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# One-Pot Synthesis of Some New Pyrido[2,3-*d*]pyrimidine Derivatives Catalyzed by Sodium Lauryl Sulfate in Aqueous Media

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**Abstract:** A series of pyrido[2,3-*d*]pyrimidine derivatives were synthesized by the three-component reaction of aromatic aldehyde, malononitrile and 6-amino-4-hydroxy-2-mercaptopyrimidine catalyzed by sodium lauryl sulfate (SDS) in aqueous media. It was interesting that further aromatization took place automatically. This method provides several advantages such as easier work-up, milder reaction conditions and environmental friendly.

**Keywords:** Green synthesis, Sodium lauryl sulfate (SDS), Pyrido[2,3-*d*]pyrimidine.

## Introduction

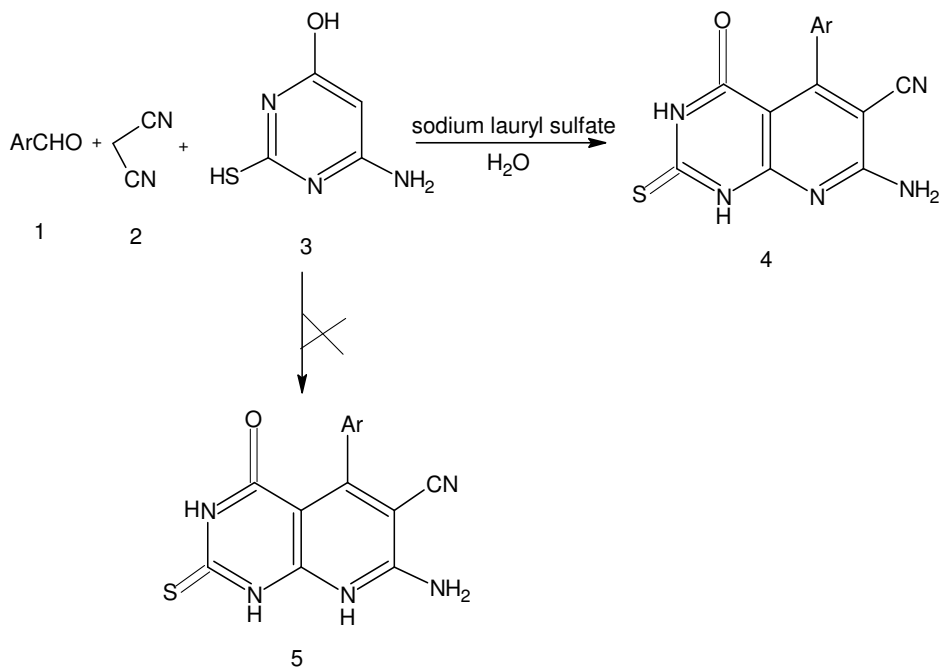
The synthesis of pyridopyrimidine and their derivatives remains of great interest in organic chemistry, because some of them exhibit significant biological and pharmacological activities, such as antifolate activity<sup>1</sup>, antibacterial activity<sup>2</sup>, tyrosine kinase activity<sup>3</sup>, antimicrobial activity<sup>4</sup>, calcium channel antagonists activity<sup>5</sup>, anti-inflammatory and analgesic activity<sup>6</sup>, antileishmanial activity<sup>7</sup>, tuber-culostatic activity<sup>8</sup>, anticonvulsants activity<sup>9</sup>, diuretic and potassium-sparing activity<sup>10</sup>, antiaggressive activity<sup>11</sup>, antitumor activity<sup>12</sup>. A number of methods have been developed for the synthesis of pyridopyrimidine derivatives<sup>13-16</sup>, which usually required longer time, complex synthetic pathways, expensive catalyst and often used organic solvent. Thus the pursuance of more convenient and practical synthetic methods for these compounds still remains an active research area.

Recently, aqueous synthesis by virtue of their unique reactivity, productivity, ease of execution and generally high selectivity have gained considerable attention from the point view of increasing environmental concerns and economic reasons, To date, more and more organic transformations have been effectively carried out in water such as Claisen rearrangement, aldol condensation, benzoin condensation, Michael addition reaction, nucleophilic additions, substitution reaction, oxidations, reductions and photochemistry<sup>17,18</sup>.

The fact that many organic materials do not dissolve in water and many reactive intermediates and catalysts are decomposed in water make it necessary to use some phase-transfer catalysis (PTC) or surfactant in aqueous media, because they could benefit the organic materials to form a uniform dispersion in water in the course of synthesis. Sodium lauryl sulfate (SDS) has been used in a number of organic reactions as a good phase transfer catalyst<sup>19,20</sup>. However, the formation of pyrido[2,3-*d*]pyrimidine derivatives catalyzed by SDS has not been reported.

In our continued interest in the development of highly expedient methods for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives, we report in this paper a novel three component one-pot synthesis of pyrido[2,3-*d*]pyrimidine derivatives catalyzed by sodium lauryl sulfate (SDS) in aqueous media.

It should be noticed that when the arylaldehyde (**1**), malononitrile (**2**), and 6-amino-4-hydroxy-2-mercaptopyrimidine (**3**) were treated with SDS in water at 90 °C, the 1,4-dihydropyrido[2,3-*d*]pyrimidine derivatives (**5**) were not obtained. Instead, pyrido[2,3-*d*]pyrimidine derivatives (**4**) which were the further aromatization products were obtained (Scheme 1), although any oxidizing agent was not added. This method that we report provides several advantages such as environmental friendly and simple work-up procedure. In addition, water was chosen as a green solvent. All of results are shown in Table 1.



**Scheme 1**

**Table 1.** Synthesis of compound **4** in aqueous media under 90 °C catalyze by SDS.

Entry	Comp.	Ar	Yields/ % <sup>b</sup>
1	<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	50
2	<b>4b</b>	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	70
3	<b>4c</b>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	67
4	<b>4d</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	81
5	<b>4e</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	28
6	<b>4f</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	47
7	<b>4g</b>	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	62
8	<b>4h</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	46
9	<b>4i</b>	4-ClC <sub>6</sub> H <sub>4</sub>	48
10	<b>4j</b>	3-ClC <sub>6</sub> H <sub>4</sub>	54

<sup>a</sup>Reaction condition: 10 mL H<sub>2</sub>O, 2 mmol **1**, 2 mmol **2**, 2 mmol **3**, 0.2 mmol SDS, <sup>b</sup>Isolated yields.

## Experimental

Melting points were measured using an X-4 apparatus. NMR spectra were taken with a Varian 400 spectrometer using TMS as internal reference and DMSO as a solvent. IR spectra were obtained using NICOLET380 spectrometer instrument (KBr). Elemental analyses were carried out using Carlo Erba 1110 analyzer.

### General procedure

A mixture of an aromatic aldehyde (**1**, 2 mmol), malononitrile (**2**, 2.5 mmol), 6-amino-4-hydroxy-2-mercaptopyrimidine (**3**, 2 mmol) and SDS (10 mol%) in water (10 mL) was stirred at 90 °C. Then the mixture was cooled to room temperature and filtered off, the obtained solid mass was washed with H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>. The crude product was further purified by recrystallization from DMF and water.

### Spectral data of the compounds

**4a**: m.p. >300 °C; <sup>1</sup>H NMR δ: 7.7 (s, 2H, NH<sub>2</sub>), 7.2~7.7 (m, 5H, ArH), 12.0 (s, 1H, NH), 12.7 (s, 1H, NH); IR (KBr) ν: 3444, 3302, 3223, 2213, 1649, 1627, 1196, 806, 757, 703 cm<sup>-1</sup>. Anal. calcd for C<sub>14</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub>S: C 56.94, H 3.07, N 23.71, S 10.86; found C 56.91, H 3.08, N 23.70, S 10.88.

**4b**: m.p. >300 °C; <sup>1</sup>H NMR δ: 7.7 (s, 2H, NH<sub>2</sub>), 7.4~8.3 (m, 4H, ArH), 12.2 (s, 1H, NH), 12.9 (s, 1H, NH); IR (KBr) ν: 3454, 3372, 3324, 3222, 2217, 1670, 1622, 1207, 1141, 801, 781, 775, 745 cm<sup>-1</sup>. Anal. calcd for C<sub>14</sub>H<sub>8</sub>N<sub>6</sub>O<sub>3</sub>S: C 49.41, H 2.37, N 24.69, S 9.42; found C 49.39, H 2.39, N 24.65, S 9.46.

**4c**: m.p. >300 °C; <sup>1</sup>H NMR δ: 7.6 (s, 2H, NH<sub>2</sub>), 7.6~8.3 (m, 4H, ArH), 12.2 (s, 1H, NH), 12.8 (s, 1H, NH); IR (KBr) ν: 3458, 3305, 3223, 2211, 1679, 1625, 1530, 1198, 1085, 999, 934, 871, 706, 736, 682 cm<sup>-1</sup>. Anal. calcd for C<sub>14</sub>H<sub>8</sub>N<sub>6</sub>O<sub>3</sub>S: C 49.41, H 2.37, N 24.69, S 9.42; found C 49.38, H 2.38, N 24.69, S 9.42;

**4d**: m.p. >300 °C; <sup>1</sup>H NMR δ: 7.9 (s, 2H, NH<sub>2</sub>), 7.6 (d, 2H, *J*=8.6, ArH), 8.2 (d, 2H, *J*=8.6, ArH), 12.7(s, 1H, NH), 12.3 (s, 1H, NH); IR (KBr) ν: 3489, 3299, 3221, 2215, 1691, 1590, 1195, 1093, 982, 857 cm<sup>-1</sup>. Anal. calcd for C<sub>14</sub>H<sub>8</sub>N<sub>6</sub>O<sub>3</sub>S: C 49.41, H 2.37, N 24.69, S 9.42; found C 49.40, H 2.38, N 24.67, S 9.43;

**4e**: m.p. >300 °C; <sup>1</sup>H NMR δ: 7.9 (s, 2H, NH<sub>2</sub>), 7.2~7.9 (m, 3H, ArH), 12.2 (s, 1H, NH), 12.8 (s, 1H, NH); IR (KBr) ν: 3381, 2919, 2224, 1643, 1594, 1152, 1050, 869, 808, 787 cm<sup>-1</sup>. Anal. calcd for C<sub>14</sub>H<sub>7</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>3</sub>S: C 46.17, H 1.94, N 19.23, S 8.80; found C 46.15, H 1.94, N 19.22, S 8.79.

**4f**: m.p. >300 °C;  $^1\text{H NMR } \delta$ : 2.5 (s, 3H,  $\text{CH}_3$ ), 7.8 (s, 2H,  $\text{NH}_2$ ), 6.9~8.4 (m, 4H, ArH), 12.0 (s, 1H, NH), 12.7 (s, 1H, NH); IR (KBr)  $\nu$ : 3401, 3295, 3100, 2219, 1693, 1624, 1191, 1145, 874, 815, 764  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{15}\text{H}_{11}\text{N}_5\text{OS}$ : C 58.24, H 3.58, N 22.64, S 10.37; found C 58.23, H 3.56, N 22.67, S 10.36.

**4g**: m.p. >300 °C;  $^1\text{H NMR } \delta$ : 8.1 (s, 2H,  $\text{NH}_2$ ), 6.5~8.1 (m, 3H, ArH), 11.5 (s, 1H, NH), 12.4 (s, 1H, NH); IR (KBr)  $\nu$ : 3409, 3327, 3223, 2168, 1733, 1690, 1129, 1029, 883, 775, 711  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{14}\text{H}_7\text{Cl}_2\text{N}_6\text{O}_5\text{S}$ : C 46.17, H 1.94, N 19.23, S 8.80; found C 46.19, H 1.92, N 19.22, S 8.81.

**4h**: m.p. >300 °C;  $^1\text{H NMR } \delta$ : 3.8 (s, 3H,  $\text{CH}_3$ ), 7.6 (s, 2H,  $\text{NH}_2$ ), 6.7~7.9 (m, 3H, ArH), 11.8 (s, 1H, NH), 12.0 (s, 1H, NH); IR (KBr)  $\nu$ : 3454, 3380, 3299, 2217, 1691, 1628, 1240, 1032, 877, 834, 804, 722  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{15}\text{H}_{11}\text{N}_5\text{O}_2\text{S}$ : C 55.38, H 3.41, N 21.53, S 9.86; found C 55.37, H 3.39, N 21.52, S 9.88.

**4i**: m.p. >300 °C;  $^1\text{H NMR } \delta$ : 7.7 (s, 2H,  $\text{NH}_2$ ), 7.3 (d, 2H,  $J=8.0$ , ArH), 7.4 (d, 2H,  $J=8.0$ , ArH), 12.0 (s, 1H, NH), 12.7 (s, 1H, NH); IR (KBr)  $\nu$ : 3455, 3296, 3217, 2215, 1694, 1622, 1269, 1089, 1014, 934, 875, 805, 764, 725  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{14}\text{H}_8\text{ClN}_5\text{OS}$ : C 50.99, H 2.45, N 21.24, S 9.72; found C 50.97, H 2.48, N 21.23, S 9.72.

**4j**: m.p. >300 °C;  $^1\text{H NMR } \delta$ : 7.4 (s, 2H,  $\text{NH}_2$ ), 6.4~7.7 (m, 3H, ArH), 12.1 (s, 1H, NH), 12.7 (s, 1H, NH); IR (KBr)  $\nu$ : 3404, 3309, 3223, 2172, 1694, 1625, 1267, 1141, 1075, 873, 803, 699  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{14}\text{H}_8\text{ClN}_5\text{OS}$ : C 50.99, H 2.45, N 21.24, S 9.72; found C 50.97, H 2.44, N 21.22, S 9.72.

## Results and Discussion

In presence of SDS, aromatic aldehyde **1**, malononitrile **2** and 6-amino-4-hydroxy-2-mercaptopyrimidine **3** were performed in water at 90 °C, 7-amino-5-argio-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile **4** were obtained in moderate to good yield. The results are summarized Table 1.

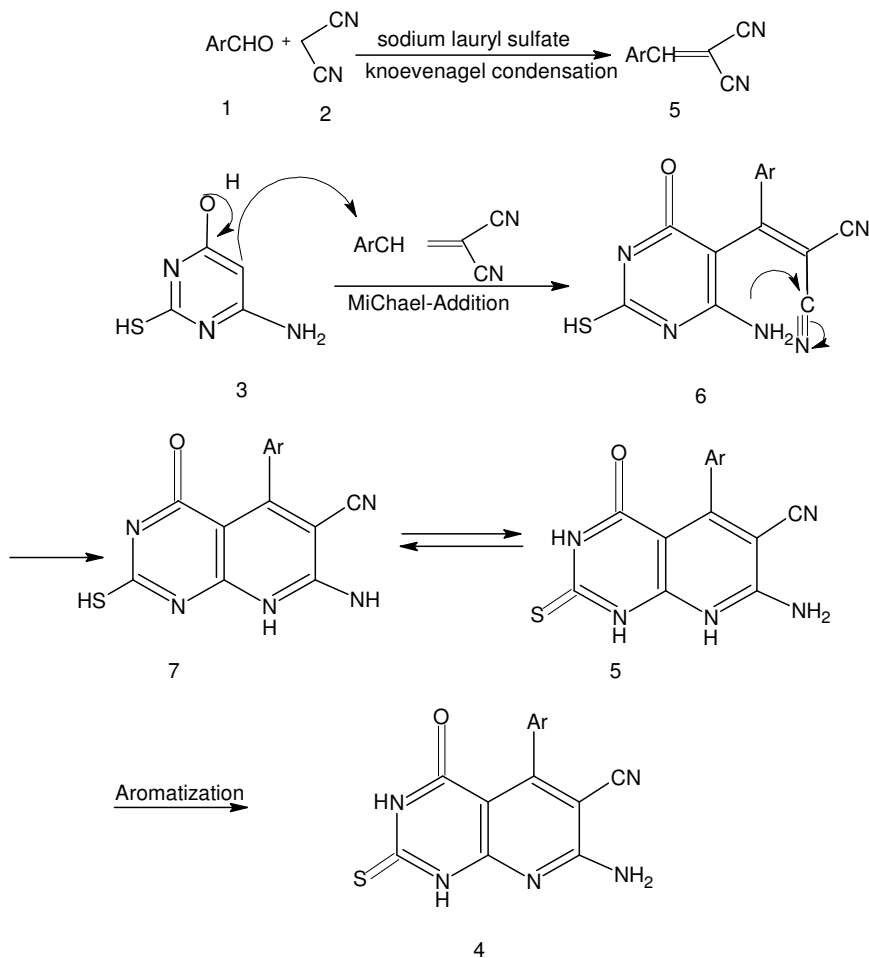
Initially, we investigated the catalytic activity of various phase-transfer catalysis (PTC) or surfactant such as hexadecyltrimethylammonium bromide (HTMAB), benzyltrimethyl ammonium bromide (BTMAB), tetrabutyl ammonium bromide (TBAB), 4-dodecylbenesulfonic acid (DBSA) and SDS. The results showed that in the presence of SDS, the reaction gives the corresponding products in good yields (81%).

The catalyst plays a crucial role in this reaction. For example, 4-nitrobenzaldehyde reacted with the other materials in the presence of 1 mol% SDS to give the product **4d** in low yield (32%) at reflux in water after 12 h. Increasing the amount of the catalyst to 5 mol%, 10 mol% and 15 mol% results in increasing the reaction yield to 62 %, 81% and 81%.

As shown in Table 1, we can find a series of aromatic aldehyde **1** were reacted with **2** and **3** in the presence of SDS in water at 90 °C, the reaction proceed smoothly to afford the corresponding products (**4**). No obvious effect of the electronic nature of substituents in the aromatic ring was observed. Benzaldehyde and aromatic aldehydes containing electron-donating groups (such as alkyl group, alkoxy group) or electron withdrawing groups (such as halide, nitro group) were employed and reacted to give the corresponding products **4** in moderate to good yield under this reaction conditions.

The structure of the compound was ascertained from spectroscopic data and elemental analysis. Take (**4d**) as the example, sharp bands at 3215  $\text{cm}^{-1}$  ( $\text{NH}_2$ ) and 2215  $\text{cm}^{-1}$  (CN) were observed in the IR spectrum of the compound. The  $^1\text{H NMR}$  spectra showed the

absence of the methylene proton of the barbituric acid and the presence of a singlet at 7.9 (NH<sub>2</sub>), the other signals appeared at  $\delta$  12.7(s, 1H, NH), 12.3 (s, 1H, NH). This also provided proof that further aromatization took place successfully. It was reported<sup>21</sup> that the dihydro pyrido[2,3-*d*]pyrimidine-2,4-diones derivatives were unstable to air and could be easily oxidized to corresponding aromatization products. According to the structure of **4** (Scheme 1), a sequential reaction of the Knoevenagel condensation, Michael addition, intramolecular cyclization followed by the aromatization may take place during the formation of the product. The possible mechanism is shown in Scheme 2.



**Scheme 2**

## Conclusion

In conclusion, we have described a convenient and practical procedure for the preparation of some new pyrido[2,3-*d*]pyrimidine derivatives by the three-component condensation of aromatic aldehyde, malononitrile and 6-amino-4-hydroxy-2-mercaptopyrimidine catalyzed by SDS in aqueous media. The milder reaction conditions, simple workup, environmental friendly and good yields are the most significant advantages of this new procedure in synthesis of these potential biologically active compounds.

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