

Multicomponent Reactions Are Accelerated in Water

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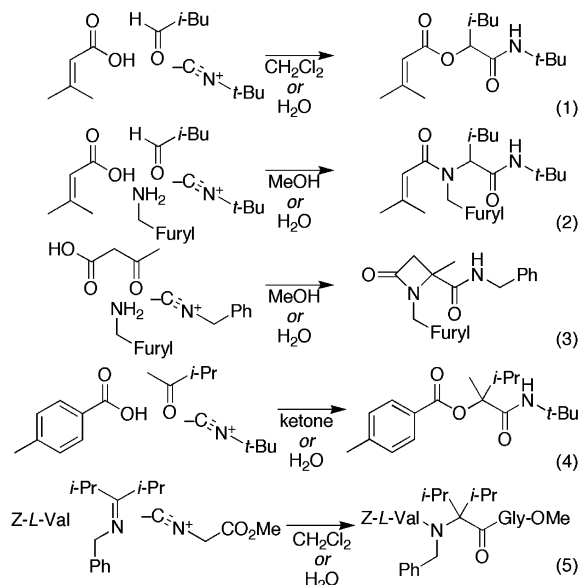
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The use of water as a solvent for organic transformations offers several "green chemistry" benefits.¹ In many reactions, such as the Diels–Alder cycloaddition,² significant rate enhancements are observed in water compared to organic solvents. This acceleration has been attributed to many factors, including the hydrophobic effect,³ enhanced hydrogen bonding in the transition state,⁴ and the high cohesive energy density of water (550.2 cal·mL⁻¹ at 25 °C).⁵ The Diels–Alder reaction is also known for its negative activation volume, owing to a transition state that is more compact than reactants. Reactions with negative activation volumes are accelerated at high pressure and, with nonpolar reactants, in water.⁶

The multicomponent reactions important in combinatorial chemistry⁷ are predicted to exhibit negative activation volumes owing to the condensation of several molecules into a single reactive intermediate and product. Promotion of the Passerini⁸ and the Ugi⁹ reactions at high pressure provides further support for this idea and suggests they could be accelerated in water. Although aqueous/organic solvent mixtures have been used in multicomponent reactions, they are not expected to show the same rate effects as for pure water as solvent. The influence of water on the rates of the Ugi or Passerini reactions has not been earlier examined.¹⁰ In organic solvent, the Passerini reaction is first order in each reactant and is believed to involve preequilibrium formation of an isonitrile–carbonyl adduct followed by protonation of this tetrahedral intermediate by the acid.¹¹ The rate-determining step follows, either the nucleophilic addition of the carboxylate to the nitrilium ion or the subsequent rearrangement reaction. As described below, not only does the use of water as solvent permit multicomponent reactions to be conducted rapidly, the products are often insoluble, facilitating their ready isolation. This method permits rapid syntheses of compound libraries.

As a prototype, the Passerini reaction in eq 1 (see Scheme 1) was studied under various conditions summarized in Table 1. In CH₂Cl₂ this reaction gives fair conversion and yield. When performed in water, the reaction is complete in 3.5 h (95% isolated) and becomes heterogeneous because the product is poorly soluble. Determination of the rates of product formation by gas chromatography (after extraction into organic solvent) showed that water provides ~18-fold acceleration over CH₂Cl₂. To address questions concerning the basis of the rate acceleration (vide infra), this reaction was examined in MeOH (no reaction) and formamide (15% conversion, 24 h). Because the hydrophobic effect is increased by ionic or nonionic solutes,⁶ the effects of LiCl and glucose were examined. At high LiCl concentration, the reaction was so fast that quality rate data could not be obtained; therefore, a lower concentration was used to demonstrate an additional 16-fold acceleration over pure water. Likewise, a high glucose concentration provided a very rapid rate, and lower glucose concentration showed 7-fold acceleration over pure water. While solute effects have earlier been used to examine the acceleration of reactions in water, temperature effects have not often been studied. At 4 °C, the rate increases 11%, and at 50 °C, the rate decreases 44%.

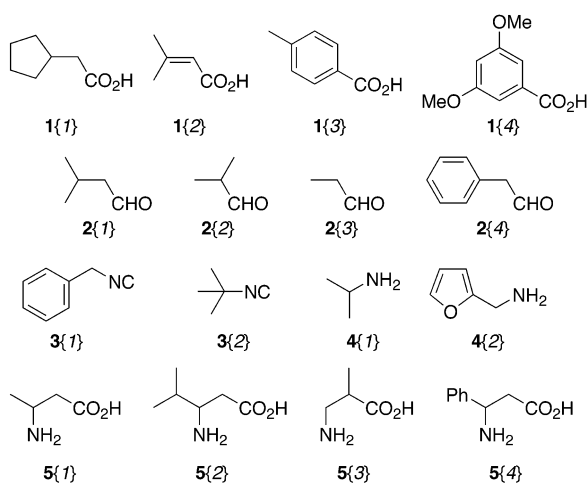
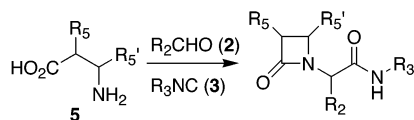
Scheme 1. Multicomponent Reactions Accelerated in Water**Table 1.** Passerini Reaction (eq 1) under Various Reaction Conditions

solvent	time (h)	temp (°C)	conversion (%)	yield (%)	rate (M ⁻² s ⁻¹) ^b
CH ₂ Cl ₂	18	25	50	45	0.01
H ₂ O	3.5	25	100	95	0.18
2.5 M aq LiCl	0.3	25	100	95	ND
1.0 M aq LiCl	0.8	25	100	95	2.86
1.0 M aq glucose	0.8	25	100	95	ND
0.5 M aq glucose	2	25	100	94	1.29
H ₂ O	2	4	100	93	0.20
H ₂ O	5	50	100	91	0.10

^a ND – not determined. ^b Percent standard deviations were 3–6%.

The broader applicability of the accelerating effect of water on multicomponent reactions is supported by a nearly 50-fold acceleration for the Ugi reaction in eq 2. Likewise, the creation of strained β -lactam rings by Ugi reaction with β -keto-acids is unknown in organic solvents, as exemplified by the complete failure of the reaction in eq 3 in MeOH, THF, or CH₂Cl₂. This reaction proceeds well in water, however (72 h, 65% yield).

Evaluation of the effects of water on multicomponent reactions known to be accelerated by high pressure also seemed germane to this work. The Passerini reaction shown in eq 4 was reported⁸ to require 16.5 h at 3 kbar in 3-methyl-2-butanone as solvent (39% isolated yield). Of course, performing a reaction in water is much more convenient than performing it at high pressure. In pure water (36 h, mechanical shaking, 44% conversion), the product can be obtained in comparable yield using only 5 equiv of ketone. In 2.5 M aqueous LiCl, the isolated yield is 65%. The Ugi reaction shown in eq 5 was reported⁹ to require 14 d at a pressure of 9 kbar in

Chart 1. Building Blocks for Multicomponent Reactions**Scheme 2.** Synthesis of a β -Lactam Library by Ugi Reaction

CH_2Cl_2 (61% isolated yield). In pure water at STP, the product is isolated in 55% yield in only 72 h, and in 2.5 M aqueous LiCl the yield is 75%.

This method for the acceleration of multicomponent reactions was applied to the parallel synthesis of 32 Passerini reaction products from building blocks **1**, **2**, and **3** (Chart 1). The acid was used in 10% excess, with the aldehyde and isocyanide in equimolar amounts. These reactions are complete in 3–6 h at 25 °C. For solid products, isolation simply involved filtration and washing with 10% aqueous NaHCO_3 . For the few liquid products, isolation was by extraction, filtration through $\text{NaHCO}_3/\text{Celite}$ and $\text{Na}_2\text{SO}_4/\text{SiO}_2$, and evaporation. Yields were 72–93% (av 87%), and crude HPLC purities were 72–100% (av 87%). Likewise, preparation of Ugi reaction products by parallel synthesis was performed in water. Amines **4** were used with building blocks **1**, **2** (except **2{4}**), and **3** to give a 48-compound library. These reactions were complete in 3 h at 25 °C, and products were isolated by extraction. The crude HPLC purities were 83–99% (av 95%), and yields were 78–95% (av 86%). These results are summarized in Tables S1 and S2.

Use of β -amino acids in the Ugi reaction (Scheme 2) produces β -lactams.¹² A library of 32 β -lactams was created by Ugi reaction in water using building blocks **2**, **3**, and **5** and isolated by extraction. The HPLC purity of the crude reaction products was 70–99% (av 89%), and the yields of these products were 71–89% (av 84%). These results are summarized in Table S3.

Identification of specific factors contributing to acceleration in water of the multistep reactions studied here is even more challenging than with concerted reactions such as the Diels–Alder reaction. Direct mechanistic involvement of water in bond-making

is a tempting alternative to hydrophobic and cohesive energy density effects or hydrogen bonding in the transition state. Significantly slower rates in the protic, hydrogen-bonding solvent methanol suggest that water plays no direct role in these reactions. Formamide has a lower cohesive energy density (376.4 cal·mL⁻¹) than water but a higher dielectric constant. The reaction in eq 1 is much slower in formamide, suggesting that cohesive energy density is more important than dielectric constant and refuting the hypothesis that stabilization of charged intermediates in water contributes to rate acceleration.

Distinguishing between hydrophobic and cohesive energy density effects on rates can be difficult because hydrophobic effects scale with the solvent-accessible surface area in the transition state and cohesive energy density effects scale with the volume of the transition state. These parameters are obviously correlated. The cohesive energy density of water decreases with temperature [554.3 at 4 °C (+0.75% vs rt); 542.2 at 50 °C (–1.45% vs rt)], which may explain the inverse temperature dependence. The much slower reaction in formamide suggests a steep dependence of the rate on cohesive energy density. Alternatively, when the rate is sensitive to hydrophobic effects, inverse temperature dependence may result from a large heat capacity of activation.¹⁴

The utility of two multicomponent reactions has been significantly expanded by conducting them in water. They can exhibit rate accelerations compared to those in organic solvents of nearly 300-fold, and the insolubility of the Passerini products in water makes isolation trivial. The crude reaction products show purity adequate for initial biological testing.

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Supporting Information Available: Tables of yields and purities for each library (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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