106.7, 111.2, 111.7, 111.9, 129.8, 130.2, 150.9, 159.4, 160.9, 162.0, 163.4, 164.7. MS (EI, 70 eV) m/z (%): 419 (M^+).

5-Methoxy-2-(8-methoxy-4-morpholino-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol (4k): White powder (80%); mp 224–226 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3442. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.45 (4H, s, CH_2), 3.75 (10H, m, 2CH_2 and 2OCH_3), 3.87 (2H, s, CH_2-Ar), 6.42−6.51 (2H, m, H-Ar), 6.7−6.76 (2H, m, H-Ar), 7.19−7.22 (1H, m, H-Ar), 8.11−8.14 (1H, m, H-Ar), 13.21 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 24.5, 48.5, 55.7, 55.8, 66.4, 97.2, 101.5, 101.9, 106.9, 111.4, 111.6, 111.8, 129.9, 130.3, 150.7, 159.5, 160.9, 161.9, 163.5, 164.4. MS (EI, 70 eV) m/z (%): 421 (M^+).

RESULTS AND DISCUSSION

Initially, the reaction of 2-hydroxybenzaldehyde (**1a**, 2 mmol), malononitrile (**2**, 1 mmol) and dimethylamine (**3a**, 1 mmol) as a simple model substrate in the presence of $ZrOCl_2·8H_2O$ in different solvents and under solvent-free conditions at room temprature was investigated to opti-

***Table* 1.** Screening of the reaction conditions



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

Entry	Solvent	$ZrOCl_2·8H_2O$	Time (h)	Yield (%)
1	H_2O	30 mol %	24	Trace
2	EtOH	30 mol %	24	80
3	CH_3CN	30 mol %	24	<40
4	CH_2Cl_2	30 mol %	24	<40
5	$CHCl_3$	30 mol %	24	<40
6	S.-F.	30 mol %	15	88
7	S.-F.	35 mol %	15	89
8	S.-F.	25 mol %	15	79
9	S.-F.	–	24	Trace

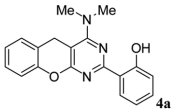
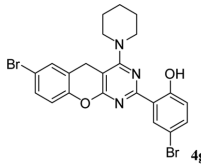
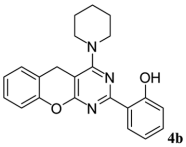
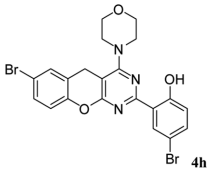
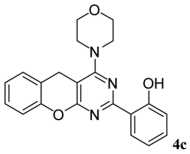
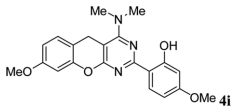
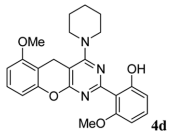
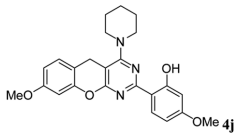
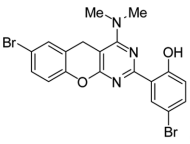
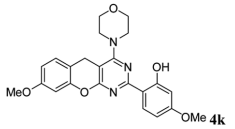
mize the reaction conditions. It was found that the reaction under solvent-free conditions after 15 h resulted in higher isolated yield (*Table* 1). Similarly, the molar ratio of $ZrOCl_2·8H_2O$ was studied with the optimum amount being 30 mol% (entry 6). When this reaction was carried out without $ZrOCl_2·8H_2O$ the yield of the expected product was trace (entry 9).

Using the optimized conditions, the generality of this reaction was examined using several types of salicylic aldehydes **1a–d** and amines **3a–c**. In all cases, the reactions gave the corresponding products in good isolated yield (*Table* 2). These reactions proceeded very cleanly under mild conditions at room temperature, and no side reactions were observed.

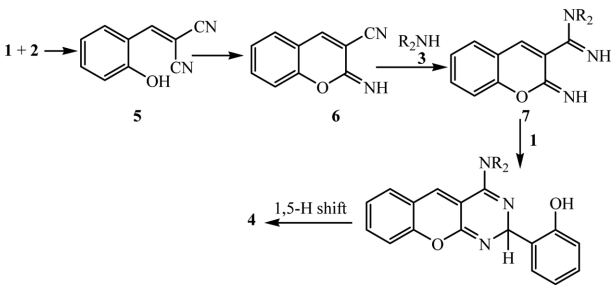
Another advantage of this approach could be related to the reusability of catalyst. We found that the catalyst could be separated from the reaction mixture simply by washing with water and reused after washing with CH_2Cl_2 and dried at 60 °C. The reusability of the catalyst was checked by the reaction of salicylaldehyde, malononotrile and dimethyl amine under optimized reaction conditions. The results show that the catalyst can be used effectively three times without any loss of its activity (*Table* 2, entry 1). Therefore, the recyclability of catalyst makes the process economically and potentially viable for commercial applications.

A possible mechanism for the formation of **4** is proposed in Scheme 2. It is reasonable to assume that product **4** results from initial Knoevenagel condensation reaction of salicylic aldehyde **1** and malonontrile **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

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

Product	Yield (%)	Product	Yield (%)
 **4a**	88 (88,85)[a]	 **4g**	81
 **4b**	79	 **4h**	85
 **4c**	90	 **4i**	77
 **4d**	91	 **4j**	79
 **4f**	73	 **4k**	80

[a]Isolated yield after recycling of catalyst



***Scheme* 2.**

molecule of salicylic aldehyde **1** followed by proton transfer to afford the product 4 (*Scheme* 2).

CONCLUSION

In conclusion, we have demonstrated that $ZrOCl_2·8H_2O$ can be used as green and reusable catalyst for efficient synthesis of (5*H*-benzopyrano[2,3-*d*]pyrimidin-2-yl)phenols under solvent-free conditions. Moreover, the cheapness, easy availability of the reagent, easy and clean workup makes this method attractive for organic chemist.

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