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Tetrahedron Letters 49 (2008) 2128–2131
Tetrahedron Letters

Utilizing the high dielectric constant of water: efficient synthesis of amino acid-derivatized cyclobutenones

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Received 20 November 2007; revised 26 January 2008; accepted 28 January 2008
Available online 1 February 2008

Abstract

This work reports the use of water as a solvent to facilitate an efficient syntheses of amino acid-derivatized cyclobutenone. Kinetics studies in different solvents reveals that high dielectric constants of the solvents are the primary attribute for the high yielding and fast rate for this reaction. This class of substitution reactions in water also proceeds efficiently with a wide range of amino acids.

As many sophisticated chemical transformations sustaining life occur in aqueous environments, we are interested in developing new methodologies and reactions that utilize the unique properties of water to enable the efficient synthesis of molecules of therapeutic potential or fundamental interests. Such efficient synthesis should support shortening of the route to the product, and lessening the use of protecting groups. Water as a solvent has been explored for many types of organic transformations.[1–9] Apart from being environmentally friendly, water offers several relatively unexplored advantageous properties to facilitate the transformation of organic reactions. First, water has the highest dielectric constant among other polar protic and aprotic solvents, which promotes the polarization of reactants to enhance their reactivity.[10] Second, the strong hydrogen bonding capability of water molecules can provide a means to activate specific bonds in a molecule through specific hydrogen bonds. Recently, there are significant advances in using hydrogen bonds albeit in organic solvents to catalyze a reaction.[11–15,9] Third, water possesses a wide range of anomalous properties as a liquid,[16] but the effect and utilization of these properties has not been explored. In a recent study, we have demonstrated that water, as a solvent, can be used to impart high chemoselectivity in a designed organic reaction between squarate derivative and cysteine amino acids, or cysteine-containing peptides.[9] In this work, we report the utilization of the high dielectric constant to facilitate a route-shortened, high yielding synthesis of amino acid-derivatized cyclobutenones using unprotected amino acids.

Cyclobutenones are strained molecules that are useful as synthetic intermediates for making complicated structures[17–21] and potential therapeutic agents.[18,22–25] Recently, amino acid-derivatized cyclobutenones are shown to exhibit antagonistic activities[25] against a class of membrane proteins (integrin) on mammalian cells, which are important targets for developing therapeutic agents.[26] In that work, the key synthesis of amino acid-derivatized cyclobutenones was carried out in two steps in organic solvents, where 3-ethoxycyclobutenone was first converted to 1,4-cyclobutandione and followed by the treatment of amino acids. This two-step synthesis was required because the authors observed that the direct substitution of 3-ethoxy cyclobutenone with amino acids did not yield any desirable conversion in organic solvents.[27,25] Here, we postulate that because of the ring strain and the conjugation, the ester characteristics in 3-ethoxycyclobutenone are more activated and more prone to hydrolysis and

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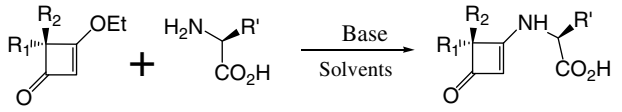
doi:10.1016/j.tetlet.2008.01.121



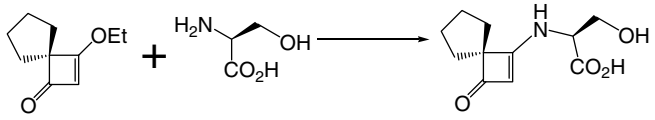
1: R_1, R_2 = -$(CH_3)_3$ -
2: R_1, R_2 = -$(CH_3)_4$ -
3: R_1 = Et, R_2 = Me

Scheme 1.

substitution than a generic ester.[28,23] As such, we set to investigate whether a polar solvent with a high dielectric constant, particularly water, can drive a direct substitution of various 3-cyclobutenones by different amino acids (Scheme 1).

Cyclobutenones **1–3** were synthesized by adopting the reported literatures.[29–31] Examining this substitution reaction in different solvents reveals that this substitution reaction indeed does not proceed well in organic solvents (Table 1).[32,33] Substitution reaction of cyclobutenone **2** with L-serine shows that the rate in DMSO-d_6 (5×10^{-5} L mol^{-1} s^{-1}) is slightly higher than that in CD_3OD (3.5×10^{-5} L mol^{-1} s^{-1}). Notably, both the yield (74%, Table 2) and the rate (10×10^{-5} L mol^{-1} s^{-1}) are the highest in water mixed with 10% DMSO. DMSO is added in water to ensure a complete solubilization of the reactants. Overall, the rate of the reaction increases when the dielectric constant of the solvent is increased. Adding urea, a weak hydrogen bond donor, to DMSO, the rate of the reaction seems to be slightly suppressed (Table 1, entry 3). When CF_3CD_2OD is used as the solvent, which has a low dielectric constant but strong hydrogen bonding capability, there is no observable transformation for this reaction (Table 1, entry 5). In contrast to ours[9] and other reports that use urea to catalyze organic reactions via hydrogen bonding,[34,35] these results suggest that hydrogen bonding is not catalyzing, nor facilitating the transformation of this substitution reaction. Consequently, the high dielectric constant of solvent appears to be the major attribute for promoting both the rate and the yield of the reaction.

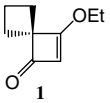
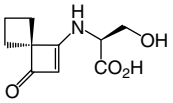
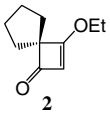
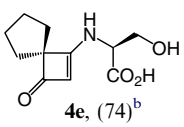
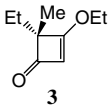
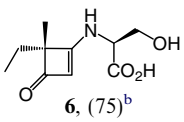
Table 1
Substitution reaction of **2** with L-serine in different solvents



Entry	Solvent	Dielectric constant[a]	k[b] (L mol^{-1} s^{-1})
1	D_2O/DMSO-d_6 (9:1)	—	100×10^{-6}
2	DMSO-d_6	46.45	50×10^{-6}
3	4 M urea in DMSO-d_6	—	30×10^{-6}
4	CD_3OD	32.66	35×10^{-6}
5	CF_3CD_2OD	26.67	—[c]

[a] Ref. 13.
[b] Reaction condition: **2** (1.0 equiv), Ser (1.0 equiv), NaOH (1.0 equiv), $C_0 = 109$ mM.
[c] Product not detected.

Table 2
Substitution reactions of different cyclobutenones with L-serine

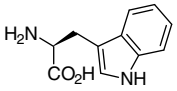
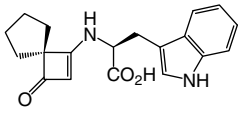
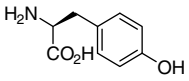
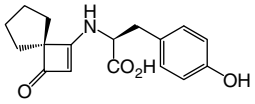
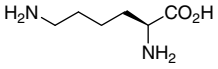
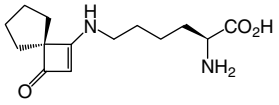
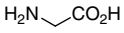
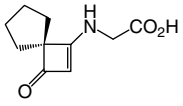
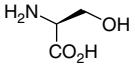
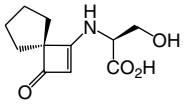
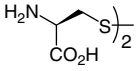
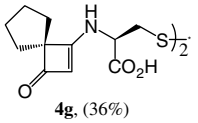
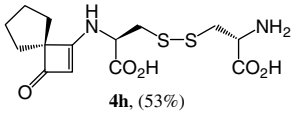
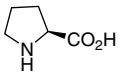
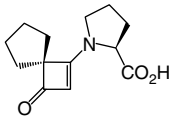
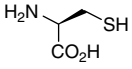
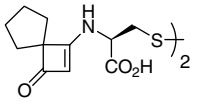
Cyclobut-enones	Product (yield (%))	k[a] (L mol^{-1} s^{-1})
 **1**	 **5**, (80)[b]	9×10^{-4}
 **2**	 **4e**, (74)[b]	1×10^{-4}
 **3**	 **6**, (75)[b]	0.2×10^{-4}

[a] Reaction conditions: cyclobutenone (1.0 equiv), Ser (1.0 equiv), NaOH (1.0 equiv), $C_0 = 109$ mM.
[b] Isolated yield.

Next, we studied the effect of the structure of the 3-ethoxycyclobutenones on their reactivity of being substituted by amino acids in water (with 10% DMSO). The structure includes bicyclic 3-ethoxy cyclobutenones **1** and **2**, and alkyl-substituted 3-ethoxy cyclobutenone **3**. As the ring size increases from cyclobutane to cyclopentane, and to an open form, the strain and the electronegativity decrease in the cyclobutenone ring of the molecules. Examining the rate of substitution of **1**, **2**, and **3** by L-serine amino acid in D_2O/DMSO-d_6 with one equivalent of NaOH indicates that the substitution of **1** is about 9 times faster than **2**, and 45 times faster than **3** (Table 2).[32] Past studies on cyclic rings have inferred an increase in the **s**-character of the ring C–H bond as the ring gets smaller, and thus impose an electron-withdrawing effect.[36,37] Consistent with this rationale, we believe that our result is consistent with the increase in the polarization of the cyclobutenone ring due to the attached cyclic alkane, which enhances the rate of the substitution of the amino acids.

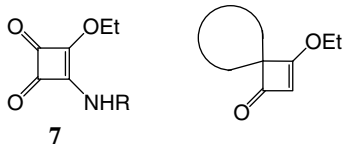
Next, we examined the scope of this substitution reaction with eight amino acids including L-tryptophan, L-tyrosine, L-lysine, L-glycine, L-serine, L-cystine, L-proline, and L-cysteine.[38] While these amino acids vary greatly in their structures, high yield is obtained for all of these amino acids except for proline (yield ~64%, Table 3, entry 7) and for cysteine (yield ~36%, Table 3, entry 8). For cysteine, we believe that the thiolate group, being a strong nucleophile in solutions with high pH values, first displaces the ethoxy group on the cyclobutenone. At high pH, this thiolate can either proceed with hydrolysis[39] or with a S→N acyl transfer that affords the observed product.[40] These two competing processes result in a low yield of the observed product. Notably, the amino acids bearing aromatic residues (tryptophan and tyrosine) afford the highest yields among this collection of amino acids.

Table 3
Substitution reactions of **2** with different amino acids[a]

Entry	Amino acids	Time (h)	Product (yield)[b]
1		3	 **4a**, (98%)
2		72	 **4b**, (91%)
3		13	 **4c**, (88%)
4		13	 **4d**, (77%)
5		10	 **4e**, (74%)
6		48	 **4g**, (36%)  **4h**, (53%)
7		13	 **4f**, (64%)
8		48	 **4g**, (38%)

[a] Reaction conditions: 2 (1.0 equiv), amino acid (1.5 equiv), NaOH (1.5 equiv), solvent: H_2O (0.9 mL)–DMSO (0.1 mL).
[b] Isolated yield.

In comparison to a recent work of water-driven chemoselective reaction,[9] it is interesting to note that squarate derivative **7** (Scheme 2) reacts with cysteine amino acids or cysteine bearing peptides at neutral pHs, whereas 3-ethoxy cyclobutenones require a basic condition for the substitution to occur (Scheme 2).



Scheme 2.

Finally, we determined the preferred conformation of the amino acid residue relative to the cyclobutenone ring in the products by using nuclear overhauser enhanced spectroscopy (NOESY) spectroscopy (see Supplementary data). In general, the amino acid-derivatized cyclobutenones adopt 'cis-like' conformations, in which the chiral carbon on the amino acids is 'cis' relative to the double bond in the cyclobutenones—a structure that appears to minimize the steric congestion between the cyclopentane ring and the amino acid residue (Scheme 1).

To conclude, while water has been used as a solvent for a wide variety of organic reactions, the demonstration of the explicit use of the high dielectric constant of water to drive a reaction is rare. In this work, we show that the substitution of 3-ethoxycyclobutenones with amino acids, which were reported not to proceed in organic solvents, proceeds with the fastest rate and the highest yield in an aqueous solution. Based on the kinetic studies of this substitution reaction in different solvents, the primary attribute of the solvent effect appears to be the high dielectric property of water rather than hydrogen bonding or hydrophobic effects. Whether water as a solvent will increase the reactivity of other strained molecules in general is the subject of our ongoing research.

Acknowledgments

We thank the Chemistry Department of SU, Syracuse Center for Excellence CARTI award supported by US Environmental Protection Agency [Grant Nos.: X-83232501-0] and NSF-CMMI [Grant No: 0727491] for financial support. We also thank Professor Boddy and Sponsler for helpful discussion.

Supplementary data

Measurement of rate constants of **1–3** reacting with L-serine in different solvents, and conformational study of **4d** and **4e** by 1H NOESY. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.121.

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32. *General procedure for the substitution reaction of cyclobutenone with amino acid—3-ethoxyspiro[3.4]-oct-2-en-1-one* (**2**) *with* L-*serine*: A solution **2** (20 mg, 0.12 mmol), L-serine (19 mg, 0.18 mmol), and NaOH (7.2 mg, 0.18 mmol) in water (0.9 mL) and DMSO (0.1 mL) was stirred at room temperature for 10 h. The solution was washed with ether (2.0 mL) twice and then acidified with 1.0 N HCl to pH ~ 5–6. Concentration under reduced pressure, followed by chromatography (SiO_2, MeCN–H_2O = 10:1–5:1) gave product **4e** (20 mg, 74%): ^{1}H NMR (MeOH-d_4) δ 4.57 (1H, s), 3.86–3.93 (3H, m), 1.71–1.96 (8H, m); ^{13}C NMR (MeOH-d_4) δ 193.91, 177.50, 174.52, 96.17, 67.34, 62.80, 30.64, 30.50, 26.83; ESIMS 226.0 $[M+1]^+$. Compound **5**: ^{1}H NMR (MeOH-d_4) δ (ppm) 4.60 (1H, s), 3.85–3.98 (3H, m), 2.46 (2H, m), 2.23 (2H, m), 1.85 (2H, m); ESIMS 213.0 $[M+D]^+$. Compound **6**: (Two diastereomers) 1H NMR (MeOH-d_4) δ (ppm) 4.62 (1H, s), 3.90 (3 H, m), 1.52–1.70 (2H, m); 1.25 (1.5H, s), 1.24 (1.5H, s), 0.86 (1.5H, t, J = 7.2 Hz), 0.85 (1.5H, t, J = 7.2 Hz); ESIMS 214.0 $[M+H]^+$.
33. Rate constant measurement: The kinetic studies are conducted in situ in deuteriated solvents in NMR tubes with 1 to 1 equiv of cyclobutenone and amino acids. By assuming a second-order reaction, the initial rate of reaction was calculated by $1/(C_{\text{cyclobutenone}}) = 2k_t + 1/C_0$, where k is the rate constant and $C_{\text{cyclobutenone}}$ is the concentration of cyclobutenone at a given time during the course of the reaction. For each kinetic studies, the yield of the reaction is calculated from the isolated pure product of amino acid-substituted cyclobutenone relative to the cyclobutenones.
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38. *Selected analytical data for* **4a**–**4d** *and* **4f**–**4g**. Compound **4a**: ^{1}H NMR (MeOH-d_4) δ (ppm) 7.60 (1H, dt, J = 7.8, 0.6 Hz), 7.29 (1H, dt, J = 8.1, 0.6 Hz), 7.06 (1H, s), 6.98–7.03 (2H, m), 4.12 (1H, m), 4.11 (1H, s), 3.42–3.48 (1H, m), 3.10–3.19 (1H, m), 1.57–1.80 (8H, m); ^{13}C NMR (MeOH-d_4) δ 193.63, 177.03, 175.54, 136.97, 128.10, 123.69, 121.30, 118.72, 118.36, 111.25, 110.36, 95.83, 67.00, 61.32, 30.67, 30.25, 28.67, 26.67, 26.64; ESIMS 325.1 $[M+1]^+$. Compound **4b**: ^{1}H NMR (MeOH-d_4) δ (ppm) 6.97 (2H, dd, J = 7.2, 2.1 Hz), 6.62 (2H, dd, J = 6.6, 2.1 Hz), 4.29 (1H, s), 4.06 (1H, m), 3.15 (1H, m), 2.85 (1H, m), 1.55–1.69 (8H, m); ^{13}C NMR (MeOH-d_4) δ 193.83, 177.43, 172.99, 156.45, 130.51, 127.70, 115.25, 96.40, 67.14, 60.32, 37.05, 30.72, 30.29, 26.67; ESIMS 302.0 $[M+H]^+$. Compound **4c**: ^{1}H NMR (MeOH-d_4) δ (ppm) 4.54 (1H, s), 3.50 (1H, s), 3.22 (2H, t, J = 6.9 Hz), 1.60–1.82 (12H, m), 1.49 (2H, m); ^{13}C NMR (MeOH-d_4) δ 193.64, 178.02, 173.56, 95.50, 67.05, 55.03, 44.95, 31.07, 30.63, 28.77, 26.78, 22.53; ESIMS 267.1 $[M+H]^+$. Compound **4d**: ^{1}H NMR (MeOH-d_4) δ (ppm) 4.54 (1H, s), 3.78 (2H, s), 1.71–1.87 (8H, m); ^{13}C NMR (MeOH-d_4) δ 193.81, 177.90, 173.58, 95.90, 67.2, 67.14, 30.57, 26.77; ESIMS 196.0 $[M+H]^+$. Compound **4f**: ^{1}H NMR (MeOH-d_4) δ (ppm) 4.55 (1H, s), 4.28 (1H, m), 4.06 (1H, m), 3.60 (1H, m), 1.60–2.30 (12H, m); ESIMS 236.1 $[M+H]^+$. Compound **4g**: ^{1}H NMR (MeOH-d_4) δ (ppm) 4.59 (2H, s), 4.10 (2H, m), 3.39 (2H, m), 3.03 (2H, m), 1.71–1.95 (16H, m); ^{13}C NMR (MeOH-d_4) δ 193.84, 177.62, 174.82, 96.24, 67.26, 59.67, 40.94, 30.78, 30.37, 26.82; ESIMS 481.1 $[M+H]^+$. Compound **4h**: ^{1}H NMR (MeOH-d_4) δ (ppm) 4.59 (1H, s), 4.10 (1H, m), 3.90 (1H, m), 3.40 (2H, m), 3.10 (1H, m), 2.93 (1H, m), 1.69–1.93 (8H, m); ^{13}C NMR (MeOH-d_4) δ 193.87, 177.49, 174.50, 96.32, 67.35, 59.41, 53.59, 40.59, 39.01, 30.70, 30.42, 26.80; ESIMS 361.0 $[M+1]^+$.
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