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Radical Cyclization of *N*-Allyl-2-halo Amide in Water

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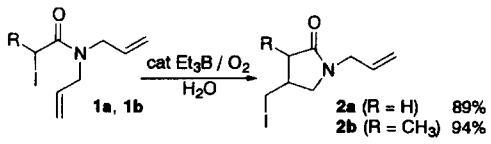
Triethylborane-induced radical cyclization of *N*-allyl-2-iodo amide proceeded smoothly in water to give the corresponding γ-lactam in good yield. Radical cyclization in acidic media was also effective. Chloroacetamide, combined with sodium iodide, was available as a substrate for the atom transfer radical cyclization in water to furnish the iodomethyl-substituted γ-lactam.

Recently, radical reaction has become one of the most powerful tools for carbon–carbon bond formation in organic synthesis and is widely used as a key step in a total synthesis of natural products and biologically active compounds.[1] γ-Lactam is a versatile building block which is found in those compounds and many radical cyclization methods have been developed for its construction.[2,3] In general, radical reaction has been performed in organic solvents such as benzene and dichloromethane. Very recently, we reported that triethylborane-induced radical cyclization reaction of allyl 2-iodoacetate proceeds effectively in water.[4] Here we wish to report further application of this new method to the cyclization of *N*-allyl-2-iodo amide in water to provide γ-lactams.[5]

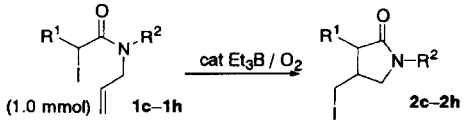
Triethylborane (1.0 M methanol solution, 0.1 mL, 0.1 mmol, 1 M = 1 mol dm^{-3}) was added to a suspension of *N*,*N*-diallyl-2-iodoacetamide (**1a**, 0.26 g, 1.0 mmol) in water (30 mL) at 25 °C and the suspension was vigorously stirred for 1 h. The product was extracted with ethyl acetate and purified by silica-gel column chromatography to give γ-lactam **2a** in 89% yield (Scheme 1). 2-Iodopropanamide **1b** also provided the corresponding atom transfer cyclized product **2b** in 94% yield (*trans*/*cis* = 75/25).

Several substrates (**1c**—**1h**), which have one allyl group and another substituent on nitrogen, have been prepared. The results of the Et_3B-mediated cyclization reaction of these substrates are shown in Table 1. Triethylborane-induced reaction



Scheme 1.

Table 1. Atom Transfer Radical Cyclization of 2-Iodo Amides



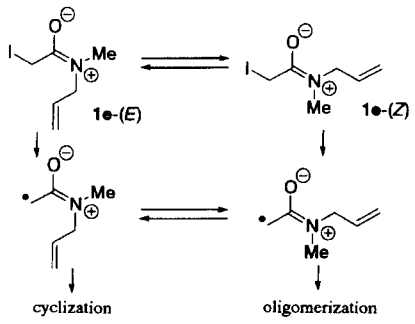
Entry		Substrate **1**		Et_3B	Reaction time	Yield of **2**[a]
		R^1	R^2	mmol	(h)	%
1	**1c**	H	SO_2CH_3	0.2	8	77
2	**1d**	H	SO_2CF_3	0.6	12	61
3	**1e**	H	CH_3	0.1	18	22[b]
4	**1e**	H	CH_3	1.0	25	38[c]
5	**1f**	H	Cyclohexyl	1.0	18	60
6	**1g**	CH_3	SO_2CH_3	0.1	5	78 (90/10)
7	**1h**	CH_3	CH_3	0.1	19	51 (71/29)[d]
8	**1h**	CH_3	CH_3	1.0	23	75 (70/30)

a) Isolated yield. Isomeric ratios were in parentheses (*trans*/*cis*). b) **1e** (72%) was recovered. c) **1e** (30%) was recovered and oligomeric products were obtained. d) **1h** (30%) was recovered.

of **1c** and **1d** in water proceeded more slowly compared to the reaction of **1a** and afforded the corresponding lactam **2c** and **2d** in 77% and 61% yield, respectively, after prolonged stirring at 25 °C. Treatment of *N*-allyl-*N*-methyl amide **1e** with Et_3B gave **2e** in only 22% yield along with the starting material (72% recovery). Using an equimolar amount of Et_3B provided **2e** in 38% yield in addition to oligomeric products. The use of cyclohexyl group in place of methyl group resulted in the formation of the corresponding lactam **2f** in 60% yield after 18 h. Contrary to our expectations, no solvent effect of water was observed in these reactions. For example, treatment of **1g** (1.0 mmol) with Et_3B (0.2 mmol) in benzene (30 mL) for 3 h afforded **2g** in 77% yield.

The low yield of the reaction of **1e** might be ascribed to the presence of the disfavored conformation for cyclization.[6] The examination of ^1H NMR of **1e** in D_2O proved that two methyl signals (42 : 58) appeared at δ = 2.82 and 3.02. The presence of two methyl signals is caused by restricted rotation around the C(O)–N bond attributed to the resonance form $C(O^-)=N^+$(Scheme 2).

The use of 0.1 M HCl solution in place of water improved the yield of the cyclized product. For instance, an addition of Et_3B (1 M methanol solution, 0.2 mL, 0.2 mmol) to a suspension of **1c** (1.0 mmol) in 0.1 M HCl (30 mL) gave **2c** in 92% yield. Whereas hydrofluoric acid (0.1 M HF) was



Scheme 2.

also effective as a solvent, hydrobromic acid was marginal. The former provided **2c** in 97% yield and the latter afforded **2c** in 62% yield in addition to 33% of starting material. In contrast, the reaction in 0.1 M HI solution did not take place and starting iodide **1c** was recovered unchanged. The higher the concentration of hydrochloric acid is, the lower the yield of **2c** becomes. In 1 M HCl solution, the yield of **2c** dropped to 36 and 40% of starting material was recovered. No reaction took place in concentrated hydrochloric acid. The effect of acidic media is not clear. We assume that the coordination of carbonyl group to proton in water promotes the cyclization reaction.[7]

N,N-Diallyl-2-chloroacetamide (**3**) could be used as a starting material instead of the corresponding iodide **1a**. Heating a solution of **3** (1.0 mmol) in water in the presence of NaI (2.0 mmol) and 4,4′-azobis(4-cyanopentanoic acid) (**4**, 0.3 mmol)[8] at 75 °C for 3 h provided **2a** in 94% yield. The reaction proceeded via tandem ionic nucleophilic displacement and radical cyclization.

Experimental

General Procedure for the Radical Cyclization of *N*-allyl-2-iodo Amide. Cyclization of *N,N*-diallyl-2-iodoacetamide (**1a**) is representative. **1a** (265 mg, 1.0 mmol) was placed in a 50 mL flask and distilled water (30 mL) was added. The mixture was flushed with argon in a toy balloon and stirred to suspend the starting material. A solution of Et_3B in methanol (1.0 M, 0.10 mL, 0.10 mmol) was then added dropwise and the toy balloon was removed to introduce air. After stirring for 1 h at 25 °C, the reaction mixture was extracted with ethyl acetate (10 ml×3) and the combined organic layer was dried over Na_2SO_4 and concentrated. Silica-gel column purification (hexane : ethyl acetate = 1 : 1) of the crude oil provided **2a** (236 mg, 0.89 mmol) in 89% yield.

Procedure for the Radical Cyclization Starting from *N,N*-diallyl-2-chloroacetamide. **3** (174 mg, 1.0 mmol) was placed in a 50 mL flask and distilled water (30 mL), sodium iodide (300 mg, 2.0 mmol) and 4,4′-azobis(4-cyanopentanoic acid) (84 mg, 0.3 mmol) was added. The mixture was flushed with argon in a toy balloon and heated at 75 °C with vigorous stirring for 3 h. After cooling, the reaction mixture was extracted with ethyl acetate and washed with aqueous sodium hydrogencarbonate and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica-gel column chromatography provided **2a** (249 mg, 0.94 mmol) in 94% yield.

Spectral data for **1a**, **2a**, **1e**, and **2e** are found in the literature. See Ref. 3.

The stereochemistry of **2b**, **2g**, and **2h** was conjectured as follows. Reduction of the major isomer of **2h** with *n*-Bu_3SnH in benzene in the presence of Et_3B gave 1,3,4-trimethyl-2-pyrrolidinone as a single product. The chemical shifts of the protons at C3 and C4 are 1.89—2.04 (m, 2H) and those at C5 are 2.90 (t, J = 9.0 Hz, 1H) and 3.36 (dd, J = 9.3, 7.5 Hz, 1H). These characteristic peaks are quite similar to the ^{1}H NMR spectra of *trans*-3,4-dimethyl-1-phenyl-2-pyrrolidinone and *trans*-3,4-dimethyl-1-propyl-2-pyrrolidinone in the literature.[9] Thus, we estimated that the major isomer was a *trans* isomer. As for **2b** and **2g**, the same procedure proved that the major isomers had *trans* stereochemistry.

***N*-Allyl-2-iodo-*N*-methylsulfonylacetamide (1c):** IR (neat) 1687, 1421, 1350, 1247, 1166, 962, 838, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 3.33 (s, 3H), 4.08 (s, 2H), 4.45 (dt, J = 5.1, 1.5 Hz, 2H), 5.30—5.38 (m, 2H), 5.86—5.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ = −2.78, 42.02, 49.00, 118.63, 132.15, 168.67. Found: C, 23.84; H, 3.23%. Calcd for $C_6H_{10}INO_3S$: C, 23.78; H, 3.33%.

4-Iodomethyl-1-methylsulfonyl-2-pyrrolidinone (2c): IR (nujol®) 1730, 1329, 1203, 1159, 984, 786 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.38—2.50 (m, 1H), 2.67—2.82 (m, 2H), 3.23—3.32 (m, 5H), 3.57 (dd, J = 10.2, 6.3 Hz, 1H), 4.05 (dd, J = 10.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 7.64, 33.19, 39.31, 40.53, 52.08, 172.76. Found: C, 24.08; H, 3.29%. Calcd for $C_6H_{10}INO_3S$: C, 23.78; H, 3.33%.

***N*-Allyl-2-iodo-*N*-methylpropanamide (1h):** Rotamer ratio = 55/45 in $CDCl_3$ at 20 °C; IR (neat) 2916, 1657, 1640, 1407, 1269, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.96 (d, J = 6.6 Hz, 1.35H), 2.00 (d, J = 6.6 Hz, 1.65H), 2.95 (s, 1.35H), 2.98 (s, 1.65H), 3.72—4.18 (m, 2H), 4.52 (q, J = 6.8 Hz, 0.45H), 4.63 (q, J = 6.8 Hz, 0.55H), 5.11—5.24 (m, 2H), 5.71—5.92 (m, 1H); ^{13}C NMR ($CDCl_3$) for major rotamer δ = 13.63, 23.69, 35.20, 50.67, 117.44, 132.24, 170.76; for minor rotamer δ = 13.09, 23.94, 34.57, 50.74, 116.57, 132.49, 171.30. Found: C, 33.28; H, 4.71%. Calcd for $C_7H_{12}INO$: C, 33.22; H, 4.78%.

4-Iodomethyl-1,3-dimethyl-2-pyrrolidinone (2h): *trans*/*cis* = 70/30; IR (nujol®) 1710, 1293, 1191, 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$): for *trans* isomer δ = 1.24 (d, J = 6.3 Hz, 3H), 2.17 (m, 2H), 2.87 (s, 3H), 3.04 (dd, J = 9.6, 8.1 Hz, 1H), 3.16 (dd, J = 9.6, 8.7 Hz, 1H), 3.39—3.49 (m, 2H); for *cis* isomer δ = 1.12 (d, J = 6.3 Hz, 3H), 2.58 (m, 1H), 2.74—2.85 (m, 1H), 2.86 (s, 3H), 3.08 (t, J = 9.9 Hz, 1H), 3.14 (dd, J = 9.9, 6.0 Hz, 1H), 3.28 (dd, J = 9.9, 6.0 Hz, 1H), 3.50 (dd, J = 9.9, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) for *trans* isomer δ = 8.07, 14.83, 29.56, 42.76, 43.64, 54.39, 175.94; for *cis* isomer δ = 4.57, 9.95, 29.51, 38.82, 40.55, 53.90, 176.26. Found: C, 33.37; H, 4.52%. Calcd for $C_7H_{12}INO$: C, 33.22; H, 4.78%.

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