Preliminary Communication

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Microwave-assisted synthesis of γ-thiolactams from ethyl isocyanoacetate

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Abstract: γ-Thiolactams were synthesized in good yields from ethyl isocyanoacetate through a sequential alkylation/isothiocyanation/radical cyclization under microwave irradiation.

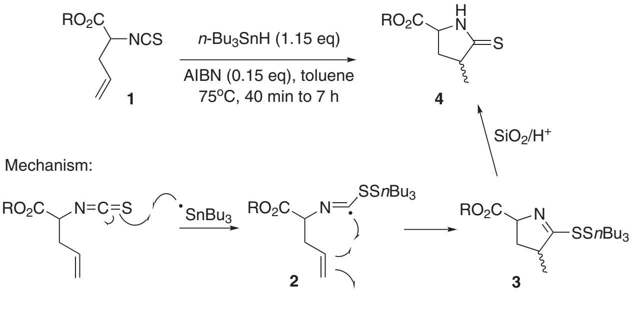
Keywords: isocyanoacetate; isothiocyanate; microwave irradiation; radical cyclization; thiolactam.

Thioamides and thiolactams are important intermediates in organic synthesis [1–3], in particular, for gaining access to heterocycles of natural products [4–7]. Several procedures have been reported for the synthesis of thiolactams by conversion of the corresponding lactams; however, direct preparation of these compounds is not common [8, 9]. In this communication, we present an improved strategy for the synthesis of γ-thiolactams from simple isocyanoacetates [10] using microwaves (MWs)-assisted flash heating technology. In the early 1990s, Bachi reported *n*-Bu_3SnH mediated radical cyclization of alkenyl isothiocyanates to give thiolactams (Scheme 1) [8, 11]. The mechanism of this reaction involves addition of organotin radical to isothiocyanate **1** to generate a tin thioimidoyl radical **2** which undergoes 5-exo cyclization onto an alkenyl side chain to give a tin thioimidate **3**, which is spontaneously hydrolyzed during chromatography to give thiolactam **4**.

Our interest in isocyanide radical chemistry and novel applications of MW technology to organic synthesis [12–14] led us to investigate the feasibility of using MW-assisted synthesis to Bachi's approach to thiolactams. Our synthetic strategy first entailed the synthesis of alkenyl isothiocyanates that could be accessed by sequential reaction of an isocyanoacetic acid ester with alkenyl halides, followed by a reaction with *tert*-butyl mercaptan. A subsequent reaction with organotin reagents would give functionalized thiolactams (Scheme 2).

We first synthesized alkenyl isocyanide **5** from commercially available ethyl isocyanoacetate and cinnamyl bromide using 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) as a base. The use of MWs afforded the desired compound in 10 min in 70% yield. Compound **5** was then allowed to react with *tert*-butyl thiol under MW irradiation to give the corresponding isothiocyanate **6** in 90% yield (Scheme 2). With isothiocyanate **6** in hand, it was then possible to perform the radical cyclization in the presence of tributyltin hydride which gave γ-thiolactams **7** and **8** in 78% isolated yield [1.6:1 mixture of diastereoisomers by proton nuclear magnetic resonance (^1H NMR)]. This reaction was also accomplished in 6 min at 140°C in the MW synthesizer. The high yield conversion of the isocyanide to isothiocyanate and the radical cyclization prompted us to perform a two-step one-pot conversion of alkenyl isocyanide **5** to the corresponding thiolactam without isolating the isothiocyanate. The reactions were performed in the same MW vessel and gave the desired thiolactams **7** and **8** in 76% overall yield (2:1 mixture of diastereoisomers by ^1H NMR). To further test this methodology, we then synthesized and reacted isocyanides **9** and **12** under the above conditions [11, 13]. Conversion of allyl isocyanide **9** directly to thiolactams **10** and **11** worked well and the desired products were obtained in high isolated yields (1:1 mixture of diastereoisomers by NMR). The reaction was completed in 12 min without isolation of the isothiocyanate (Scheme 3).

When bis-allylated isocyanide **12** was treated with *tert*-butyl thiol and *n*-Bu_3SnH under standard MW conditions,



Scheme 1 Bachi's synthesis of thiolactams from isothiocyanates.

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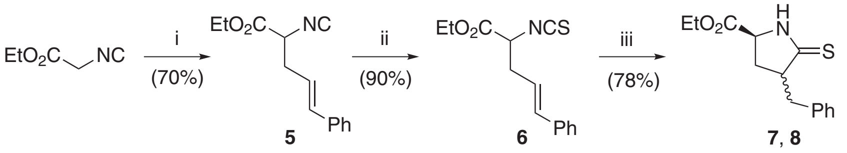
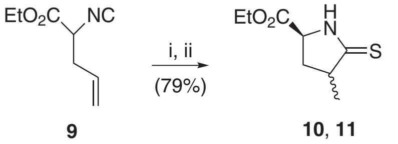
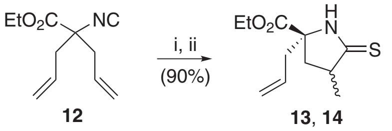


Scheme 2 Reagents and conditions: (i) cinnamyl bromide, BEMP, acetonitrile, MW 10 min at 110°C; (ii) *t*-BuSH (1.5 eq), azobisisobutyronitrile (AIBN) (0.2 eq), toluene, MW 6 min at 140°C; (iii) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, MW 6 min at 140°C.



Scheme 3 Reagents and conditions: (i) *t*-BuSH (1.5 eq), AIBN (0.2 eq), toluene, MW 6 min at 140°C; (ii) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, MW 6 min at 140°C.



Scheme 4 Reagents and conditions: (i) *t*-BuSH (1.5 eq), AIBN (0.2 eq), toluene, MW 6 min at 140°C; (ii) *n*-Bu_3SnH (1.15 eq), AIBN (0.2 eq), toluene, MW 6 min at 140°C.

the corresponding thiolactams **13** and **14** were obtained in 90% yield as a 1:1 diastereomeric mixture (Scheme 4).

In conclusion, MW flash heating methodology was successfully employed to quickly and efficiently synthesize γ-thiolactams in a two-step one-pot procedure in good yields from alkenyl isocyanides that are accessible from commercially available ethyl isocyanoacetate. This methodology additionally provides quick access to isothiocyanates from isocyanides by MW-assisted radical reaction with *tert*-butyl thiol.

Experimental

Flash column chromatography was performed using Sorbsil C60 (40–60 mesh silica gel). Dichloromethane and toluene were distilled from calcium hydride. ^{1}H NMR (400 MHz) and carbon-13 nuclear magnetic resonance (^{13}C NMR) (100 MHz) spectra were obtained in $CDCl_3$ on a Bruker AVANCE III spectrometer. Infrared (IR) spectra were recorded on a Fourier-transform infrared spectroscopy (FTIR) Perkin-Elmer 2000 spectrometer coupled with an AutoIMAGE FTIR microscope. Mass spectrometry data were obtained on a ThermoQuest gas chromatograph-mass spectrometer configured for open access, on a Waters ZMD mass-spectrometer, single quadrupole, liquid chromatography-mass spectrometry (LC-MS) and a VG analytical 70-250-SE double-focusing mass spectrometer. MW reactions were performed on a CEM MW synthesizer.

Ethyl 2-isocyano-5-phenyl-pent-4-enoate (5)

To a thick Pyrex tube were added ethyl isocyanoacetate (250 μL, 2.17 mmol), cinnamyl bromide (450 mg, 2.17 mmol), BEMP (600 μL, 2.17 mmol) and 3.0 mL of dry acetonitrile. The tube was then flushed with nitrogen and capped. Heating was applied by means of microwave irradiation at 110°C for 10 min. The tube was then cooled and the solvent was removed under reduced pressure. Purification by flash chromatography eluting with hexane/ethyl acetate (7:1) afforded compound **5**: yield 348 mg (70%); ^{1}H NMR ($CDCl_3$): δ 1.3 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 2.65–2.95 (2H, m, $CHCH_2$), 4.3 (3H, q, $J=7.0$ Hz, CH_2O), 4.4 (1H, t, $J=7.0$ Hz, CHN) 6.1–6.25 (1H, m, C*H*=CHPh), 6.6 (1H, d, $J=16.0$ Hz, PhC*H*=CH), 7.2–7.4 (5H, m, PhH); ^{13}C NMR ($CDCl_3$): 14.4, 36.8, 53.8, 57.0, 63.1, 121.9, 126.8, 128.3, 129.0, 135.7, 136.8, 161.0, 166.4; IR (neat): ν_{max} 2139, 1742, 1250, 1209, 1060 cm^{-1}; GC/MS (CI): *m/z* 230 (85%, $[M+H]^+$); 247 (47%, $[M+NH_4]^+$). HRMS (EI). Calcd for $C_{14}H_{15}NO_2$, M^+: *m/z* 229.11042. Found: *m/z* 229.11028.

Ethyl 2-isothiocyanato-5-phenylpent-4-enoate (6)

A thick Pyrex tube was charged with dry toluene (2.0 mL), compound **5** (176 mg, 0.769 mmol), *tert*-butyl thiol (112 μL, 1.0 mmol) and AIBN (23 mg, 0.146 mmol). The tube was flushed with argon and capped. Heating was then applied by means of microwave irradiation at 140°C for 6 min. After cooling, the mixture was concentrated and the residue was subjected to column chromatography eluting with dichloromethane. The isothiocyanate **6** was obtained as a brownish liquid; yield 180 mg (90%); ^{1}H NMR ($CDCl_3$): δ 1.2 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 2.7–2.9 (2H, m, $CHCH_2CH$=CH), 4.18 (3H, q, $J=7.0$ Hz, CH_3CH_2O), 4.25 (1H, t, $J=7.0$ Hz, CHN) 6.0–6.1 (1H, m, C*H*=CHPh), 6.48 (1H, d, $J=14.0$ Hz, PhC*H*), 7.1–7.3 (5H, m, Ph*H*); ^{13}C NMR ($CDCl_3$): 14.3, 37.4, 59.6, 62.7, 122.4, 126.5, 127.9, 128.7, 135.4, 136.7, 168.0; IR (neat): ν_{max} 2049, 1743, 1199, 1023 cm^{-1}; GC/MS (CI): *m/z* 262 (66%, $[M+H]^+$); 279 (18%, $[M+NH_4]^+$); HRMS (EI). Calcd for $C_{14}H_{15}NO_2S$, M^+: *m/z* 261.08235. Found *m/z* 261.08235.

Mixture of ethyl *cis*-4-benzyl-5-thioxopyrrolidine-2-carboxylate (7) and ethyl *trans*-4-benzyl-5-thioxopyrrolidine-2-carboxylate (8)

A mixture of anhydrous toluene (2 mL), compound **6** (128 mg, 0.559 mmol), tri-*n*-butyltin hydride (46.2 μL, 0.166 mmol) and AIBN (3.6 mg, 0.022 mmol) in a sealed Pyrex tube under argon atmosphere was heated by means of MW irradiation at 140°C for 6 min. After cooling, the solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography eluting with hexane/ethyl acetate (7:1) to afford compounds **7** and **8** as an inseparable diastereomeric mixture in the ratio of 1.6:1; yield 22.6 mg (78%); ^{1}H NMR (CDCl$_3$) for **7**: δ 1.19 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.90 (1H, dt, *J* = 13.0, 9.0 Hz, NCHC*H*H), 2.43 (1H, dt, 13.0, 8.0 Hz, NCHCH*H*), 2.52 (1H, dd, *J* = 14.0, 10.5 Hz, PhCH*H*), 3.0 (1H, m, PhCH$_2$C*H*), 3.56 (1H, dd, *J* = 14.0, 4.0 Hz, PhC*H*H), 4.04 (1H, dd, *J* = 9.0, 5.0 Hz, CHN), 4.14 (2H, q, *J* = 7.0 Hz, CH$_2$O), 7.82 (1H, br s, N*H*); ^{1}H NMR (CDCl$_3$) for **8**: δ 1.21 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 2.15–2.30 (2H, m, NCHC*HH*), 2.69 (1H, dd, *J* = 13.5, 9.5 Hz, PhCH*H*), 3.07–3.15 (1H, m, PhCH$_2$C*H*), 3.36 (1H, dd, *J* = 13.5, 4.0 Hz, PhC*H*H), 4.11 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.30 (1H, t, *J* = 8.0 Hz, CHN), 7.70 (1H, br s, N*H*); GC/MS (EI): *m/z* 263 ([M]$^+$), 91 (PhCH$_2^+$). HRMS (EI). Calcd for C$_{14}$H$_{17}$NO$_2$S, [M]$^+$: *m/z* 263.09800. Found: *m/z* 263.09789.

Ethyl-2-isocyanopent-4-enoate (9)

A mixture of ethyl isocyanoacetate (3.0 mL, 25.8 mmol), allyl bromide (2.21 mL, 25.8 mmol), tetra-*N*-butylammonium bromide (832.6 mg, 2.59 mmol), finely ground potassium carbonate (10.7 g, 77.5 mmol) and acetonitrile (50 mL) was heated under reflux with stirring for 20 h. The mixture was then cooled, filtered and the solution was concentrated *in vacuo*. The resultant brownish oil was subjected to silica gel chromatography eluting with hexane/ethyl acetate (7:1). Compound **9** was obtained as a yellow oil; yield 2.38 g (62%); ^{1}H NMR (CDCl$_3$): 1.3 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 2.6–2.7 (2H, m, CHC*H*$_2$), 4.23 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.3 (1H, t, *J* = 5.0 Hz, NCH), 5.2–5.3 (2H, m, CH=C*H*$_2$), 5.7–5.9 (1H, m, C*H*=CH$_2$); ^{13}C NMR (CDCl$_3$): 14.1, 37.1, 56.4, 62.8, 120.6, 130.5, 160.3, 166.2; IR (neat): ν_{max} 2145, 1753 cm^{-1}.

Mixture of ethyl *cis*-4-methyl-5-thioxo-pyrrolidine-2-carboxylate (10) and *trans*-4-methyl-5-thioxo-pyrrolidine-2-carboxylate (11)

These compounds were obtained by using the procedure described earlier for the mixture of **7** and **8**. Purification by silica gel chromatography eluting with hexane/ethyl acetate (8:1) afforded compounds **10** and **11** as an inseparable 1:1 diastereomeric mixture; yield 115 mg (79%); ^{1}H NMR (CDCl$_3$) for **10**: δ 1.22 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.30 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.89 (1H, dt, *J* = 12.0, 9.0 Hz, NCHC*H*H), 2.76 (1H, dt, 12.0, 8.0 Hz, NCHCH*H*), 2.80–2.97 (1H, m, CH$_3$C*H*), 4.23 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.4 (1H, m, CHN), 8.0 (1H, br s, N*H*); ^{1}H NMR (CDCl$_3$) for **11**: δ 1.22 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.30 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 2.15 (1H, dt, *J* = 13.0, 7.5 Hz, CH$_3$CHC*H*H), 2.54–2.62 (1H, m, fCH$_3$CHCH*H*), 2.80–2.97 (1H, m, CH$_3$C*H*), 4.23 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.4 (1H, m, CHN), 8.0 (1H, br s, N*H*); ^{13}C NMR (CDCl$_3$) for the mixture: δ 14.5, 19.2, 19.3, 35.2, 35.5, 46.7, 47.4, 60.2, 60.3, 62.4, 170.3, 170.5, 211.2; GC/MS (EI) for the mixture: *m/z* 188, [M + H]$^+$; HRMS (EI) for the mixture. Calcd for C$_8$H$_{13}$NO$_2$S, [M]$^+$: *m/z* 187.06670. Found: *m/z* 187.06715.

Mixture of ethyl 2-allyl-*cis*-4-methyl-5-thioxo-pyrrolidine-2-carboxylate (13) and ethyl 2-allyl-*trans*-4-methyl-5-thioxo-pyrrolidine-2-carboxylate (14)

A mixture of compound **12** (108 mg, 0.559 mmol), *tert*-butyl thiol (81.5 μL, 0.727 mmol) and AIBN (17.5 mg, 0.111 mmol) in 2.0 mL of dry toluene in a sealed Pyrex tube under an argon atmosphere was microwave-irradiated at 140°C for 6 min. After cooling, the mixture in the tube was treated with tri-*n*-butyltin hydride (170 μL, 0.614 mmol) and AIBN (23 mg), flushed with argon, capped and heated again at 140°C for 6 min as described earlier. After removal of the solvent under reduced pressure, the residue was subjected to silica gel chromatography eluting with hexane/ethyl acetate (7:1). Compounds **13** and **14** were obtained as an inseparable diastereomeric mixture in the ratio of 1:1; yield 113 mg (90%); GC/MS (EI): *m/z* 227 (86%, [M]$^+$, 154 (96%). HRMS (ESI). Calcd for C$_{11}$H$_{18}$NO$_2$S, [M + H]$^+$: *m/z* 228.1053. Found: *m/z* 228.1055.

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