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An Unexpected Guanidine-catalyzed Amination Reaction Leading to (*Z*)-α-Aminocinnamamides

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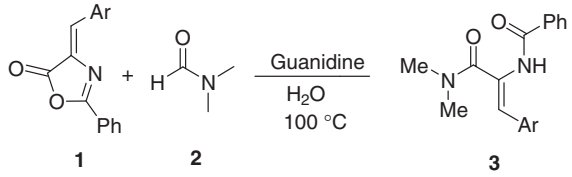
An unexpected guanidine-catalyzed amination reaction between 4-(arylmethylidene)-2-phenyloxazol-5-ones and *N*,*N*-dimethylformamide in water for selective synthesis of new (Z)-α-aminocinnamamides was described. This method has the advantages of short synthetic route, operational simplicity, and minimal environment impact.

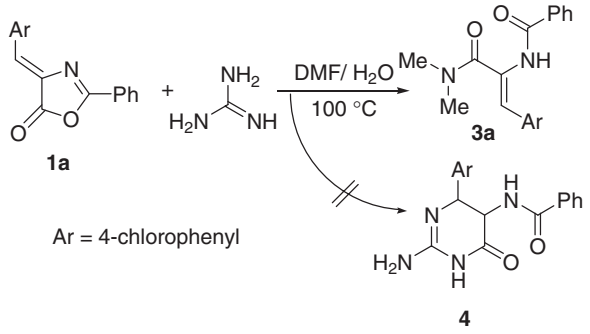
The development of efficient and environmentally friendly chemical processes for the preparation of new biologically active molecules constitutes a major challenge for chemists in organic synthesis.[1] In this regard, organic reactions in water without using harmful organic solvents have received much attention. In addition to being a safe, readily available, and environmentally friendly solvent,[2] water has also been recognized as an effective reaction medium with unique properties and possibilities for many organic reactions such as Mannich reactions,[3] Kröhnke reactions,[4] and esterification reactions.[5] The continued development of new reaction types in aqueous media is becoming an interesting area for chemists.

Catalytic amination reactions are among the oldest and most often used reactions in organic synthetic chemistry extensively employed for the protection and further manipulation of the carboxylic acid functional group.[6] Amination processes are widespread in the industrial synthesis of a variety of end-products. In view of their importance, amination protocols should occupy a prominent place in the desire to advance benign and sustainable chemical technologies into industrial process development. However, amination reactions are equilibrium reactions and generally require removal of water and/or use of excess amount of the reactants for satisfactory conversion rate.[7] For the preparation of substituted amines, the major drawbacks of these common methods are separation of the metal catalyst supported on a solid support and, moreover, the removal of adsorbed products from the catalyst is quite difficult and requires a large excess of volatile organic solvents.[8] Therefore, numerous modern versions of the amination reaction have been developed to overcome the drawbacks of the classical method. In general, the improved methodology relies on the screening of catalytic systems.[9] Quite surprisingly, mild base-catalyzed amination reactions in water using 4-(arylmethylidene)-2-phenyloxazol-5-ones as precursors have not stimulated much interest so far. As a continuation of our research devoted to the development of green organic chemistry using water as reaction media,[10] herein we report unexpected solvent-involved amination reactions for environmentally benign synthesis of (Z)-α-aminocinnamamides[11] using guanidine carbonate as a mild base catalyst and water as reaction media (Scheme 1).

Our strategy for synthesizing the (Z)-α-aminocinnamamides was through the reaction of preformed 4-(arylmethylidene)-2-phenyloxazol-5-ones with *N*,*N*-dimethylformamide (DMF). In



Scheme 1. Synthetic route of (Z)-α-aminocinnamamides.



Scheme 2. The optimized conditions for formation of **3**.

our recent efforts aiming at synthesizing pyrimidines **4**, the treatment of 4-(arylmethylidene)oxazol-5-ones **1a** with guanidine carbonate in DMF were performed at 100 °C (Scheme 2). After six hours, white product was obtained. Surprisingly, spectroscopic data (IR and ^{1}H NMR) indicated that this product was not the desired compound **4**. Suitable crystals of the purified product **3f** were grown and the relative stereochemistry was elucidated by X-ray diffraction in the case of (Z)-α-aminocinnamamides **3f** (Figure 1).[12]

Next, the model reaction of 4-(arylmethylidene)oxazol-5-ones **1a** with DMF and guanidine carbonate was carried out to optimize the catalysis conditions, including solvents and amount of catalyst, in order to achieve the best results in the amination reactions (Table 1). The experimental results showed that guanidine carbonate in a medium consisting of 1:1 DMF–H_2O was highly efficient, and 100 °C as reaction temperature could provide high yield. In order to evaluate the influence of guanidine carbonate concentration, this reaction was carried out using different amounts of guanidine carbonate. The reaction proceeded in the presence of 0.1 equivalent of guanidine to give the product **3a** in 42% yield at 100 °C. Increasing the reagent to 0.15 equivalent, 0.2 equivalent, and 0.3 equivalent successively resulted in the increasing of the yield to 51%, 60%, and 74%, respectively. Use of just 0.4 equivalent was sufficient to reach the highest yield. Further increase of the amount of the catalyst failed to improve the yield.

To extend the scope of this amination procedure for the synthesis of α-aminocinnamamides, substrates **1b**–**1h**, with elec-

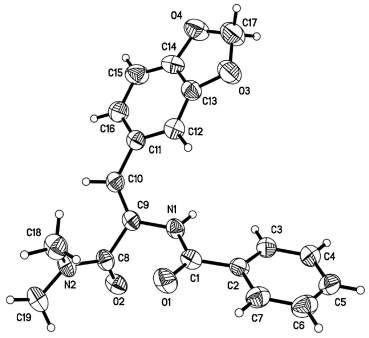


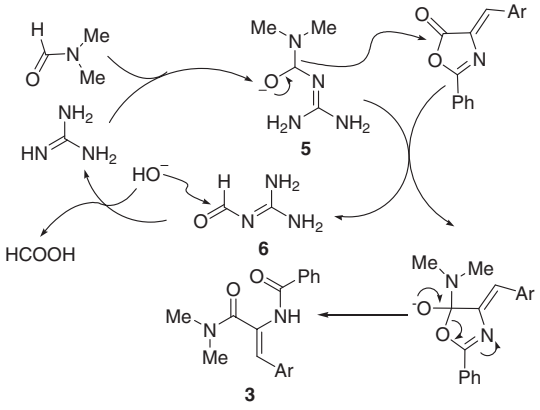
Figure 1. The ORTEP drawing of **3f**.

Table 1. Solvent optimization for the synthesis of **3a**

Entry	Solvent	Time/h	Yield/%
1	DMF	6	68
2	DMF/water (v/v: 1:1)	6	82
3	DMF/water (v/v: 2:1)	6	79
4	DMF/water (v/v: 1:2)	6	68
5	DMF/THF (v/v: 1:1)	6	42
6	DMF/CH_3CN (v/v: 1:1)	6	49

Table 2. Synthesis of (Z)-α-aminocinnamamide derivatives **3**[13]

Entry	**3**	Ar	Time/h	Yield/%
1	**3a**	4-Chlorophenyl (**1a**)	6	82
2	**3b**	4-Bromophenyl (**1b**)	6	84
3	**3c**	4-Fluorophenyl (**1c**)	6	79
4	**3d**	2-Chlorophenyl (**1d**)	6	75
5	**3e**	3-Nitrophenyl (**1e**)	6	87
6	**3f**	Benzo[*d*][1,3]dioxol-5-yl (**1f**)	7	75
7	**3g**	4-Methoxyphenyl (**1g**)	8	73
8	**3h**	3,4,5-Trimethoxyphenyl (**1h**)	7	70



Scheme 3. Mechanism of the formation of **3**.

tron-donating or electron-withdrawing groups on the phenyl rings, were then examined for their reactions with DMF under the optimized conditions. As a result, a series of products **3b**–**3h** was obtained in excellent yields of 70–87% (Table 2, Entries 2–8).

A reasonable mechanism for the formation of the product **3** is outlined in Scheme 3. The formation of the α-aminocinnamamide **3** is expected to proceed via initial nucleophilic attack of NH to the C=O group to afford intermediates **5** and **6**. The intermediate **5** then undergoes in situ intermolecular nucleophilic addition with 4-(arylmethylidene)-2-phenyloxazol-5-ones to give open-chain product **3**. The intermediate **6** hydrolyzed to the guanidine in the presence of base.

In summary, we have developed highly efficient amination reactions in water using guanidine as a nontoxic, inexpensive, and promising eco-friendly catalyst for the selective production of a series of (Z)-α-aminocinnamamides. The chemistry has several advantages: (1) the guanidine carbonate, as a mild base-catalyst, shows good catalytic activity in water; (2) the methodology is compatible with a wide range of 4-(arylmethylidene)-2-phenyloxazol-5-ones and DMF; (3) the amides produced can be isolated conveniently in high yields and purity; (4) the chemistry has high stereoselectivity. The versatility of this chemistry offers a valuable addendum to methodology for the clean synthesis of cinnamamides.

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12 The single-crystal growth was carried out in ethanol at rt. Crystal data for $C_{19}H_{18}N_2O_4$, $M_r = 338.35$, monoclinic, space group $P2(1)/n$, $a = 12.502(2)$ Å, $b = 20.539(3)$ Å, $c = 13.585(3)$ Å, $V = 3468.8(10)$ Å^3, $Z = 8$, $T = 298(2)$ K, $\mu = 0.092$ mm^{-1}, 18096 reflections measured, 6116 unique reflections, $R = 0.0556$, $R_w = 0.1105$; CCDC 760208.
13 Experimental section sees Supporting Information, which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

