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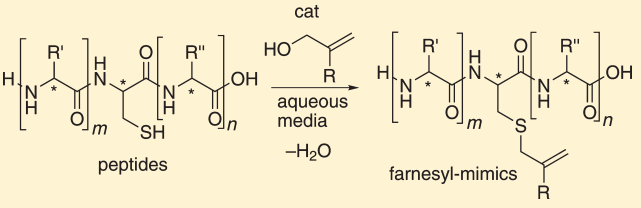
Catalytic Dehydrative *S*-Allylation of Cysteine-Containing Peptides in Aqueous Media toward Lipopeptide Chemistry

Parasuraman Jaisankar, Shinji Tanaka, and Masato Kitamura*

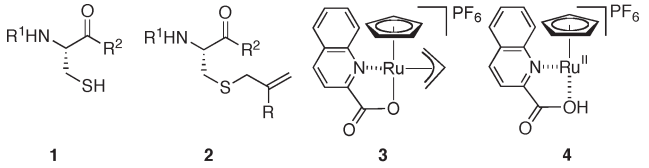
Research Center for Materials Science and the Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-8602, Japan.

Supporting Information

ABSTRACT: Thiol-containing peptides and cysteine have been successfully *S*-allylated with various allyl alcohols in aqueous medium containing a catalytic amount of [CpRu-(η^3-C_3H_5)(2-quinolinecarboxylato)]PF_6. Quick and easy install of 2-propen-l-ol having a long-chain alkyl group at C(2) facilitates the synthesis of a new series of artificial lipopeptides, indicating a potential application to synthetic biology.



Natural and unnatural *S*-allylated cysteine and peptides, including *S*-allyl-(*R*)-glutathione, Ras, and Rab, show various biological activities.[1] In order to efficiently generate a series of chemical libraries aimed at optimizing biological activities direct *S*-allylation of thiol-containing amino acids and peptides **1** in the native form, which are hydrophilic in nature, to give an *S*-allylated product **2** is favored.[2] Thus, the development of catalytic systems to facilitate dehydrative allylation of such hydrophilic target molecules in aqueous medium is one strategy, among many other methods.[3−5] We recently reported a catalytic system consisting of either [CpRu(II)$(CH_3CN)_3$]PF_6 and 2-quinolinecarboxylic acid (QAH) or the π-allyl Ru(IV) complex **3** that can operate in various solvents, including water, alcohols, DMF, DMA, acetone, ethers, and toluene, to realize dehydrative *S*-allylation of thiols and thioic *S*-acids using allyl alcohols without any stoichiometric activation of esters or halides.[6] Herein, we report the application of this chemistry for synthesizing a number of *S*-allyl-peptides **2** from **1**, which is directed toward the synthesis of lipopeptides.



1 **2** **3** **4**

a: R^1 = H; R^2 = OH
b: R^1 = $HO_2CCH(NH_2)(CH_2)_2CO$-; R^2 = HO_2CCH_2NH-
c: R^1 = $C_2H_5O_2CCH(NH_2)(CH_2)_2CO$-; R^2 = $C_2H_5O_2CCH_2NH$-
d: R^1 = NH_2CH_2CO-; R^2 = HO_2CCH_2NH-

Initially, the reaction was optimized by using (*R*)-cysteine (**1a**) as the substrate under standard conditions of [**1a**] = [2-propen-1-ol] = 100 mM, [[CpRu(η^3-C_3H_5)(QA)]PF_6 (**3**)] = 1 mM, 1:1 H_2O−CH_3OH, 27 °C. The results are listed in Table 1. The standard gave **2a** in 40% yield after 24 h (entry 1), while addition of just 1 molar equiv of HCl into the system or use of

Table 1. *S*-Allylation of (*R*)-Cysteine (1a) in Aqueous Media[a]

entry	acid	solvent	time (h)	yield (%)
1		H_2O−CH_3OH[b]	24	40
2	HCl	H_2O−CH_3OH[b]	1	>99
3	CH_3COOH	H_2O−CH_3OH[b]	15	26
4	C_6H_5COOH	H_2O−CH_3OH[b]	24	30
5		buffer (pH 4.7)−CH_3OH[b]	6	>99
6		buffer (pH 7.0)−CH_3OH[b]	24	0
7		buffer (pH 8.0)−CH_3OH[b]	24	0

[a] Conditions: solvent = 1:1 H_2O−CH_3OH; [acid] = [**1a**] = [2-propen-1-ol] = 100 mM; [**3**] = 1 mM; 27 °C. [b] 1:1 ratio.

1a/HCl salt dramatically increased the reactivity (entry 2). The reaction was complete in 1 h to give nearly pure **2a**/HCl in quantitative yield just after concentration of the reaction mixture, providing the biggest advantage in preparation of polar compounds that are not easily isolated or separated. *p*-TsOH, TfOH, and TFA were also usable. C_6H_5COOH and CH_3COOH were not effective (entries 3 and 4), but CH_3COOH/CH_3COONa buffer (pH 4.7) could be used as a cosolvent of CH_3OH (entry 5). No reaction occurred in $PO(OH)_2(ONa)$/$PO(OH)(ONa)_2$ buffer (pH 7 and 8) (entries 6 and 7). This nonreactivity may be due to the fact that [CpRu(II)QAH]PF_6 (**4**) is converted to unreactive neutral CpRu(II)QA, which has no "redox-mediated donor−acceptor bifunctional catalyst (RDACat) ability"[7,8] through carboxylic acid deprotonation of QAH in **4** by **1a**.[8c] Use of HCl salt as well as a pH 4.7 buffer would avoid the formation of CpRu(II)QA, thereby maintaining [CpRu(II)-QAH]PF_6 (**4**) during the course of catalysis.

Regretfully, use of prenyl alcohol, instead of 2-propen-1-ol, stopped the reaction (eq 1), indicating little applicability of the

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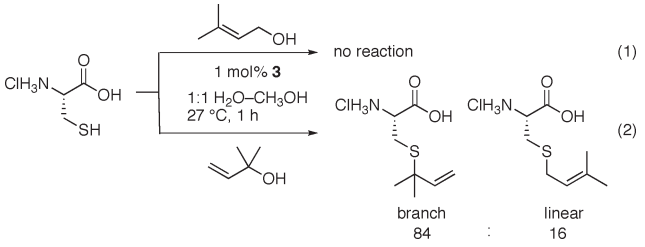
present system to farnesylation, which is one of the most attractive subjects in lipopeptide chemistry.[1a,2] Isoprenyl alcohol smoothly afforded the *S*-allylation product but with preference of branch isomer over the desired linear isomer (84:16) (eq 2). The prenyl alcohol/catalyst complex **5** results in severe steric repulsion between quinoline C(8)H and C(3)CH_3 of the allylic substrate, thereby impeding the reaction via **6**. With isoprenyl alcohol, the complex **7** is easily generated to move to the π-allyl complex **8**, which then reacts with thiol at the more substituted π-allyl carbon.[9] The high branch/linear ratio would be ascribed partly due to the contribution of a carbocationic character of **8**.[10]



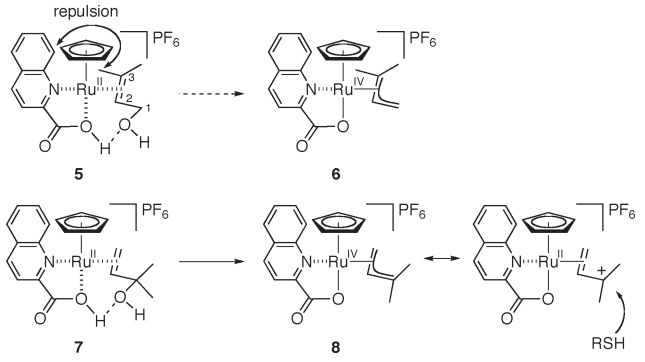
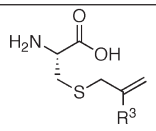
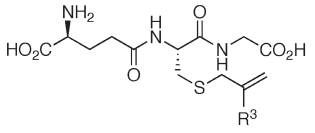
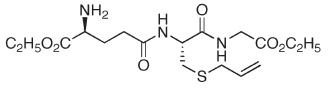
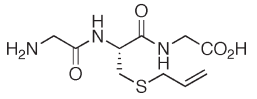


Table 2 illustrates the application of the present method to C(2)-substituted or -unsubstituted 2-propen-1-ols, where there are no issues concerning regiochemistry. (*R*)-Cysteine was quantitatively allylated with 2-methyl-2-propen-1-ol as well as undecyl- and phenyl-substituted allyl alcohols (entries 1−3). Glutathione (γ-Glu-Cys-Gly) (**1b**) was also efficiently allylated both in H_2O−CH_3OH and in pH 4.7 buffer−CH_3OH medium (entries 4−8). The successful introduction of a long-chain alkyl unit facilitates the generation of a new class of artificial lipopeptides. Dehydrative allylation of the diethyl ester of glutathione (**1c**) and Gly-Cys-Gly (**1d**) gave the corresponding allyl sulfides **2c**−**d** (R = H, entries 9−10) in nearly quantitative yields. The simplest allyl sulfide moiety is now recognized as a privileged substrate for aqueous cross-metathesis in site-selective protein modification.[11] A combination of the Davis method[11] with our dehydrative but aqueous allylation will offer a novel approach for synthesizing lipopeptides.

In conclusion, we have established an efficient synthetic method for generating *S*-allylated cysteine and SH-containing peptides. The catalytic reaction is attained with high reactivity and *S*-selectivity among amino, carboxy groups in aqueous media,[12] which is ideally suited to hydrophilic amino acids and peptides. Various allyl alcohols can be used directly without the need for activation as esters or halides. Water is the only coproduct, simplifying the isolation of highly polar products. Successful one-step introduction of a long-chain alkyl group at

Table 2. [CpRu(η^3-C_3H_5)(QA)]PF_6 (3)-Catalyzed Allylation of (*R*)-Cysteine and Its Peptides Using C(2)-Substituted 2-Propen-1-ols and 2-Propen-1-ol[a]

Entry	1	2	Time (h)	Yield (%)[b]
	a			
1		R = CH_3	3.5	97 (94)
2		R = $(CH_2)_{10}CH_3$	4	95 (91)
3		R = C_6H_5	4	95 (89)
	b			
4		R = H	4	98 (93)[c]
5		R = CH_3	4.5	97 (92)
6		R = $(CH_2)_5CH_3$	4	>95 (91)
7		R = $(CH_2)_{10}CH_3$	4	>95 (93)
8		R = C_6H_5	4	95 (91)
9	c		4.5	98 (90)
10	d		5	95 (95)

[a] Conditions: solvent = 1:1 H_2O−CH_3OH; [HCl] = [**1**] = [allyl alcohol] = 100 mM; [**3**] = 1 mM; 27 °C. [b] Yield was determined by ^{1}H NMR analysis using mesitylene as internal standard. The value in parentheses is the isolated yield. For details, see the Experimental Section. [c] The same result was obtained in 1:1 pH 4.7 buffer−CH_3OH medium.

C(2) of the allyl moiety as farnesyl mimics[13] will be advantageous in making a series of chemical libraries for developing novel artificial lipopeptides with biological applications and in creating new activities via a posttranslational modification approach.[14] Our current focuses are (i) measurement of log Pow and membrane affinity of these new lipopeptides and (ii) introduction of 2-propen-l-ol having a peptide- or sugar-containing alkyl chain into peptides or proteins toward synthetic biology.[14b]

EXPERIMENTAL SECTION

General Synthetic Procedure Exemplified by the Synthesis of *S*-(2-Propen-1-yl)glutathione (2b, R = H). A 20-mL Young-type Schlenk tube was first charged with glutathione (**1b**) (307 mg, 1.00 mmol). A 1:1 mixture of H_2O−CH_3OH (10.0 mL) was then added to the tube followed by 12 M HCl (89.0 μL, 1.00 mmol) and 2-propen-1-ol (R = H, 68.0 μL, 1.00 mmol). The resulting solution was degassed by three consecutive freeze−thaw cycles. To this solution was added complex **3** (5.24 mg, 10.0 μmol) under a stream of argon. The resulting orange solution was stirred at 27 °C for 4 h. Solvent was

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removed under vacuum to give a pale yellow solid (375 mg). The product was subjected to ^{1}H NMR analysis (9:1 DMSO-d_6−TFA), which essentially detected a single compound, *S*-allylglutathione hydrochloride: ^{1}H NMR (9:1 DMSO-d_6−TFA) δ1.95−2.09 (2H, m), 2.29−2.42 (2H, m), 2.55 (1H, dd, J = 8.95, 13.77 Hz), 2.79 (1H, dd, J = 4.82, 13.77 Hz), 3.13 (2H, d, J = 6.89 Hz), 3.75 (2H, dd, J = 3.44, 5.51 Hz), 3.93 (1H, dd, J = 6.20, 11.71 Hz), 4.46−4.45 (1H, m), 5.03 (1H, d, J = 8.95 Hz), 5.15 (1H, d, J = 17.21 Hz), 5.68−5.75 (1H, m), 8.24−8.27 (4H, m), 8.36 (1H, t, J = 5.51 Hz); ^{13}C NMR (9:1 DMSO-d_6−TFA) δ26.5, 31.1, 33.0, 34.4, 41.2, 52.2, 52.5, 117.6, 134.7, 171.1, 171.3, 171.4, 171.6; HRMS (FAB) calcd for $C_{13}H_{22}N_3O_6S$ $[M + H]^+$ 348.1229, found 348.1230. The yield was determined by ^{1}H NMR analysis as follows. To the whole crude mixture was added mesitylene (1.00 M solution in DMSO-d_6, 1.00 mL, 1.00 mmol). The solution was then subjected to ^{1}H NMR analysis with 10 s repetitions so that the resulting integrations of the ^{1}H signal areas were sufficient to allow accurate quantification. The 0.980:9.00 ratio of the signal intensities of the product (δ5.70−5.79, m, −CH=CH$_2$) and mesitylene (δ.19, s, 3 × CH$_3$) was used to determine the yield as 98%. A part of the crude product (30.0 mg) was purified by a reversed silica-gel chromatography (Wakogel 50C18 (38−63 μm particle size; 7 mm ϕ × 200 mm); 9:1 H$_2$O−CH$_3$OH eluent) to give a pure **2b** (R = H) (28.0 mg, 93% isolated yield). The purity was confirmed by HPLC analysis (Develosil C30-UG-5; 9:1 H$_2$O−CH$_3$CN containing 0.1% TFA; 0.5 mL/min flow rate; 220-nm detection; t_R 48.0 min).

S-Allylated peptides were synthesized by the same procedure as that of *S*-allylglutathione described above. The amount of substrate and corresponding spectral data of the products are listed below. For the purification and purity analysis, the same columns as those described above were used unless otherwise specified. The loading amount, eluent, isolated yield, and t_R are reported.

***S*-(2-Methyl-2-propen-1-yl)glutathione. 1b** (307 mg, 1.00 mmol): ^{1}H NMR (9:1 CD$_3$OD−TFA) δ 1.81 (3H, s), 2.15−2.30 (2H, m), 2.60 (2H, t, J = 6.89 Hz), 2.69 (1H, dd, J = 8.95, 13.77 Hz,), 2.93 (1H, dd, J = 6.89, 13.77 Hz), 3.14 (1H, d, J = 13.08 Hz), 3.19 (1H, d, J = 13.08 Hz), 3.94 (2H, d, J = 17.21 Hz), 4.07 (1H, t, J = 6.20 Hz), 4.54−4.58 (1H, m), 4.86 (1H, s), 4.91 (1H, s); ^{13}C NMR (9:1 CD$_3$OD−TFA) δ 20.7, 27.1, 32.6, 33.4, 40.1, 41.9, 53.6, 54.1, 114.6, 142.4, 171.7, 171.8, 173.5, 174.6; HRMS (FAB) calcd for $C_{14}H_{24}N_3O_6S$ $[M + H]^+$ 362.1386, found 362.1390. Purification and purity analysis: 30.0 mg; 9:1 H$_2$O−CH$_3$OH; 27.6 mg (92% yield); 90 min (9:1 H$_2$O−CH$_3$CN/0.1% TFA).

***S*-(2-Hexyl-2-propen-1-yl)glutathione. 1b** (307 mg, 1.00 mmol). The product (420 mg) was precipitated after the reaction and then isolated from the mixture by filtration and washing with methanol: ^{1}H NMR (9:1 CD$_3$OD−TFA) δ 0.90 (3H, t, J = 6.89 Hz), 1.28−1.35 (6H, m), 1.42−1.48 (2H, m), 2.15−2.20 (3H, m), 2.22−2.28 (1H, m), 2.58 (2H, t, J = 7.57 Hz), 2.68 (1H, dd, J = 8.95, 13.77 Hz), 2.92 (1H, dd, J = 5.51, 13.77 Hz), 3.17 (1H, d, J = 13.77 Hz), 3.20 (1H, d, J = 13.77 Hz), 3.94 (2H, d, J = 15.15 Hz), 4.03 (1H, t, J = 6.20 Hz), 4.56 (1H, dd, J = 5.51, 8.95 Hz), 4.88 (1H, s), 4.94 (1H, s); ^{13}C NMR (9:1 CD$_3$OD−TFA) δ 14.4, 23.7, 27.1, 28.7, 30.1, 32.5, 32.9, 33.6, 34.8, 38.6, 41.8, 38.6, 53.6, 54.0, 113.7, 146.4, 171.5, 172.7, 173.2, 174.4; HRMS (FAB) calcd for $C_{19}H_{34}N_3O_6S$ $[M + H]^+$ 432.2168, found 432.2164. Purification and purity analysis: 20.0 mg; CH$_3$OH; 18.2 mg (91% yield); 9.3 min (1:1 H$_2$O−CH$_3$CN/0.1% TFA).

***S*-(2-Undecyl-2-propen-1-yl)glutathione. 1b** (307 mg, 1.00 mmol). The product (480 mg) was precipitated after the reaction and then isolated from the mixture by filtration and washing with methanol: ^{1}H NMR (9:1 DMSO-d_6−TFA) δ 0.83 (3H, t, J = 6.89 Hz), 1.22 (16H, brs), 1.37 (2H, brs), 1.95−2.08 (4H, m), 2.28−2.41 (2H, m), 2.49−2.54 (1H, br), 2.74 (1H, dd, J = 4.82, 12.39 Hz), 3.10 (1H, d, J = 13.77 Hz), 3.14 (1H, d, J = 13.77 Hz), 3.75 (2H, t, J = 5.51 Hz), 3.93−3.96 (1H, m), 4.46−4.49 (1H, m), 4.81 (1H, s), 4.91 (1H, s), 8.25 (2H, brm), 8.35 (1H, brm); ^{13}C NMR (9:1 DMSO-d_6−TFA) δ 14.0, 22.3, 26.2, 27.1, 28.8(8), 28.9(4), 29.1, 29.1(9), 29.2(3), 30.8, 31.5, 33.0, 33.5, 37.0, 40.9, 51.9, 52.1, 63.8, 112.9, 144.9, 170.9, 171.0, 171.1, 171.2; HRMS (FAB) calcd for $C_{24}H_{44}N_3O_6S$ $[M + H]^+$ 502.2951, found 502.2949. Purification and purity analysis: 25.0 mg; CH$_3$OH; 23.2 mg (93% yield); 55.2 min (1:1 H$_2$O−CH$_3$CN/0.1% TFA).

***S*-(2-Phenyl-2-propen-1-yl)glutathione. 1b** (46.1 mg, 0.150 mmol): ^{1}H NMR (9:1 CD$_3$OD−TFA) δ 2.11−2.26 (2H, m), 2.50−2.58 (2H, m), 2.71 (1H, dd, J = 8.95, 14.12 Hz), 2.98 (1H, dd, J = 5.51, 13.77 Hz), 3.68 (2H, s), 3.92 (2H, s), 4.02, (1H, t, J = 6.89 Hz), 4.56 (1H, dd, J = 5.51, 8.61 Hz), 5.29 (1H, s), 5.46 (1H, d, J = 1.38 Hz), 7.26 (1H, t, J = 7.57 Hz), 7.32 (2H, t, J = 7.57 Hz), 7.47 (2H, d, J = 7.57 Hz); ^{13}C NMR (9:1 CD$_3$OD−TFA) δ 27.1, 32.4, 34.0, 37.4, 41.8, 53.5, 54.0, 115.9, 127.5, 128.9, 129.4, 140.6, 145.2, 171.5, 172.7, 173.2, 174.4; HRMS (FAB) calcd for $C_{19}H_{26}N_3O_6S$ $[M + H]^+$ 424.1542, found 424.1548. Purification and purity analysis: 13.2 mg; 9:1 H$_2$O−CH$_3$OH; 12.0 mg (91% yield); 38.5 min (8:2 H$_2$O−CH$_3$CN/0.1% TFA).

***S*-(2-Propen-1-yl)glutathione diethyl ester. 1c** (32.4 mg, 0.100 mmol): ^{1}H NMR (CD$_3$OD) δ 1.26 (3H, t, J = 7.57 Hz), 1.34 (3H, t, J = 7.57 Hz), 2.12−2.26 (2H, m), 2.55 (2H, t, J = 6.89 Hz), 2.71 (1H, dd, J = 8.95, 13.77 Hz), 2.95 (1H, dd, J = 5.51, 14.46 Hz), 3.19 (2H, d, J = 6.89 Hz), 3.91−3.95 (2H, m), 4.10 (1H, t, J = 6.89 Hz), 4.18 (2H, q, J = 7.57 Hz), 4.32 (2H, t, J = 7.57 Hz), 4.53−4.57 (1H, m), 5.10 (1H, d, J = 9.64 Hz), 5.18 (1H, d, J = 17.21 Hz), 5.76−5.84 (1H, m); ^{13}C NMR (CD$_3$OD) δ 14.4, 14.5, 27.0, 32.2, 33.4, 35.6, 42.1, 53.6, 54.1, 62.3, 63.8, 117.9, 135.4, 170.2, 171.0, 173.3, 174.1; HRMS (FAB) calcd for $C_{17}H_{30}N_3O_6S$ $[M + H]^+$ 403.1850, found 403.1850. Purification and purity analysis: 15.0 mg; 1:1 H$_2$O−CH$_3$OH; 13.5 mg (90% yield); 6.4 min (CH$_3$CN/0.1% TFA).

Gly-Cys(*S*-allyl)-Gly. 1d (17.7 mg, 75.0 mmol): ^{1}H NMR (9:1 CD$_3$OD−TFA) δ 2.72 (1H, dd, J = 8.59, 13.75 Hz), 2.96 (1H, dd, J = 5.73, 13.75 Hz), 3.19 (2H, d, J = 7.45 Hz), 3.71−3.78 (2H, m), 3.96 (2H, s), 4.60−4.64 (1H, m), 5.11 (1H, d, J = 9.16 Hz), 5.18 (1H, d, J = 17.18 Hz), 5.75−5.85 (1H, m); ^{13}C NMR (9:1 CD$_3$OD−TFA) δ 33.5, 35.6, 41.5, 41.8, 41.9, 54.0, 135.3, 167.3, 171.4, 172.9; HRMS (FAB) calcd for $C_{10}H_{18}N_3O_4S$ $[M + H]^+$ 276.1018, found 276.1020. Purification and purity analysis: 10.0 mg; 9:1 H$_2$O−CH$_3$OH; 9.5 mg (95% yield); 7.7 min (8:2 H$_2$O−CH$_3$CN/0.1% TFA).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H and ^{13}C NMR spectra and HPLC charts for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: kitamura@os.rcms.nagoya-u.ac.jp.

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