Application of Microwave Activation Techniques to the *N*-Alkenyl Protection of Lactams

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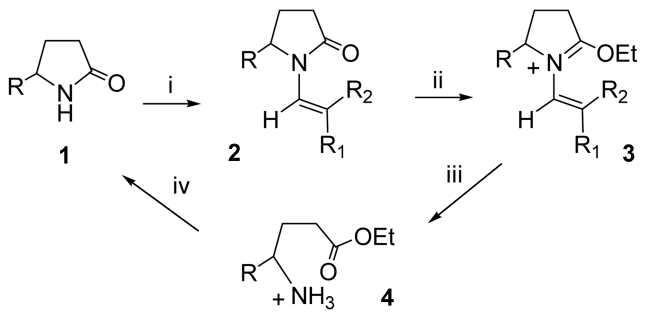
Rapid and facile syntheses of *N*-alkenyl lactam series *via* condensation between lactams and a variety of aldehydes such as *n*-propanal, isobutanal, *n*-butanal, *n*-hexanal, *n*-octanal and phenylacetaldehyde were studied under microwave or conventional heating. Various solid catalysts and solvents were examined to maximize the yields of condensation reactions.

Key Words : Pyrrolidin-2-one, Ethyl pyroglutamate, *N*-Alkenylation, Aldehyde condensation, Microwave irradiation

Introduction

Pyrrolidin-2-one analogue, **1** is a useful intermediate with a variety of synthetic and medicinal uses.[1] Syntheses involving lactam analogues usually require protection steps and are well established in fundamental organic synthesis. Representative literature examples of protecting groups for the lactam amine functionality include *t*-Boc,[2] Cbz,[3] *N*-benzyl,[4] *N*-acetate,[5] and *N*-alkenyl protecting groups.[6] Among these protecting groups, the *N*-alkenyl group appeared to be a valuable protecting functionality due to its high stability toward oxidation, reduction, and many other reaction conditions.[1a-c] For example, the pyrrolidin-2-one derivative, **2** is known to be a useful 'pro-γ-aminobutyric acid' since 2-ethoxy-*N*-vinylpyrrolidiniminium tetrafluoroborate salt, **3** prepared from the reaction of **2** with triethyloxonium tetrafluoroborate[1c,6a] undergo hydrolysis in neutral water to give the corresponding amino ester, **4**. It is noteworthy that adjusting a solution of **4** to the pH = 8-9 led to isolation of the deprotected lactam, **1** (Scheme 1).[7]

In recent years, a variety of microwave enhanced organic reactions have been described in the literature and tremendous attention has been focused on the application of microwave irradiation technique for organic functional group transformations.[8] We have demonstrated that Knoevenagel type condensations between active methylene and aldehydes,[9] Michael type addition,[10] nitration or *O*-alkylation in the aromatic rings,[11] and Friedlander type quinoline synthesis[12] can be facilitated by solvent-free microwave irradiation technique. In the course of our investigation, aimed at the synthesis of γ-vinyl amino butyric acid,[1a-c] we needed to prepare protected lactam derivatives. It has been reported that lactams undergo condensation with aldehydes using conventional heat using Dean-Stark apparatus. To carry out these condensations, it is usually required to reflux the reaction mixture for 10 hours or even more than 24 hours until a maximum amount of water is produced.[7a-b] Herein, we wish to report that lactam N-H can be successfully condensed with aldehydes within a short period of time to give *N*-alkenyl analogues, **2** under microwave irradiation conditions. To the best of our knowledge, microwave enhanced *N*-alkenyl condensation of lactam using aldehydes represents the first successful application of microwave irradiation for the synthesis of lactam protecting groups.



Scheme 1. (i) aldehydes, benzene, *p*-TsOH, microwave irradiation. (ii) $Et_3O^+BF_4^-$ (iii) H_2O (iv) pH = 8-9. **1** and **2**; R = (a) H or (b) CO_2Et, R_1 = CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $(CH_2)_5CH_3$, Ph, R_2 = H or CH_3. **3** and **4**; R = H, R_1 = (a) H (b) CH_2CH_3, R_2 = H

Results and Discussion

We initially investigated the solvent-free catalyst effects of lactam *N*-alkenylation reactions. These were carried out under open vessel conditions using a conventional microwave oven. Without catalyst and support, the yield was as low as 5% with the majority of starting materials recovered (Table 1, entry 1). When the reactions were carried out in the presence of various solid catalysts such as bentonite, K_{10}, KSF, *p*-TsOH, and P_2O_5 in Al_2O_3, under microwave irradiation condition, the yields were slightly increased but were not satisfactory. Microwave irradiation using Al_2O_3 as a solid support gave a sharp rise in temperature within a few minutes. Yields were low due to evaporation loss of the aldehyde starting material (Table 1, entries 2-6). We next examined a variety of solvents to increase the yield of the condensation products using a domestic microwave oven. The best yield (45%) was obtained after 10 minutes when the reaction was performed in benzene as shown in Table 1, entry 10. Water or water-soluble solvents such as ethanol

Table 1. Condensations between pyrrolidin-2-one and octanal[a] using different solid supports and solvents in domestic microwave oven (Reaction time: 10 min)[b]

Entry	Solid Catalyst	Solvent	Yield (%)[c]
1	none	none	5
2	Bentonite in Al_2O_3	none	7
3	K_{10} in Al_2O_3	none	12
4	KSF in Al_2O_3	none	9
5	*p*-TsOH in Al_2O_3	none	20
6	P_2O_5 in Al_2O_3	none	20
7	*p*-TsOH	xylene	29
8	*p*-TsOH	toluene	38
9	*p*-TsOH	chlorobenzene	41
10	*p*-TsOH	benzene	45
11	*p*-TsOH	EtOH or H_2O	0
12	*p*-TsOH	DMF	0

[a]Reaction of 5.55 mmol scale; mole ratio of pyrrolidin-2-one:octanal, 1 : 1.2. [b]The reactions were carried out in a 2450 MHz commercial microwave oven (Samsung Model # RE-555 TCW). [c]Isolated yields based on starting pyrrolidin-2-one. Yields were not optimized.

and DMF did not give any condensation products (Table 1, entries 11-12).

Using a CEM Focused Microwave™ reactor equipped with a reflux condenser clearly increases the yield and proved to be fast and the most suitable for the condensation of lactams. Compared to results with a conventional microwave oven (open vessel), the yields were significantly increased. Maximum yield of 82% was obtained when pyrrolidin-2-one and *n*-octanal (1 : 1.2 equivalent ratio) was reacted using the CEM microwave reactor as shown in Table 2, entry 2. An excess of octanal (> 1.2 equivalents) did not increased the yield (Table 2, entries 3, 4 and 5). Various aldehydes having different alkyl or phenyl groups were reacted with pyrrolidin-2-ones (**1a** and **1b**) in benzene in the presence of a catalytic amount of *p*-TsOH. The corresponding alkenyl pyrrolidinone analogues were obtained in moderate to high yields using the CEM microwave reactor and the results are summarized in Table 3. *E/Z* isomer identification was made on the basis of coupling constants from ^{1}H NMR. *E* isomers appeared to predominate with large coupling constants of alkenyl hydrogens (J = 14-15 Hz). In order to examine the specific (non-thermal) MW effects, the results obtained under microwave irradiation (MWI) were compared to conventional heating (Table 3, entries 1, 3, 4, 7 and 8). Conventional heating experiments were carried out using a preheated oil bath under the same reaction conditions used under MW (mole ratio, time, temperature, vessel size, etc.). In all cases, considerably lower yields were obtained clearly proving the efficacy of MW. Enhancement of reactivity (specific MW effects) results from lowering the activation energy due to the polarization of the intermediate species in the rate-determining step. The electric field induces dipole-dipole electrostatic interactions in the transition state (TS) that are more polar than the ground state (GS) on account of ionic dissociation as shown in Figure 1. The formation of *N*-alkenyl product, **2** is accelerated by microwave irradiation

Table 2. Tabulated results of the condensation reaction between pyrrolidin-2-one and octanal in various mole ratios with the CEM microwave reactor *versus* a domestic microwave oven

Entry	Mole ratio[a]		Yields (%)[b]	
	1	Octanal	MWI (CEM, Discover)[c]	MWI (domestic oven)[d]
1	1	1	64.5	–
2	1	1.2	82	45
3	1	1.5	78	–
4	1	3	75	–
5	1	5	75	48

[a]Reaction of 6.09 mmol scale, solvent: benzene, catalyst: *p*-TsOH, time: 10 min. [b]Isolated yields based on starting pyrrolidin-2-one. Yields were not optimized. [c]CEM Focused Microwave™ Synthesis System equipped with a reflux condenser. [d]Samsung Model # RE-555 TCW (2450 MHz).

since the intramolecular nucleophilic addition of lactam nitrogen to the aldehyde carbonyl carbon in the GS involves the formation of a dipolar TS which is stabilized under microwave conditions.

Summary

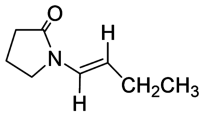
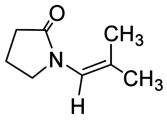
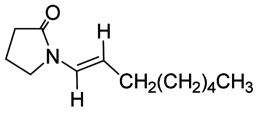
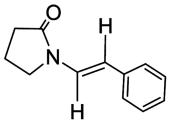
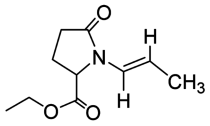
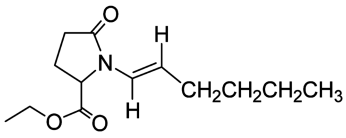
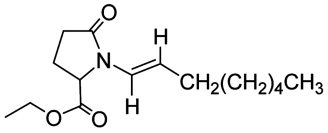
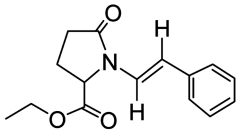
In conclusion, we have described a fast and facile microwave enhanced *N*-alkenyl condensation between lactams and various aldehydes such as *n*-propanal, isopropanal, *n*-butanal, *n*-hexanal, *n*-octanal and phenylacetaldehyde in moderate (55%) to high yields (86%) using a CEM Discover Focused Microwave™ Synthesis System. We are currently expanding the advantages of microwave irradiation to make it applicable for the protection of other functionalized lactams or thiolactams.

Experimental Section

Pyrrolidin-2-one, *p*-toluenesulfonic acid monohydrate (98.5%), bentonite, K_{10}, KSF, P_2O_5, Al_2O_3, *n*-propanal, isopropanal, *n*-butanal, *n*-hexanal, *n*-octanal and phenylacetaldehyde were purchased from Sigma-Aldrich (Korea) and used as received. Benzene, toluene, DMF, chlorobenzene and xylene were either used as supplied or purified by standard techniques. TLC was performed on precoated glass plate-silica gel 250-μm (Baker Si250F) with detection by UV light. Flash column chromatography was performed on silica gel (230-400 mesh). The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz on a FT-NMR Bruker 300. Chemical shifts are given in ppm and referenced to internal tetramethylsilane (TMS, δ = 0 ppm) standard. GC/MS spectra were measured on a Shimazu QP 5000 spectrometer.

Typical microwave procedure for *N*-alkenyl pyrrolidin-2-one; Synthesis of 1-oct-1-enyl-pyrrolidin-2-one, 2 (R=H, R_1=$(CH_2)_5CH_3$, Table 3, entry 3): A mixture of pyrrolidin-2-one (1 equiv. 0.5 g, 6.09 mmol), *n*-octanal (1.2 equiv. 0.94 g, 7.31mmol) and *p*-TsOH (11.5 mg, 0.06 mmol, 0.01 equiv.) were dissolved in 20 mL of benzene, fitted with a reflux condenser. The solution was homogenized and then

Table 3. Condensation reaction between pyrrolidin-2-ones, **1** and various aldehydes under microwave irradiation (MWI) and conventional heating

Entry	**1** (R_1) [a]	Aldehyde[a]	Product [b]	Yield (%)[c]	
				MWI[d]	Δ[e]
1	H	$CH_3CH_2CH_2CHO$		72	6
2	H	$(CH_3)_2CHCHO$		69	–
3	H	$CH_3(CH_2)_5CH_2CHO$		82	5
4	H	$PhCH_2CHO$		85	5
5	CO_2Et	CH_3CH_2CHO		55	–
6	CO_2Et	$CH_3(CH_2)_3CH_2CHO$		79	–
7	CO_2Et	$CH_3(CH_2)_5CHO$		64	5
8	CO_2Et	$PhCH_2CHO$		86	7

[a]Mole ratio of pyrrolidin-2-ones : octanal= 1 : 1.2, solvent: benzene). [b]Catalyst: *p*-TsOH, reaction time: 15 min. [c]Isolated yields after purification. All products were characterized by ^1H and ^{13}C NMR, IR, MS. [d]CEM Focused Microwave™ Discover. [e]Oil bath temperature = 89 °C.

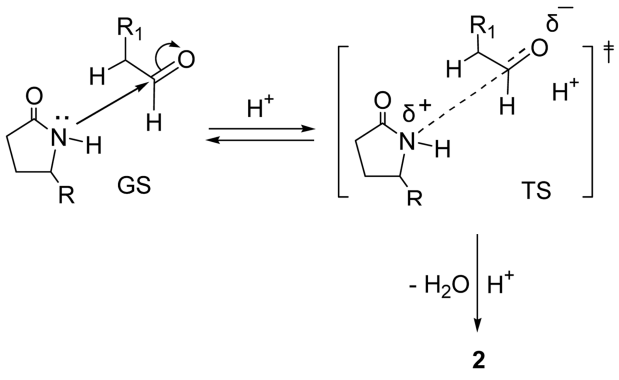


Figure 1. Transition state between lactam and aldehydes by dipole-dipole electrostatic interactions.

submitted for 15 min to microwave irradiation in a microwave reactor (CEM Labmate). After cooling to room temperature, the volatiles were evaporated under vacuum. The crude product was purified by column chromatography eluting with methanol/methylene chloride (2 : 98, v/v, R_f = 0.43) to give 1-oct-1-enyl-pyrrolidin-2-one (0.99 g, 4.99 mmol) in 82% yield as a colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.79 (1H, d, J = 14.6 Hz, m, N-*CH* =), 4.89 (1H, m, =*CH*-CH_2), 3.45 (2H, m, lactam *CH_2*N), 2.45 (2H, m, lactam C- *CH_2*-C), 2.08 (4H, m, lactam *CH_2*-C=O and C=C-*CH_2*), 1.30 (8H, m, 4 *CH_2* chain), 0.87 (3H, t, terminal *CH_3*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.82, 123.15, 112.52, 45.12, 30.98, 32.05, 30.21, 29.04, 23.24, 22.30, 17.29, 14.51 ppm. IR (neat): 2925.59, 2856.72, 1699.82,

1669.22, 1409.12, 1291.20 and 952.41 cm^{-1}. GC/MS (m/e): 195 (M^+, 8), 124 (100), 96 (9), 86 (38).

But-1-enyl-pyrrolidin-2-one (Table 3, entry 1): Colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.85 (1H, d, J = 14.5 Hz), 5.01 (1H, m), 3.47 (2H, t), 2.45 (2H, t), 2.01-2.18 (4H, m), 1.01 (3H, t, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.55, 122.98, 113.89, 45.12, 31.12, 23.08, 17.31, and 14.31 ppm. IR (neat): 2979.32, 2933.31, 1690.45, 1631.24, 1451.29, 1272.38, and 953.42 cm^{-1}. GC/MS (m/e): 139 (M^+, 73), 124 (100, base), 110 (15), 96 (29), 84 (30), 69 (23), 55 (10), 41 (26).

1-(2-Methyl-propenyl)-pyrrolidin-2-one (Table 3, entry 2): Colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.90 (1H, s), 3.60 (2H, t), 2.43 (2H, t), 2.10 (2H, m), 1.79 (3H, s), 1.69 (3H, s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.97, 127.63, 118.90, 48.71, 30.12, 22.49, 18.18, 17.65 ppm. IR (neat): 2993.12, 2901.21, 1691.45, 1412.39, 1315.20 and 800.49 cm^{-1}. GC/MS (m/e): 139 (M^+, 19), 84 (69), 41 (100), 39 (69).

Styryl-pyrrolidin-2-one (Table 3, entry 4): mp = 127-128 °C (Lit. 125-127, 130-131 °C).[7b,13] ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60 (1H, d, J = 14.5 Hz), 7.38-6.98 (5H, m, aromatic H), 5.82 (1H, d, J = 14.5 Hz), 3.61 (2H, m, lactam CH_2-N), 2.47 (2H, m, lactam CH_2-CH_2-CH_2), 2.09 (2H, m, CH_2-C=O) ppm.

Typical microwave procedure for *N*-alkenyl pyrrolidin-2-carboxylic acid ethyl ester; **Oxo-1-propenyl-pyrrolidine-2-carboxylic acid ethyl ester (Table 3, entry 5):** 5-Carbethoxy-2-pyrrolidinone, **1b** was prepared from glutamic acid according to previous procedures.[1d,e] A mixture of **1b** (0.45 g, 2.86 mmol, 1 equiv.), *n*-propanal (0.20 g, 3.43 mmol, 1.2 equiv.) and *p*-TsOH (5.4 mg, 0.0286 mmol, 0.01 equiv.) were dissolved in 20 mL of benzene, fitted with a reflux condenser. The solution was homogenized and then submitted for 15 min to microwave irradiation inside a microwave reactor (CEM Discover). After cooling to room temperature, the volatiles were evaporated under vacuum. The crude product was purified by column chromatography eluting with methanol/methylene chloride (5 : 95, v/v, R_f = 0.3) to give oxo-1-propenyl-pyrrolidine-2-carboxylic acid ethyl ester (0.31 g, 1.57 mmol) in 55% yield as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 6.77 (1H, d, J = 13.05 Hz, NCH=), 4.85-4.76 (1H, m, =CH), 4.30 (1H, m, N-CH), 4.16 (2H, q, J = 5.64 Hz, O$CH_2$$CH_3$), 2.58-2.55 (1H, m, lactam C$H_a$$H_b$-CH), 2.44-2.28 (2H, m, CH_2C=O), 2.08-2.01 (1H, m, lactam C$H_a$$H_b$-CH), 1.64 (3H, d, J = 5.01 Hz, =CCH_3) and 1.23 (3H, t, J = 5.64 Hz, O$CH_2$$CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.12, 171.97, 123.92, 107.57, 61.97, 58.96, 30.11, 23.28, 15.62 and 14.50 ppm. Infrared (neat): 3464.1, 2980.1, 1745.0, 1710.5, 1671.7, 1403.6, 1378.6, 1336.1, 1284.3, 1195.3, 1041.9, 951.9 and 792.8 cm^{-1}. Mass spectrum: CIMS, m/s 197 (M^+).

Hex-1-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (Table 3, entry 6): Colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (1H, d, J = 17.61 Hz), 4.83 (1H, quintet, J = 7.20 Hz), 4.36-4.32 (1H, m), 4.20 (2H, q, J = 6.93 Hz), 2.62- 2.59 (1H, m), 2.48-2.31 (2H, m), 2.12-1.99 (3H, m), 1.34-1.23 (7H, m) and 0.86 (3H, t, J = 6.93 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.24, 172.02, 123.14, 113.25, 62.00, 59.06, 32.43, 30.20, 30.09, 23.23, 22.36, 14.54 and 14.25 ppm. Infrared (neat): 2958.0, 2929.2, 1745.1, 1712.5, 1665.7, 1466.0, 1400.4, 1282.6, 1233.6, 1192.5, 1043.0 and 951.7 cm^{-1}. Mass spectrum: CIMS, m/s 239 (M^+).

1-Oct-1-enyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (Table 3, entry 7): Colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (1H, d, J = 14.64 Hz), 4.84 (1H, quintet, J = 7.11 Hz), 4.35 (1H, dd), 4.20 (2H, q, J = 6.90 Hz), 2.60-2.44 (1H, m), 2.40-2.31 (2H, m), 2.12-1.98 (3H, m), 1.34-1.23 (12H, m) and 0.86 (3H, t, J = 6.90 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.25, 172.03, 123.12, 113.30, 62.01, 59.03, 32.05, 30.45, 30.27, 30.21, 29.04, 23.24, 22.30, 14.56 and 14.48 ppm. Infrared (neat): 2957.3, 2927.9, 2855.9, 1747.1, 1714.9, 1666.2, 1468.3, 1400.5, 1334.1, 1286.2, 1233.5, 1193.3, 1041.9 and 946.1 cm^{-1}. Mass spectrum: CIMS, m/s 267.1 (M^+).

5-Oxo-1-styryl-pyrrolidine-2-carboxylic acid ethyl ester (Table 3, entry 8): ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, d, J = 15.06 Hz), 7.38-7.17 (5H, m), 5.82 (1H, d, J = 15.03 Hz), 4.55 (1H, d, J = 13.68 Hz), 4.30-4.22 (2H, m), 2.78-2.66 (1H, m), 2.58-2.40 (2H, m), 2.23-2.16 (1H, m) and 1.33-1.12 (3H, t) ppm. m.p = 89-91 °C. Mass spectrum: CIMS, m/s 259.1 (M^+).

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