Water-mediated synthesis of disubstituted 5-aminopyrimidines from vinyl azides under microwave irradiation

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\textbf{ABSTRACT}

An efficient and ecofriendly method for the synthesis of disubstituted 5-aminopyrimidines from vinyl azides and urea or thiourea was developed. This reaction proceeds under microwave irradiation conditions in the presence of water as a solvent. The remarkable features of this new protocol are high conversion, short reaction times, cleaner reaction profiles and straightforward procedure.

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1. Introduction

Heterocyclic molecules are of biological interest due to their potential physical and chemical properties (1). Among these, the pyrimidine compounds occupy a unique position in pharmaceutical chemistry, as they are components of nucleic acids. Pyrimidines are correlated with various therapeutic activities, e.g. anti-HIV (2), anti-tubercular (3), antitumor (4), antineoplastic (5), anti-inflammatory (6), diuretic (7), antimalaria (8), and cardiovascular (9). These compounds also have diverse applications such as bactericidal (10), fungicidal (11), and analgesics (12). It is worthy to note that only a few direct synthesis of 5-aminopyrimidines have been described in the literature. One of the most common methods used for the preparation of 5-aminopyrimidines employs the reduction of 5-nitropyrimidines with multiple steps (13), or vinyl azides using base (14) or toxic solvents (Scheme 1) (15). In this regard, the development of a facile and green synthetic method to access the disubstituted 5-aminopyrimidine is needed.

Vinyl azide is a key synthon for the formation of nitrogen-containing heterocycles (azaheterocycles) (16). Especially, it has been reported that vinyl azide was employed with various transition metals in pyrrole synthesis (15).

In continuation of our research program focusing on the preparation of heterocyclic and therapeutic agents (17) and the development of more ecofriendly process and synthesis (18), we decided to optimize the synthesis of disubstituted 5-aminopyrimidines from vinyl azide and urea or thiourea in water, under microwave irradiations (Scheme 2).

2. Results and discussion

2.1. Optimization of reaction conditions

First, to optimize the reaction conditions, the coupling of 2-azido-3-(4-bromophenyl)-1-phenylprop-2-en-1-one...
with urea was selected as the model reaction (Table 1). Initially, we found out that the use of a two-fold molar excess of urea is the good ratio as described by Yu and coworkers (15). The use of the excess of urea was necessary to ensure complete formation of the product and also for the compensation of the decomposed urea to $\text{CO}_2 + \text{NH}_3$. As shown in Table 1, different solvents were tested (entries 1–7). Starting from MeOH or CH$_3$CN (entries 1 and 2), low yields were obtained. When toluene or dioxane was employed, increased yields were observed, 53% and 46%, respectively (entries 5 and 6). Moreover, the use of dimethylformamide (DMF) or tetrahydrofuran (THF) led to the described product with good yields. However, we were pleased to find that water was the most effective solvent with a highly improved chemical yield of 97%, despite the quite poor solubility of substrates, in only 10 min of microwave irradiation (entry 7).

**Scheme 1.** Previous procedure developed by Yu and coworkers for the preparation of 5-aminopyrimidines.

**Scheme 2.** Green synthesis of disubstituted 5-aminopyrimidines from vinyl azides under microwave irradiation.

| Entry | Solvent | Reaction time (min) | Yield (%)$^b$ |
|-------|---------|---------------------|-------------|
| 1     | CH$_3$OH | 10                  | 36          |
| 2     | CH$_3$CN | 10                  | 12          |
| 3     | THF     | 10                  | 79          |
| 4     | DMF     | 10                  | 82          |
| 5     | Toluene | 10                  | 53          |
| 6     | Dioxane | 10                  | 46          |
| 7     | Water   | 10                  | 97          |

$^b$Reaction conditions: vinyl azide (0.25 mmol, 1.0 equiv.), urea (0.5 mmol, 2.0 equiv.), solvent (5 mL).

Table 2. Reactions of various vinyl azides with urea or thiourea.$^a$

| Entry | $R_1$ | $R_2$ | $X$ | Product | Yields$^b$ (Time, min)$^c$ |
|-------|-------|-------|-----|---------|---------------------------|
| 1     | Br    | O     | O   | 3a      | 97% (10)                  |
| 2     | Br    | Br    | O   | 3b      | 88% (10)                  |
| 3     | Br    | O     | O   | 3c      | 71% (20)                  |
| 4     | Cl    | O     | O   | 3d      | 79% (20)                  |
| 5     | Cl    | O     | O   | 3e      | 76% (20)                  |
| 6     | Cl    | Cl    | O   | 3f      | 97% (10)                  |
| 7     | Cl    | F     | O   | 3g      | 96% (10)                  |
| 8     | Cl    | Br    | O   | 3h      | 94% (10)                  |
| 9     | Cl    | S     | O   | 3i      | 70% (20)                  |

$^b$The yield of the isolated product.

(Continued)
2.2. Typical procedure for the synthesis of 5-amino-6-(4-bromophenyl)-4-phenyl-1H-pyrimidine-2-one 3a

To a 10-mL glass microwave vial, a mixture of vinyl azide 1 (0.25 mmol) and urea 2 (0.5 mmol) in water (5 mL) was added. The mixture was heated in a microwave for 10 min at 160 W (120°C). After completion of the reaction, the mixture was cooled and the crude product was filtered. The crude product was purified by recrystallization (EtOH/Water (4/1)) to afford 5-amino-6-(4-bromophenyl)-4-phenyl-1H-pyrimidine-2-one 3a.

As known the heating azides, or mixtures which contain azides, result in a rapid decomposition of the material, and often in an explosion. This process releases a large volume of gases. In our case, we have worked on a small amount of azides to avoid any problem. In our cases, we did not meet any difficulty.

2.3. Extension of the methodology

Having in hands the optimal reaction condition, the scope of the reaction was studied using a series of vinyl azides and urea or thiourea. The vinyl azides were readily prepared according to the literature (19).

The presence of an electron-donor group (CH₃ or OCH₃) on the ring of R₁ or R₂ decreased the reactivity of vinyl azides towards urea or thiourea (Table 2, entries 3, 5, 10, 13, 15, and 20). However, yields were higher than those observed by Yu and coworkers. When R₁ or R₂ consisted in an electron-withdrawing group such as Cl, Br, and F, the reactivity of the corresponding vinyl azides was increased and higher yields were achieved (entries 1, 2, 4, 6–8, 11, 12, 14, and 16–18). The use of vinyl azide bearing a thienyl at the R₂ position (Table 2, entries 9 and 19) gave lower yield than the other products.

In conclusion, we have developed a simple, fast, efficient, and ecofriendly method for the synthesis of disubstituted 5-aminopyrimidine-2(1H)-ones or 5-aminopyrimidine-2(1H)-thiones, from readily available α-azidovinyl ketones and urea or thiourea under microwave irradiation, in water as non-toxic and environmentally benign green solvent in mild conditions to obtain the corresponding products in good yields. The reaction is realized by 1,4-Michael addition and subsequent rearrangement. This method is very attractive and can contribute to reduce environmental problems.

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