Research Article

A Simple and Green Procedure for the Synthesis of 5-Arylidenerhodanines Catalyzed by Diammonium Hydrogen Phosphate in Water

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A simple and efficient procedure for the synthesis of 5-arylidenerhodanines by condensation of aromatic aldehydes with rhodanine in water using diammonium hydrogen phosphate as catalyst is described. The procedure offers several advantages including environmentally friendly, mild reaction conditions, short reaction times, high yields, and simple experimental and work-up procedures.

1. Introduction

Rhodanine derivatives, especially arylidenerhodanines, have shown a wide range of pharmacological activities, which include anticonvulsant, antibacterial, antiviral, and antidiabetic effects [1–3]. Arylidenerhodanines are generally prepared by reacting aldehydes and rhodanine in organic solvents and in the presence of organic bases like piperidine [2, 4–8]. Recently, catalysts such as 2,2,6,6-tetramethyl piperidine [9, 10], NH₄Cl/NH₄OH [11], K₂CO₃/[bmim]BF₄/H₂O [12], NaOAc/HOAc [3, 13, 14], glycine [15], ammonium acetate [16, 17], 1-butyl-3-methyl imidazolium hydroxide [18, 19], tetrabutylammonium bromide [20], and K₂CO₃/Al₂O₃ [21] have been used in this reaction. Although these methods are valuable, most of them suffer from some disadvantages such as a long reaction time, low yields, the use of toxic solvent, expensive catalyst, requiring a promoter, such as microwave, and tedious work-up procedures. Thus, the development of a new procedure for the synthesis of arylidenerhodanines would be highly desirable.

Water is abundant, inexpensive, safe, and clean. Among various solvents, water is the most preferred solvent. The use of water as a solvent is the strategy commonly used toward greener chemistry. A wide range of reactions that can be conducted in or on water have been developed [22–24]. Diammonium hydrogen phosphate has been used as an efficient, nontoxic, and cheap catalyst in organic synthesis [25–28]. As a part of our endeavors towards the development of efficient, and environmentally benign synthetic methodologies in water [29–32], we report herein a simple, efficient, and practical method for the synthesis of 5-arylidenerhodanines by the condensation of rhodanine with aromatic aldehydes in the presence of diammonium hydrogen phosphate in water (Scheme 1).

2. Results and Discussion

In order to get the best experimental reaction conditions, the reaction of rhodanine 1 and 2,4-dichlorobenzaldehyde 2a in the presence of 10 mol% of diammonium hydrogen phosphate in water has been considered as a standard model reaction. Effects of reaction temperature on the yields of the product were studied by performing the model reaction at 80°C, 90°C, and 100°C, respectively (Table 1, entries 1–3). The yield of product 3a was increased as the reaction was raised from 80 to 90°C. However, no increase in the yield of product 3a was observed as the reaction temperature was raised from 90 to 100°C (Table 1, entries 2-3). Therefore, 90°C was chosen as the reaction temperature for all further reactions.
Moreover, we found that the yields were obviously affected by the amount of diammonium hydrogen phosphate loaded. When the amount of the catalyst decreased to 5 mol% from 10 mol% relative to the substrates, the yield of product 3a was reduced (Table 1, entries 2 and 5). However, the use of 20 mol% of the catalyst showed the same yield and the same time was required (Table 1, entry 6). So, the use of 10 mol% of catalyst is sufficient to push the reaction forward. It is noteworthy that, in the absence of a catalyst under the reaction conditions, no product formation was observed after 60 min (Table 1, entry 4). This result indicates that the catalyst exhibits a high catalytic activity in this transformation.

Using these optimized reaction conditions, the scope and efficiency of this approach were explored for the synthesis of a wide variety of 5-arylidenerhodanines and the obtained results are summarized in Table 2. The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group and electron-donating group and the corresponding products were obtained with high yields in short times.

A plausible mechanism for this reaction has been suggested in Scheme 2. Ionization of diammonium hydrogen phosphate leads to the formation of hydroxide ion and ammonium ion. Subsequent reaction between the hydroxide ion and rhodanine gives rise to a rhodanine anion 5. Meanwhile, aldehyde can form iminium ion 4 [26]. The iminium ion 4 condenses with rhodanine anion 5 to form intermediate 6, which could be converted to 5-arylidenerhodanines 3 after elimination of ammonia.

| Entry | (NH₄)₂HPO₄ (mol%) | Temperature (°C) | Time (min) | Yield (%) |
|-------|-------------------|-----------------|------------|-----------|
| 1     | 10                | 80              | 45         | 85        |
| 2     | 10                | 90              | 18         | 86        |
| 3     | 10                | 100             | 18         | 86        |
| 4     | 0                 | 90              | 60         | 0         |
| 5     | 5                 | 90              | 18         | 75        |
| 6     | 20                | 90              | 18         | 86        |

*aReaction condition: 2,4-dichlorobenzaldehyde (2.5 mmol), rhodanine (2.5 mmol), and water (3 mL).

In summary, a simple, efficient, and green procedure has been developed for the synthesis of 5-arylidenerhodanines in water by the condensation of rhodanine with aldehydes in the presence of diammonium hydrogen phosphate. This method provides a simple and efficient protocol in terms of environmentally friendly, mild reaction conditions, short reaction times, high yields, and simple experimental and work-up procedures.
Table 2: Diammonium hydrogen phosphate catalyzed synthesis of 5-arylidenerhodanines.

| Entry | R          | Time (min) | Product | Yield (%)b | Mp (°C) found | Mp (°C) reported |
|-------|------------|------------|---------|------------|---------------|-----------------|
| 1     | 2-ClC₆H₄   | 18         | 3a      | 86         | 233–235       | 233-234 [12]    |
| 2     | 4-CH₂C₆H₄  | 14         | 3b      | 85         | 222–224       | 221-223 [12]    |
| 3     | 4-CH₃OC₆H₄ | 17         | 3c      | 88         | 248–250       | 249-250 [12]    |
| 4     | 2-CIC₆H₄   | 10         | 3d      | 88         | 180–181       | 181-182 [12]    |
| 5     | 4-FC₆H₄    | 9          | 3e      | 80         | 218–219       | 219 [1]         |
| 6     | 4-HOC₆H₄   | 13         | 3f      | 83         | 308–310       | 310 [16]        |
| 7     | 4-BrC₆H₄   | 15         | 3g      | 82         | 228–230       | 229-230 [12]    |
| 8     | 3-NO₂C₆H₄  | 16         | 3h      | 90         | 263–265       | 263–265 [12]    |
| 9     | 4-CIC₆H₄   | 13         | 3i      | 81         | 228–230       | 229-230 [12]    |
| 10    | C₆H₅       | 8          | 3j      | 86         | 204–206       | 205–207 [12]    |
| 11    | 2-HOC₆H₄   | 16         | 3k      | 84         | 222–223       | 221-222 [21]    |
| 12    | 2-Furyl     | 4          | 3l      | 85         | 227–229       | 228-229 [12]    |
| 13    | 4-HO-3-CH₃OC₆H₄ | 11 | 3m | 84 | 231-232 | 231–231.5 [21] |

*Reaction condition: aldehyde (2.5 mmol), rhodanine (2.5 mmol), (NH₄)₂HPO₄ (0.25 mmol), 90°C, and water (3 mL).

bIsolated yield.

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