Preparation of α,β-Unsaturated Lactams through Intramolecular Electrophilic Carbamoylation of Alkenes

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Abstract: A general synthetic method for the preparation of α,β-unsaturated lactams starting from alkenylchloroformamides has been developed. The reaction was complete within five minutes at 150 °C in *N*-methylpyrrolidone with a catalytic amount of HBr under microwave irradiation. Not only six-membered lactams, but also five- and seven-membered lactams were obtained in high yields.

Key words: lactam, cyclization, electrophilic addition, acid catalyst, microwave

An α,β-unsaturated lactam is a structural motif that is often found in bioactive molecules such as rebamipide,[1] microcolins,[2] vitexlactam A,[3] and echinophyllins,[4] and is frequently used as a synthetic intermediate.[5,6] In recent years, we have focused on the formation of lactams through transition-metal catalyzed reactions starting from carbamoyl derivatives.[7] Examples are shown in Scheme 1. When carbamoyl cyanide **A** (X = CN, R^1 = H), having a 1,1-disubstituted alkene, was treated with palladium catalyst, lactam **B** was formed through cyanoamidation.[8] On the other hand, chloroformamide **A** (X = Cl, R^1 = Me), having a 1,1,2-trisubstituted alkene, was converted into vinyllactam **C** through a Heck-type reaction.[9] During the course of those studies, we found that carbamoyl chloride **A** (X = Cl) could be converted smoothly into α,β-unsaturated lactam **D** without the use of a transition-metal catalyst.[10] Details of this transformation are described herein.

The lactam-forming reaction was accidentally found when carbamoyl chloride **1** was heated in dioxane under microwave irradiation (Table 1, entry 1). After one hour at 150 °C, quinolone **2** was isolated in 21% yield along with 76% of unreacted starting material. The choice of solvent was crucial for this reaction; although the reaction in diglyme, toluene or acetonitrile gave poor conversion (entries 2–4), when *N*-methylpyrrolidone (NMP) was used, quinolone **2** was obtained in 81% yield (entry 5). A reduction of the reaction time to five minutes led to an incomplete reaction (entry 6). More polar solvents such as dimethyl sulfoxide or water gave disappointing results owing to decomposition of the starting material (entries 7 and 8).

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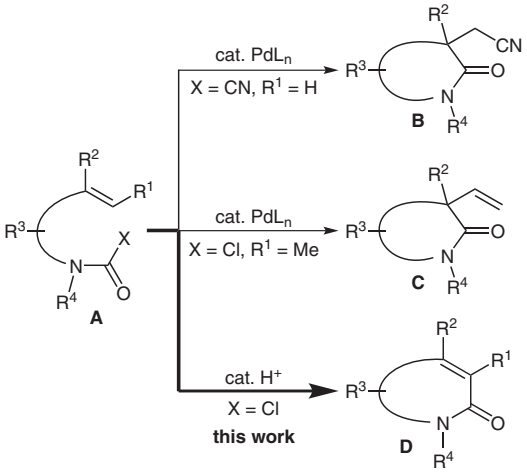
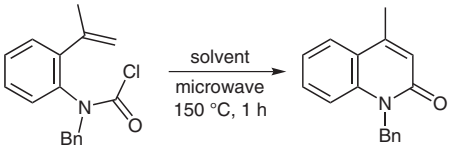


Scheme 1 Synthesis of functionalized lactams from alkenyl carbamoyl derivatives

Table 1 Formation of Quinolone **2** in Various Solvents



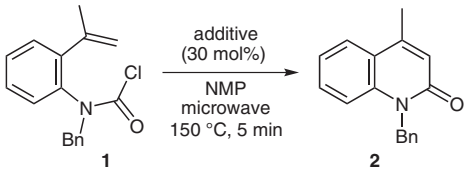
Entry	Solvent	Yield of **2** (%)	Recovery of **1** (%)
1	dioxane	21	76
2	diglyme	6	88
3	toluene	1	93
4	MeCN	16	82
5	NMP	81	3
6[a]	NMP	40	53
7	DMSO	0	0[b]
8	H_2O	25	0

[a] Reaction time was 5 min.
[b] *N*-Benzyl-2-(2-propenyl)aniline was isolated in ~60% yield.

Next, we made efforts to find an effective additive that could induce the completion of the reaction in a shorter period (Table 2). The reaction was carried out in NMP for five minutes at 150 °C under microwave irradiation in the

presence of 30 mol% of various additives. After several attempts, we found that the halide ion plays an interesting role in this reaction. When tetrabutylammonium halide (TBAX; X = F, Cl, Br, I) was tested, TBABr and TBAI promoted the reaction dramatically (entries 1–4). Other bromide salts such as KBr were less active, but HBr had an effect similar to that of TBABr (entries 5 and 6). Neither changing the heating method to an oil bath nor reducing the amount of acid improved the yield (entries 7 and 8). Among the acids investigated, HCl was inactive but trifluoromethanesulfonic acid (TfOH) showed a similar effect to HBr (entries 9 and 10). On the basis of these results, we propose the effect of the halogen to be as described below. When chloroformamides are converted to lactams, an equal amount of HCl appears. When bromide or iodide ions are present in the reaction mixture, a stronger acid such as HBr or HI should be obtained from the equilibrium. We assume that these strong acids somehow promote the reaction, which seems consistent with the case of TfOH.

Table 2 Effect of Additives on the Formation of Quinolone **2**

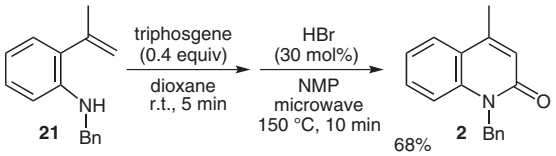


Entry	Additive	Yield of **2** (%)	Recovery of **1** (%)
1	TBAF	13	16
2	TBACl	43	40
3	TBABr	86	6
4	TBAI	82	2
5	KBr	53	42
6	HBr[a]	89	0
7[b]	HBr[a]	54	30
8	HBr[a,c]	80	11
9	HCl[d]	44	31
10	TfOH	80	0

[a] HBr was generated in situ from AcBr (30 mol%) and MeOH (30 mol%).
[b] Reaction was performed in an oil bath.
[c] HBr (5 mol%) was used.
[d] HCl was generated in situ from AcCl (30 mol%) and MeOH (30 mol%).

A variety of α,β-unsaturated lactams were obtained under the optimized conditions (NMP, 150 °C, 5 min with 30 mol% HBr) determined above (Table 3). Quinolones **4** and **6**, with different substituents, were obtained in high yields (entries 1 and 2). Furthermore, the reaction was expanded to aliphatic chloroformamides. Chloroformamides **7**, **9** and **11**, which were derived from but-3-enylamines, gave the corresponding six-membered unsaturated lactams in high yields (entries 3–5). It is worth noting that the substituents on the alkene have little effect in this reaction. Propenylamine derivative **13** did not cyclize, presumably because of the difficulty of 5-*endo*-trig cyclization (entry 6). On the other hand, seven-membered lactam **16** was cleanly formed through 7-*endo-trig* cyclization from styrene derived chloroformamide **15** (entry 7). An interesting observation was that when chloroformamide **17**, which contains a 4-methylpent-4-enyl group, was subjected to the reaction (entry 8), instead of formation of the seven-membered lactam, the five-membered lactam **18** with an *exo*-alkene was isolated. Styrene derivative **19** also afforded a mixture of five-membered lactams **20a** and **20b**. We suppose these reactions proceed through electrophilic attack of the carbamoyl chloride on the olefin with elimination of HCl. For all entries in Table 3, the electrophilic attack seems to proceed in a manner that generates the more stable cation intermediate. Even the reactions of compounds **17** and **19**, which gave five-membered lactams with an *exo*-alkene, proceeded in this manner. In these reactions, the difficulty in forming the seven-membered ring likely resulted in alkene isomerization to generate the trisubstituted olefins, which then underwent cyclization through tertiary cation intermediates. In contrast, compound **15**, having a double bond, was prevented from isomerization and gave the seven-membered ring via a benzylic cation intermediate.

In addition, it was found that quinolone **2** can be formed, through a one-pot procedure, from aniline **21** (Scheme 2). Thus, aniline **21** was treated with triphosgene (0.4 equiv) in dioxane and, after five minutes, HBr (30 mol%) and NMP were added. Microwave irradiation for ten minutes afforded quinolone **2** in 68% yield.

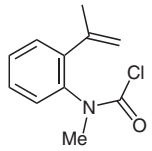
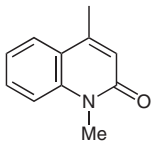
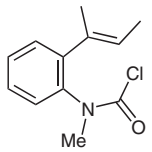
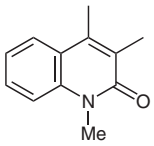
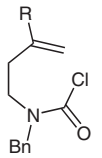
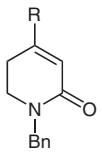
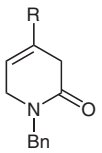
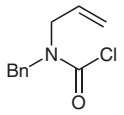
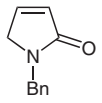
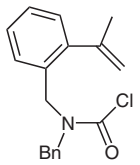
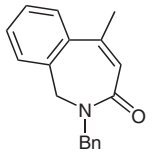
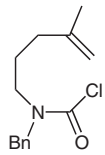
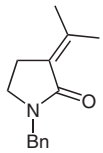
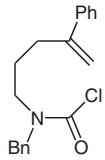
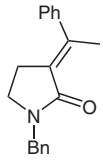
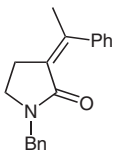


Scheme 2 ne-pot synthesis of quinolone **4**

In conclusion, we have developed a new method for constructing α,β-unsaturated lactams from alkenylchloroformamides. The combination of suitable solvent and catalyst allowed the completion of the reaction in five minutes with high yield. Because of the simple reaction conditions, this reaction should be useful for the synthesis of a variety of α,β-unsaturated lactams.

^{1}H NMR spectra were recorded at 500 MHz, and chemical shifts (δ) are reported relative to TMS (δ = 0.00 ppm). ^{13}C NMR spectra were recorded at 125 MHz, and chemical shifts are reported relative to $CDCl_3$ (δ = 77.0 ppm). Infrared spectra were recorded from KBr pellets or thin films on NaCl plates. Only charged molecular ion data are reported for low-resolution mass spectra (LRMS). All microwave irradiation experiments were carried out in a CEM Discover microwave apparatus.

Table 3 Synthesis of α,β-Unsaturated Lactams through Intramolecular Electrophilic Carbamoylation of Alkenes[a]

Entry	Substrate	Product(s)			Yield (%)[b]
1	 **3**	 **4**			93
2	 **5**	 **6**			76
3		**7** (R = H)		**8a** (R = H)		**8b** (R = H)	70 (70:30)
4		**9** (R = Me)		**10a** (R = Me)		**10b** (R = Me)	76 (86:14)
5		**11** (R = Ph)		**12a** (R = Ph)		**12b** (R = Ph)	64 (84:16)
6	 **13**	 **14**			–[c]
7	 **15**	 **16**			79
8	 **17**	 **18**			91
9	 **19**	 **20a**	 **20b**		87 (75:25)

[a] Reaction conditions: HBr (30 mol%), MW (150 °C), 5 min, NMP.
[b] Ratios (**a**/**b**) of isomers are shown in parentheses.
[c] **13** was recovered in 63% yield.

1-Benzyl-4-methylquinolin-2(1*H*)-one (2);[11] Typical Procedure
A mixture of chloroformamide **1** (141 mg, 0.493 mmol), AcBr (11 μL, 0.15 mmol), NMP (0.17 mL) and MeOH (6 μL, 0.15 mmol) was placed in a reaction vessel and stirred under Ar for 5 min at r.t. The vessel was then placed in a microwave reactor and heated at 150 °C for 5 min by microwave irradiation (48 W). After cooling to 0 °C, the reaction mixture was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was basified to pH 9 with sat. aq $NaHCO_3$ and extracted with EtOAc (10 × 5 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified by silica gel column chromatography (hexane–EtOAc, 10:0→5:5) to give quinolone **2**.

Yield: 110 mg (89%); white solid; mp 112–113 °C (Lit.[11] 110.5–111.5 °C).

IR (KBr): 1651, 1594 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.71 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1 H), 7.41 (ddd, J_1 = 1.7 Hz, J_2 = 7.8 Hz, J_3 = 7.9 Hz, 1 H), 7.29–7.25 (m, 3 H), 7.23–7.19 (m, 4 H), 6.70 (d, J = 1.2 Hz, 1 H), 5.56 (s, 2 H), 2.51 (d, J = 1.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 162.1, 146.9, 139.0, 136.5, 130.3, 128.6, 127.0, 126.4, 125.1, 121.9, 121.5, 120.8, 115.2, 45.5, 19.0.

LRMS (EI): *m*/*z* = 249 [M$^+$].

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.03; H, 6.23; N, 5.67.

1,4-Dimethylquinolin-2(1*H*)-one (4)[11]
White solid; mp 131.5–132.5 °C (Lit.[11] 129.5–130.5 °C).

IR (KBr): 1654, 1592 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.71 (dd, J_1 = 1.2 Hz, J_2 = 8.1 Hz, 1 H), 7.57 (ddd, J_1 = 1.2 Hz, J_2 = J_3 = 8.1 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 1 H), 7.26 (ddd, J_1 = 1.2 Hz, J_2 = J_3 = 8.1 Hz, 1 H), 6.60 (s, 1 H), 3.71 (s, 3 H), 2.47 (d, J = 1.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 161.8, 146.1, 139.6, 130.2, 125.0, 121.7, 121.2, 120.9, 114.2, 29.0, 18.7.

LRMS (EI): *m*/*z* = 173 [M$^+$].

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.04; H, 6.36; N, 8.07.

1,3,4-Trimethylquinolin-2(1*H*)-one (6)[12]
White solid; mp 109–110 °C (Lit.[12] 106.5–107.5 °C).

IR (KBr): 1633, 1593 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.75 (dd, J_1 = 1.1 Hz, J_2 = 8.0 Hz, 1 H), 7.51 (ddd, J_1 = 1.1 Hz, J_2 = J_3 = 8.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.25 (dd, J_1 = J_2 = 8.0 Hz, 1 H), 3.75 (s, 3 H), 2.46 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 162.2, 140.7, 138.1, 129.0, 127.0, 124.6, 121.6, 121.4, 113.9, 29.7, 15.2, 13.8.

LRMS (EI): *m*/*z* = 187 [M$^+$].

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.78; H, 6.96; N, 7.22.

1-Benzyl-5,6-dihydropyridin-2(1*H*)-one (8a)[13] and 1-Benzyl-1,6-dihydropyridin-2(3*H*)-one (8b)
Mixture of **8a/8b** (70:30); yellow oil.

IR (thin film): 1663, 1607 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (* peaks of minor isomer) = 7.34–7.25 (m, 5 H), 6.55 (dt, J_1 = 4.6 Hz, J_2 = 9.8 Hz, 1 H), 6.00 (dt, J_1 = 1.7 Hz, J_2 = 9.8 Hz, 1 H), 5.78–5.75* (m), 5.69–5.66* (m), 4.67* (s), 4.63 (s, 2 H), 3.83–3.80* (m), 3.32 (t, J = 6.9 Hz, 2 H), 3.06–3.03* (m), 2.34–2.30 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ (* peaks of minor isomer) = 167.1*, 164.5, 139.3, 137.4, 136.7*, 128.6*, 128.5, 128.1*, 127.9, 127.4*, 127.3, 125.3, 122.5*, 120.8*, 49.6, 48.2*, 44.5, 32.1*, 24.1.

LRMS (EI): *m*/*z* = 187 [M$^+$].

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.69; H, 7.08; N, 7.43.

1-Benzyl-5,6-dihydro-4-methylpyridin-2(1*H*)-one (10a)[14] and 1-Benzyl-1,6-dihydro-4-methylpyridin-2(3*H*)-one (10b)
Mixture of **10a/10b** (86:14); yellow oil.

IR (thin film): 1669, 1619 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (* peaks of minor isomer) = 7.33–7.24 (m, 5 H), 5.80–5.79 (m, 1 H), 5.38–5.35* (m), 4.66* (s), 4.61 (s, 2 H), 3.78–3.75* (m), 3.29 (t, J = 7.5 Hz, 2 H), 2.94* (t, J = 4.0 Hz), 2.25 (t, J = 7.5 Hz, 2 H), 1.90 (s, 3 H), 1.72* (s).

^{13}C NMR ($CDCl_3$): δ (* peaks of minor isomer) = 167.4*, 165.1, 150.6, 137.6, 136.8*, 130.4*, 128.5*, 128.5, 128.0*, 127.9, 127.4*, 127.2, 120.5, 114.8*, 49.4*, 49.3, 48.1*, 44.4, 36.7*, 29.3, 22.7, 21.8*.

LRMS (EI): *m*/*z* = 201 [M$^+$].

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.67; H, 7.65; N, 6.89.

1-Benzyl-5,6-dihydro-4-phenylpyridin-2(1*H*)-one (12a) and 1-Benzyl-1,6-dihydro-4-phenylpyridin-2(3*H*)-one (12b)
Mixture of **12a/12b** (84:16); white solid; mp 97–98 °C.

IR (KBr): 1649, 1603 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (* peaks of minor isomer) = 7.51–7.26 (m, 10 H), 6.38 (s, 1 H), 6.07* (br s), 4.74* (s), 4.69 (s, 2 H), 4.01* (dd, J_1 = 4.1 Hz, J_2 = 8.1 Hz), 3.46 (t, J = 6.9 Hz, 2 H), 2.75 (t, J = 6.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ (* peaks of minor isomer) = 167.2*, 165.3, 149.3, 138.1*, 137.5, 137.4, 136.6*, 132.7*, 129.5, 128.7, 128.7*, 128.6, 128.2*, 128.04, 127.98*, 127.6*, 127.4, 125.7, 124.8*, 119.8, 116.3*, 49.6, 49.5*, 48.5*, 44.6, 34.1*, 26.6.

LRMS (EI): *m*/*z* = 263 [M$^+$].

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.97; H, 6.53; N, 5.26.

2-Benzyl-1,2-dihydro-5-methylbenzo[*c*]azepin-3-one (16)
White solid; mp 109–110 °C.

IR (KBr): 1633, 1594 cm^{-1}.

^{1}H NMR ($CDCl_3$, 50 °C): δ = 7.44 (d, J = 8.0 Hz, 1 H), 7.32 (dd, J_1 = J_2 = 8.0 Hz, 1 H), 7.28–7.18 (m, 6 H), 6.90 (d, J = 8.0 Hz, 1 H), 6.42 (s, 1 H), 4.65 (br s, 2 H), 4.11 (br s, 2 H), 2.30 (s, 3 H).

^{13}C NMR ($CDCl_3$, 50 °C): δ = 166.5, 143.3, 137.6, 137.3, 136.6, 128.6, 128.4, 128.2, 128.0, 127.34, 127.32, 126.7, 125.1, 50.4, 49.8, 23.8.

LRMS (EI): *m*/*z* = 263 [M$^+$].

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.29; H, 6.63; N, 5.32.

1-Benzyl-3-(propan-2-ylidene)pyrrolidin-2-one (18)[15]
White solid; mp 81.5–82.5 °C (Lit.[15] 77–79 °C).

IR (KBr): 1682, 1656 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.33–7.25 (m, 5 H), 4.50 (s, 2 H), 3.21 (t, J = 6.9 Hz, 2H), 2.63–2.60 (m, 2 H), 2.32–2.31 (m, 3 H), 1.78 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 168.9, 141.7, 136.9, 128.5, 128.2, 127.3, 123.8, 46.8, 42.9, 23.9, 23.5, 18.8.

LRMS (EI): *m*/*z* = 215 [M$^+$].

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.32; H, 8.10; N, 6.49.

(*E*)-1-Benzyl-3-(1-phenylethylidene)pyrrolidin-2-one (20a)
Yellow oil.

IR (thin film): 1674 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.37–7.32 (m, 4 H), 7.29–7.25 (m, 4 H), 7.22–7.20 (m, 2 H), 4.54 (s, 2 H), 3.15 (t, J = 6.3 Hz, 2 H), 2.62 (t, J = 1.7 Hz, 3 H), 2.59–2.55 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 169.2, 144.3, 143.8, 136.7, 128.6, 128.3, 128.2, 127.5, 127.3, 126.8, 126.3, 47.0, 43.3, 25.7, 18.9.

LRMS (EI): *m*/*z* = 277 [M$^+$].

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.43; H, 6.99; N, 5.26.

(*Z*)-1-Benzyl-3-(1-phenylethylidene)pyrrolidin-2-one (20b)
White solid; mp 112.5–113.5 °C.

IR (KBr): 1686, 1660 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.36–7.33 (m, 2 H), 7.31–7.28 (m, 3 H), 7.28–7.22 (m, 5 H), 4.44 (s, 2 H), 3.28 (t, *J* = 6.9 Hz, 2 H), 2.80–2.77 (m, 2 H), 2.08 (t, *J* = 1.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.8, 142.8, 141.3, 136.8, 128.5, 128.3, 127.7, 127.5, 127.4, 127.0, 125.9, 46.9, 42.7, 24.5, 24.1.

LRMS (EI): *m*/*z* = 277 [M^+].

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.21; H, 6.98; N, 5.02.

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