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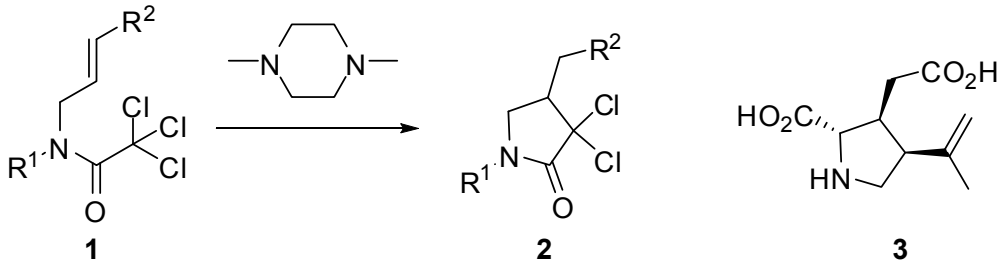
WATER IN AMINE-MEDIATED SINGLE ELECTRON TRANSFER REACTION OF *N*-ALLYLIC TRICHLOROACETAMIDES

Tsuyoshi Taniguchi, Masamichi Sasaki, and Hiroyuki Ishibashi*

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan. E-mail: isibasi@p.kanazawa-u.ac.jp

Abstract – Water contaminating 1,4-dimethylpiperazine was thought to play an important role in effecting a single electron transfer reaction **(**radical cyclization) of *N*-allylic trichloroacetamides.

We have recently reported that *N*-allylic trichloroacetamides (**1**), upon heating in 1,4-dimethylpiperazine (1,4-DMP), gave γ-lactams (**2**) in good yields (Scheme 1).[1-3] These reactions might involve a single electron transfer reaction of 1,4-dimethylpiperazine to **1**. Compounds (**1**) gave dichloro-substituted carbamoylmethyl radicals after removal of a mono-chlorine atom. Cyclization of these radicals to an olefinic bond and successive addition reaction of a H-atom at the resulting terminal radical intermediates gave γ-lactams (**2**). Our attention was next turned to the application of this method to synthesis of (–)-kainic acid (**3**).[4,5] We report herein that water contaminating 1,4-dimethylpiperazine plays an important role in effecting a radical cyclization.

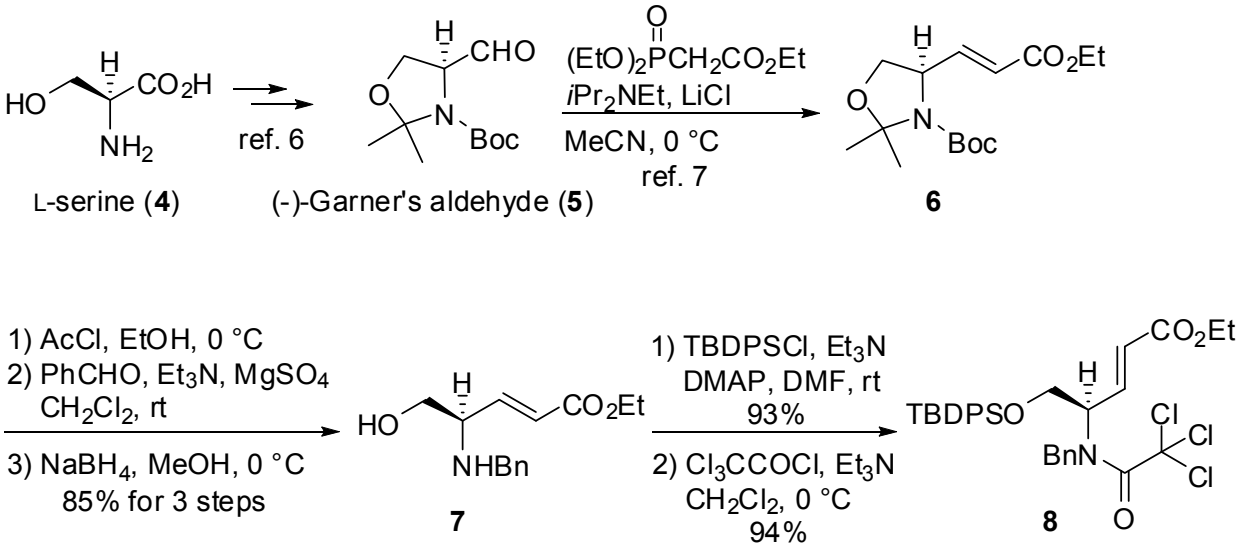


1 **2** **3**

Scheme 1

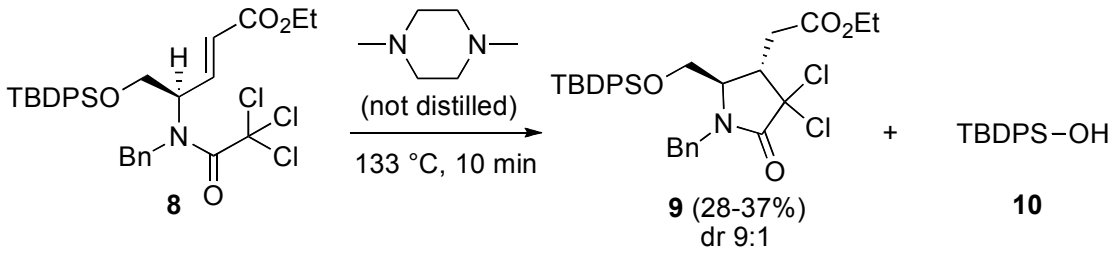
This paper is dedicated to Prof. Emeritus Akira Suzuki (Hokkaido University) on the occasion of his 80th birthday.

We initiated our investigation by examining the cyclization of compound (**8**) giving (+)-kainic acid in boiling 1,4-dimethylpiperazine in place of that giving the desired (–)-kainic acid. Synthesis of radical precursor (**8**) was begun by conversion of L-serine (**4**) into (–)-Garner's aldehyde (**5**).[6] Horner-Wadsworth-Emmons reaction of compound (**5**) gave the known *E*-ester (**6**).[7] After transformation of compound (**6**) into **7**, the hydroxy group of compound (**7**) was protected with a *tert*-butyldiphenylsilyl (TBDPS) group and the nitrogen atom was trichloroacetylated to give radical precursor (**8**) (Scheme 2).



Scheme 2

When compound (**8**) was heated in 1,4-dimethylpiperazine (1,4-DMP), which is commercially available and was used without further purification, the expected radical cyclization product (**9**) (stereoisomers' ratio = 9:1) was obtained in 28-38% yield together with *tert*-butyldiphenylsilanol (**10**)[8] after 10 min of heating (Scheme 3).



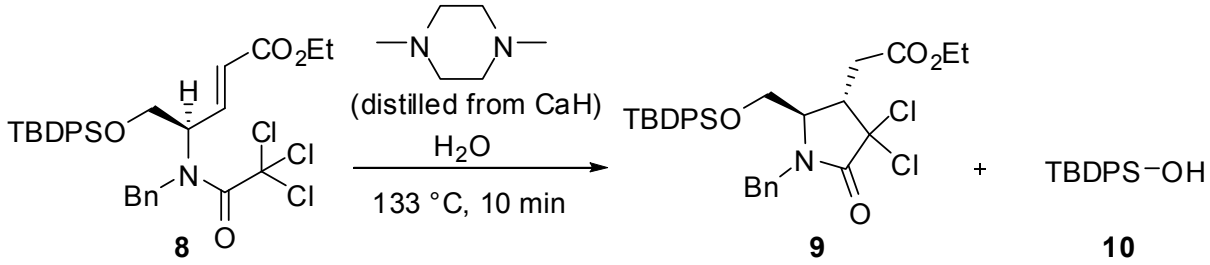
Scheme 3

The stereochemistry between C4 and C5 of the major isomer of compound (**9**) was probably *trans*-configuration.[9] We next carried out a similar reaction in pure 1,4-DMP, since reproducibility was

not observed, and the yield of product (**9**) was relatively low. However, the yield of **9** from compound (**8**) in distilled (pure) 1,4-DMP was found to be lower (7%) than that using non-distilled 1,4-dimethylpiperazine (Table 1, Entry 1). In this case, silanol (**10**) was obtained as a major product in 67% yield.

We soon found that the yield of compound (**9**) was improved to 57% by addition of 5 equiv of water to distilled 1,4-DMP (Table 1, Entry 2). The addition of 0.2 equiv of water gave a similar result (56% yield of **9**) (Table 1, Entry 3). However, when 100 equiv of water was added to 1,4-DMP, compound (**9**) was obtained in only 19% yield with an increase in the yield of silanol (**10**) (80%) (Table 1, Entry 4). Therefore, an appropriate quantity of water was found to play an important role in effecting a single electron transfer reaction (radical cyclization).

Table 1. Effect of water in amine-mediated radical cyclization of **8**



		Yield (%)	
Entry	H_2O (equiv)	**9**	**10**
1	none	7	67
2	5	57	11
3	0.2	56	11
4	100	19	80

It was thought that the formation of silanol (**10**) might involve elimination of **8** to give diene (**11**), which

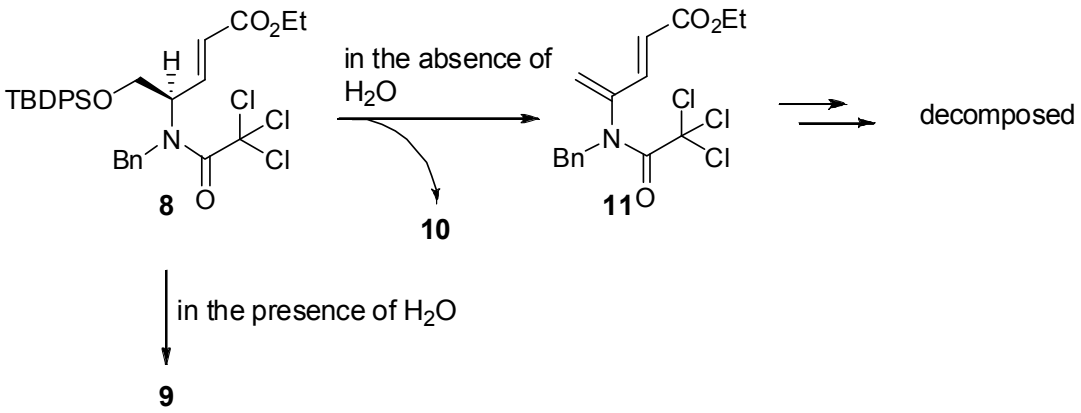


Figure 1

was decomposed under the present reaction conditions (Figure 1). The presence of a small quantity of water might accelerate the radical cyclization to give compound (**9**) in good yield. The exact reason, however, is not clear at the moment.

We found that water contaminating 1,4-dimethylpiperazine played an important role in effecting a single electron transfer reaction (radical cyclization).

EXPERIMENTAL

Ethyl (*ER*)-4-(*N*-benzylamino)-5-hydroxy-2-pentenoate (7) Acetyl chloride (2.30 g, 29.4 mmol) was added dropwise to EtOH (20 mL) at 0 °C over 5 min, and the mixture was stirred at the same temperature for 10 min. To the resultant solution was added dropwise a solution of **6** (4.40 g, 14.7 mmol) in EtOH (10 mL) at 0 °C over 5 min. After the mixture was stirred at room temperature for 20 h, the solution was concentrated to give brown oil. To a solution of the reside in CH_2Cl_2 (70 mL) were added successively Et_3N (1.50 g, 14.7 mmol), $MgSO_4$ (4.40 g, 36.7 mmol) and benzaldehyde (2.30 g, 22.0 mmol) at 0 °C and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through Celite® and the filtrate was concentrated. The residual yellow oil was diluted with MeOH (50 mL) and to the resultant solution was added $NaBH_4$ (4.50 g, 36.7 mmol) in portion at 0 °C. The reaction was quenched by addition of water and the reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 3:1 to 1:1 to 1:2) to give **7** (3.10 g, 85%) as an yellow oil: $[\alpha]_D^{24}$ -63.8 (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) ν 1715 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.30 (3H, t, J = 7.1 Hz), 2.39 (2H, br s), 3.33-3.41 (1H, m), 3.44 (1H, dd, J = 10.1, 7.4 Hz), 3.64 (1H, dd, J = 10.1, 3.6 Hz), 3.64 (1H, d, J = 13.0 Hz), 3.84 (1H, d, J = 13.0 Hz), 4.20 (2H, q, J = 7.1 Hz), 6.00 (1H, dd, J = 15.8, 0.8 Hz), 6.79 (1H, dd, J = 15.8, 7.3 Hz), 7.25-7.35 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 51.0, 60.1, 60.5, 63.8, 123.4, 127.2, 128.1, 128.4, 139.4, 146.5, 166.0; HRMS calcd for $C_{14}H_{19}NO_3$: 249.1365. Found: 249.1363.

Ethyl (*E,R*)-4-(*N*-benzyl-*N*-trichloroacetylamino)-5-(*t*-butyldiphenylsilyloxy)-2-pentenoate (8) To a solution of **7** (500 mg, 2.01 mmol) in DMF (2 mL) were added Et_3N (507 mg, 5.02 mmol), DMAP (25.0 mg, 0.201 mmol) and TBDPSCl (1.10 g, 4.01 mmol) and the mixture was stirred at room temperature for 2 h. The resultant suspension was diluted with a saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:0 to 40:1 to 20:1 to 8:1) to give ethyl (*R*)-4-(*N*-benzylamino)-5-(*t*-butyldiphenylsilyloxy)-2-pentenoate (910 mg, 93%) as a colorless oil: $[\alpha]_D^{25}$ -32.4 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν 1715 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.28 (3H, t, J = 7.1 Hz), 2.10 (1H, s), 3.36-3.43 (1H, m), 3.60 (1H, dd, J = 10.1, 3.1 Hz), 3.63 (1H, d, J = 13.5 Hz), 3.68

(1H, dd, *J* = 10.1, 4.8 Hz), 3.85 (1H, d, *J* = 13.5 Hz), 4.18 (2H, q, *J* = 7.1 Hz), 5.99 (1H, dd, *J* = 15.8, 1.0 Hz), 6.78 (1H, dd, *J* = 15.8, 7.4 Hz), 7.23-7.45 (11H, m), 7.58-7.62 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2, 19.2, 26.8, 51.2, 60.1, 60.3, 65.8, 123.3, 126.9, 127.7, 128.0, 128.4, 129.8, 132.9, 133.0, 135.50, 135.51, 140.1, 147.4, 166.2; HRMS calcd for $C_{30}H_{37}NO_3Si$: 487.2543. Found: 487.2545.

To a solution of thus obtained amine **(**910 mg, 1.87 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (378 mg, 3.73 mmol) and trichloroacetyl chloride (441 mg, 2.43 mmol) at 0 °C and the mixture was stirred at room temperature for 30min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 20:1) to give **8** (1.11 g, 94%) as a colorless oil: $[\alpha]_D^{25}$ -38.8 (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) ν 1680, 1715 cm^{-1}; ^{1}H and ^{13}C NMR spectra of **8** showed it to contain two rotamers. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01 (s), 1.06 (total 9H, both s), 1.20-1.35 (3H, m), 3.75-3.85, 4.00-4.40 (total 5H, both m), 4.88 (br d, *J* = 16.0 Hz), 5.38 (d, *J* = 16.2 Hz), 5.52 (d, *J* = 16.2 Hz), 6.03 (br d, *J* = 15.5 Hz), 6.95 (br dd, *J* = 16.0, 6.3 Hz), 7.07-7.60 (15H, m); HRMS calcd for $C_{32}H_{36}{}^{35}Cl_3NO_4Si$: 631.1480. Found: 631.1481.

(4*S*,5*R*)-1-Benzyl-5-(*t*-butyldiphenylsilyloxymethyl)-3,3-dichloro-4-(ethoxycarbonylmethyl)pyrrolidin-2-one (9) A mixture of **8** (30.0 mg, 0.0474 mmol), 1,4-dimethylpiperazine (541 mg, 4.74 mmol) and H_2O (4.30 mg, 0.237 mmol) was heated at reflux for 10 min. After cooling, the reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by preparative thin layer chromatography (hexane/AcOEt, 3:1) to give **9** (16.2 mg, 57%) as a colorless oil: IR ($CHCl_3$) ν 1725, 1730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, for a major isomer) δ 1.09 (9H, s), 1.26 (3H, t, *J* = 7.1 Hz), 2.45 (1H, dd, *J* = 15.9, 6.1 Hz), 2.89 (1H, dd, *J* = 15.9, 6.8 Hz), 3.08 (1H, dt, *J* = 8.1, 2.4 Hz), 3.57-3.64 (3H, m), 3.73 (1H, dd, *J* = 12.0, 2.4 Hz), 4.14-4.22 (2H, m), 5.10 (1H, d, *J* = 15.1 Hz), 6.81-6.83 (2H, m), 7.19-7.21 (3H, m), 7.38-7.42 (2H, m), 7.44-7.47 (3H, m), 7.50-7.53 (1H, m), 7.61-7.63 (2H, m), 7.68-7.69 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$, for a major isomer) δ 14.0, 19.1, 26.7, 32.7, 44.3, 46.7, 58.2, 59.8, 61.1, 85.6, 127.6, 127.7, 127.8, 128.0, 128.7, 130.0, 130.2, 132.3, 132.3, 134.6, 135.6, 135.8, 167.0, 170.3; HRMS calcd for $C_{32}H_{37}{}^{35}Cl_2NO_4Si$: 597.1869. Found: 597.1860, calcd for $C_{32}H_{37}{}^{37}Cl_2NO_4Si$: 601.1810. Found: 601.1812.

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