Journal of Organometallic Chemistry 696 (2011) 1018–1022

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Communication

Organometallic peptide NHC complexes of Cp*Rh(III) and arene Ru(II) moieties from L-thiazolylalanine

Jessica Lemke, Nils Metzler-Nolte*

Lehrstuhl für Anorganische Chemie I – Bioanorganische Chemie, Fakultät für Chemie und Biochemie, Ruhr-Universität Bochum, Universitätsstraße 150, 44801 Bochum, Germany

ARTICLE INFO

Article history:
Received 31 October 2010
Received in revised form
28 December 2010
Accepted 29 December 2010

Keywords:
Bioorganometallic chemistry
NHC complexes
Peptide bioconjugates
Rhodium compounds
Ruthenium compounds
Thiamine
Thiazolylalanine

ABSTRACT

The 3-ethyl thiazolium peptide salts Boc-Thia-Leu-OMe and Boc-Thia-Leu-Phe-OMe based on the unnatural amino acid thiazolylalanine (Thia) have been prepared. After deprotonation, they reacted rapidly via the silver carbene transfer reaction with $[RhCp^*Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ to yield the corresponding thiazole-based carbene complexes **7**–**10** in acceptable yield. All new compounds were characterized by multinuclear NMR spectroscopy, mass spectrometry, and elemental analysis. These complexes constitute the first examples of thiazolylalanine-2-ylidene metal bioconjugates.

Thiamine (vitamin B_1) belongs to the water-soluble B complex vitamins. It consists of a pyrimidine and a substituted thiazole ring. In particular its diphosphate salts are vital in the metabolism of sugars. Thiamine is not naturally produced in humans and thus needs to be supplied by our diet. Its deficiency leads to diseases like Beriberi, with fatal outcome if thiamine is not supplemented by a suitable diet. Metal coordination (Zn^{2+}, Cd^{2+}, Hg^{2+}) to thiamine diphosphate occurs via the pyrimidine nitrogen atom and phosphate groups [1,2].

Although it is accepted that thiamine forms a free carbene as an intermediate during benzoin condensation, [3] no carbene-type metal complexes of thiamine itself or its derivatives are known. As much simpler compounds, thiazolyl-2-ylidene complexes mainly from thiazole itself were reported [4–6]. They were usually prepared from *N*-alkyl functionalised thiazolium salts as ligand precursors which were transformed to the lithium carbene and then reacted with metal carbonyls to form the desired complexes. Compared to the much better investigated N-heterocyclic carbene (NHC) complexes derived from imidazole, thiazolyl-2-ylidene complexes only have one substituent at the nitrogen atom of the heterocycle, whereas the imidazole-based NHC complexes may have two different substituents on both nitrogen atoms. As bioorganic derivatives of thiazole, amino acids such as thiazolylalanine (Thia) [7], have been described, but again no metal complexes of such compounds were reported. In view of this, we set out to prepare thiazolium peptides and the first carbene-type metal complexes thereof via the Ag_2O transmetallation route [8].

Biomolecules conjugated to metal complexes have been used in several biochemical and medicinal applications, ranging from biosensors to radioimaging and drugs [9,10]. A special interest lies in the field of organometallic bionconjugates, where the metal complex is covalently bound to a biomolecule, e.g. DNA, PNA and peptides [11–13]. Our group has reported covalent organometallic bioconjugates based on ferrocene-peptide and PNA conjugates [14], as well as cobaltcarbonyl-alkyne peptides [15] and scorpionate derivatives [16]. Recently, the syntheses of NHC-metal peptide conjugates have been published [17–19], as well as the syntheses of NHC-sugar conjugates [20] and NHC-gold amino acid conjugates [20,21].

To form the di- and tripeptide derivatives, Boc-*l*-thiazolylalanine was activated with *N*-methylmorpholine and isobutyl chloroformate in THF to which solutions of the deprotonated *l*-leucine methylester or the deprotonated dipeptide Leu-Phe-OMe (**2**) in THF were added [22]. After filtration and extraction, the thiazolylalanine peptides **3** and **4** were obtained as white-yellow powders in excellent yields. The dipeptide **3** and the tripeptide **4** were transformed into the 3-ethyl thiazolium salts using literature conditions (Scheme 1) [23].

* Corresponding author. Tel.: +49 (0)234 32 28152; fax: +49 (0)234 32 14378.
E-mail address: nils.metzler-nolte@rub.de (N. Metzler-Nolte).

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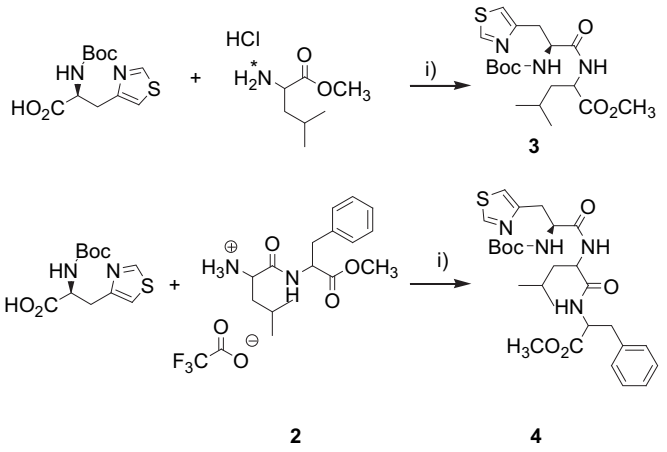
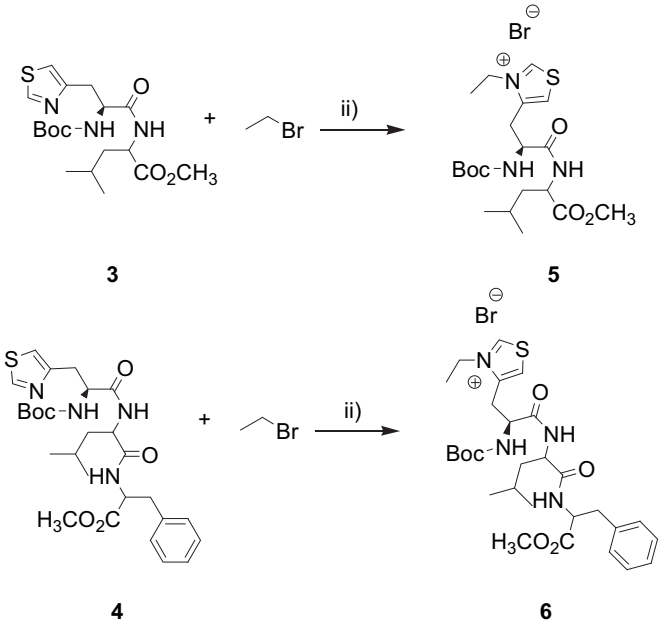
doi:10.1016/j.jorganchem.2010.12.044



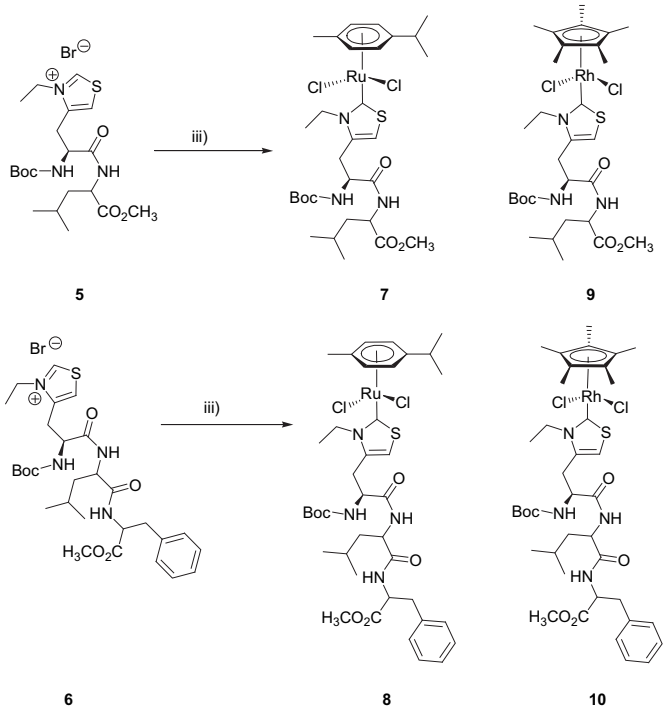
Scheme 1. Synthesis of the thiazolylalanine peptides. i) *N*-methylmorpholine, isobutyl chloroformiate, NEt_3, THF, 1 h.

The crude thiazolium salts were purified via flash column chromatography. Thiazolium peptide salts **5** and **6** were obtained as white powders after lyophilisation from water-acetonitrile mixtures in moderate yields (Scheme 2).

The NHC-rhodium(III) and -ruthenium(II) complexes were synthesised by addition of Ag_2O to the thiazolium salts in dichloromethane, containing molecular sieves to absorb the formed water. After shaking the mixture overnight, the chloro-bridged metal dimers (dichloro(Cp*)rhodium(III) and dichloro (*p*-cymene)ruthenium(II) dimer) were added. Almost instantly, the carbene transfer reaction started, indicated by the precipitation of a white solid, likely to be silver bromide. After 24 h, the mixtures were filtered through celite and the crude products were purified by flash column chromatography. Complexes **7**–**10** were obtained as orange powders in moderate yields after recrystallization from dichloromethane/pentane (Scheme 3). In all cases, the reaction did not give full conversion. This is likely due to the ligand precursors losing reactivity upon elongation of the peptide chain.



Scheme 2. Synthesis of the 3-ethyl thiazolylalanine peptide salts. ii) 1 eq. peptide, 1 mL ethylbromide/100 mg peptide, acetonitrile, N_2, 90 °C, 60 h.



Scheme 3. Synthesis of the rhodium and ruthenium carbene complexes. iii) 2 eq. thiazolium salt, 1 eq. Ag_2O, 1 eq. $[(p\text{-cymene})RuCl_2]_2$ or $[Cp^*RhCl_2]_2$, CH_2Cl_2, molecular sieve, N_2.

All products were comprehensively characterized by mass spectrometry, NMR spectroscopy and elemental analysis. A characteristic feature of the thiazolium peptides **5** and **6** is the downfield-shifted signal of the acidic N=C*H*-S proton at 10.61 ppm (**5**) and 10.20 ppm (**6**) with a ^4J coupling of about 2 Hz in the ^1H NMR spectra. In the ^{13}C NMR spectra, the signals around 145–152 ppm (N=C*H*-S) of the thiazolium salts are downfield shifted as well, compared to the signal for the C=C*H*-S carbon atom around 120 ppm. Upon metal complexation, the downfield-shifted proton signal disappears and the C=C*H*-S proton signal becomes a singlet. In the ^{13}C NMR spectra, the metal-carbene carbon signals are observed at 170 ppm for the rhodium carbenes and at 172 ppm for the ruthenium carbenes. All spectroscopic data are well in agreement with values reported for other NHC complexes of Ru(arene) or Rh(Cp*) fragments, respectively. In electrospray ionisation mass spectrometry (ESI-MS pos.), the metal complexes, as well as the thiaozolium salts, show the $[M\text{-halide}]^+$ peak as the base peak. Further, for the rhodium conjugates **9** and **10**, a second peak occurs, which was identified as the $[M - Et - H + K]^+$ peak (Fig. 1).

In summary, we have demonstrated that thiazolyl-2-ylidene rhodium(III) and ruthenium(II) complexes, where the ligand precursors themselves are peptide conjugates, are easily accessible via the silver carbene transfer reaction. Such compounds are of fundamental interest as they constitute the first metal thiazolyl-2-ylidene bioconjugates. Based on the rich chemistry of imidazole-based NHC complexes especially in catalysis, related applications of functional thiazolyl carbenes may be envisaged. In bio-organometallic chemistry in particular, Ru(arene) complexes were extensively studied for their antiproliferative activity [24–27]. While the aqueous chemistry of the Rh(Cp*) fragment and binding to amino acids and nucleobases has been extensively investigated [28,29], the thiazolylalanine complexes described herein are the first peptide bioconjugates of this metal fragment [30]. Gilbertson et al. have demonstrated how carefully designed peptides may serve as

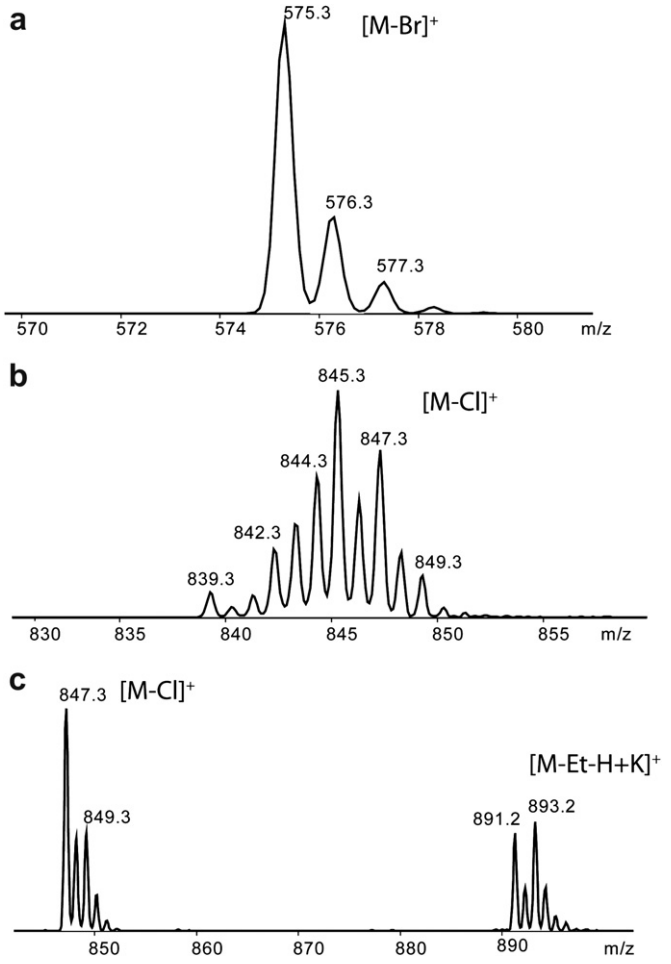


Fig. 1. Comparison of the ESI-MS (pos.) of the thiazolium peptide salt **6** and the corresponding ruthenium and rhodium complexes. (a) **6** $[M - Br]^+$, (b) **8** $[M - Cl]^+$ and (c) **10** $[M - Cl]^+$ and $[M - Et - H + K]^+$.

ligands for metal-catalyzed transformation with high enantioselectivity [31–34]. In their work, amino acids with phosphine side chains were used. These amino acids are not commercially available and required careful control of the reaction conditions due to oxidation of the phosphine groups. In principle, the present paper suggests that thiazolylalanine may be a more convenient alternative for such applications, in addition to the above mentioned use in medicinal inorganic chemistry [35]. Further work along these lines of thought is in progress in our laboratory.

1. Experimental

1.1. General

All reagents were purchased from commercial sources and used as received. *l*-amino acids were purchased from Novabiochem and IRIS Biotech. Although the final products are stable to air and moisture, all reactions were carried out under an inert N_2 gas atmosphere in dry solvents. Solvents were distilled over $CaCl_2$ (CH_2Cl_2) and CaH_2 (acetonitrile). Glassware was used oven dry. NMR spectra were recorded on either Bruker DPX 250 (250 MHz) or on Bruker DRX 400 (400 MHz) spectrometers. The NMR chemical shifts (δ) are reported in ppm relative to the residual proton chemical shifts of the deuterated solvent set relative to external TMS. Microanalysis was performed on an Analytik Jena multi EA 3100. Electrospray ionisation mass spectra (ESI) were recorded with a Bruker Esquire 6000.

1.2. Syntheses of new compounds

1.2.1. **1**

To a stirred solution of Boc-leucine monohydrate (2.49 g, 10 mmol) in THF (50 mL) was added *N*-methylmorpholine (1.12 mL, 10 mmol) followed by the addition of isobutyl chloroformiate (1.32 mL, 10 mmol), resulting in a precipitation of a white solid. In a second flask, phenylalanine methylester hydrochloride (2.15 g, 10 mmol) was suspended in THF (50 mL) containing triethylamine (1.38 mL, 10 mmol). Both suspensions were mixed and stirred for 1 h at room temperature. After removal of the white precipitates by filtration, the solvent was removed under reduced pressure and the residual oil dissolved in $CHCl_3$ (100 mL). The solution was washed with water (50 mL) and the aqueous solution was back-extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ solutions were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the product as a white solid (3.76 g, 96%). ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 7.29–7.07 (6H, m, $C_{Ar,Phe}H$, NH_{Leu}),6.47 (1H, d, $^3J_{H,H}$ = 7.6 Hz, NH_{Phe}), 4.84–4.67 (1H, m, $C_{\alpha,Phe}H$), 4.12–3.90 (1H, m, $C_{\alpha,Leu}H$), 3.63 (3H, s, CO_2CH_3), 3.19–3.00 (2H, m, $C_{\beta,Phe}H$), 2.17–1.93 (1H, m, $C_{\gamma,Leu}H$), 1.60–1.47 (2H, m, $C_{\beta,Leu}H$), 1.41 (9H, s, NH-$CO_2(CH_3)_3$), 0.89 (6H, dd, $^3J_{H,H}$ = 6.1 Hz, $^4J_{H,H}$ = 2.4 Hz, $C_{\delta,Leu}H$). – $C_{21}H_{32}N_2O_5$ calc. C, 64.26; H, 8.22; N, 7.14; found C, 63.43; H, 8.46; N, 6.76.

1.2.2. **2**

To a solution of **1** (3.6 g, 9.18 mmol) in CH_2Cl_2 (30 mL) was added TFA (20 mL) at 0 °C. The solution was stirred for 1 h. The solvent was removed under reduced pressure and the residue was taken up in diethylether and stirred for 30 min to yield a white precipitate which was then dried in vaccuo (2.98 g, 80%). ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 7.34 (1H, d, $^3J_{H,H}$ = 7.2 Hz, NH_{Leu}), 7.29–7.00 (6H, m, $C_{Ar,Phe}H$, NH_{Phe}), 4.78–4.62 (1H, m, $C_{\alpha,Phe}H$), 4.10–3.95 (1H, m, $C_{\alpha,Leu}H$), 3.69 (3H, s, CO_2CH_3), 3.07 (2H, d, $^3J_{H,H}$ = 6.7 Hz, $C_{\beta,Phe}H$), 1.72–1.46 (3H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$), 0.94–0.76 (6H, m, $C_{\delta,Leu}H$). – MS (ESI^+): 293.15 $[M\text{-}TFA]^+$. – $C_{18}H_{25}F_3N_2O_5$ calc. C, 53.20; H, 6.20; N, 6.89; found C, 53.02; H, 6.50; N, 6.72.

1.2.3. **3**

To a stirred solution of Boc-thiazolylalanine (0.2 g, 0.74 mmol) in THF (10 mL) was added *N*-methylmorpholine (83 μL, 0.74 mmol) followed by the addition of isobutyl chloroformiate (98 μL, 0.74 mmol), resulting in a precipitation of a white solid. In a second flask leucine hydrochloride (134 mg, 0.74 mmol) was dissolved in THF (10 mL), containing triethylamine (102 μL, 0.74 mmol). Both suspensions were mixed and stirred for 1 h at r.t.. After removal of the precipitation by filtration, the solvent was removed under reduced pressure and the residual oil was dissolved in $CHCl_3$ (50 mL). The solution was washed with water (50 mL) and the aqueous solution was back-extracted with $CHCl_3$ (3 × 50 mL). The combined organic solutions were dried over Na_2SO_4. Evaporation of the solved and lyophilisation from a mixture of acetonitrile/water yielded **3** as a yellow-white powder (228 mg, 77%). ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 8.69 (1H, d, $^3J_{H,H}$ = 2.0 Hz, N=C*H*-S), 7.04 (1H, d, $^3J_{H,H}$ = 2.0 Hz, C=C*H*-S), 6.69 (1H, br.s, NH_{Leu}) 6.12 (d, $^3J_{H,H}$ = 6.5 Hz, NH_{Thia}), 4.51–4.31 (2H, m, $C_{\alpha,Leu}H$, $C_{\alpha,Thia}H$), 3.59 (3H, s, CO_2CH_3), 3.21 (2H, dq, $^3J_{H,H}$ = 5.7 Hz, $^2J_{H,H}$ = 14.7 Hz, $C_{\beta,Thia}H$), 1.45–1.34 (3H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$), 1.36 (9H, s, Boc), 0.75 (6H, dd, $^3J_{H,H}$ = 6.3 Hz, $^4J_{H,H}$ = 2.4 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 173.0 (CO_{Thia}), 171.1 (CO_2CH_3), 155.6 ($C_{q,Thia}$), 153.1 (CO_{Boc}), 153.0 (N=*C*H-S), 115.5 (N-C=*C*H-S), 80.1 ($C_{q,Boc}$), 54.2 ($C_{\alpha,Thia}$), 52.2 (CO_2CH_3), 50.6 ($C_{\alpha,Leu}$), 41.4 ($C_{\beta,Leu}$), 33.2 ($C_{\beta,Thia}$), 28.3 (C_{Boc}), 24.5, 23.0 ($C_{\delta,Leu}$), 21.8 ($C_{\gamma,Leu}$). – MS (ESI^+): 400.17 $[M + H]^+$,

422.18 $[M + Na]^+$. – $C_{18}H_{29}N3O_5S$ calc. C, 54.12; H; 7.32, N; 10.52, S; 8.03; found C, 51.61, H, 7.25; N, 10.02; S, 7.2.

1.2.4. ***4***

To a stirred solution of Boc-thiazolylalanine (0.2 g, 0.74 mmol) in THF (10 mL) was added *N*-methylmorpholine (83 μL, 0.74 mmol) followed by the addition of isobutyl chloroformiate (98 μL, 0.74 mmol), resulting in a precipitation of a white solid. In a second flask **2** (0.3 g, 0.74 mmol) was dissolved in THF (10 mL), containing triethylamine (102 μL, 0.74 mmol). Both suspensions were mixed and stirred for 1 h at r.t.. After removal of the precipitation by filtration, the solvent was removed under reduced pressure and the residual oil was dissolved in $CHCl_3$ (50 mL). The solution was washed with water (50 mL) and the aqueous solution was back-extracted with $CHCl_3$ (3 × 50 mL). The combined organic solutions were dried over Na_2SO_4. Evaporation of the solved and recrystallization from THF/hexane at 4 °C yielded **4** as a yellow-white powder (245 mg, 61%). ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 8.72 (1H, d, $^3J_{H,H}$ = 1.9 Hz, N=C*H*-S), 7.32–6.99 (8H, m, $C_{Ar,Phe}H$, N$H_{Phe,}$ NH_{Leu}, C=C*H*-S), 6.16 (d, $^3J_{H,H}$ = 7.4 Hz, NH_{Thia}), 4.80 (1H, dd, $^3J_{H,H}$ = 6.5 Hz, 14.0 Hz, $C_{\alpha,Phe}H$), 4.63–4.39 (2H, m, $C_{\alpha,Leu}H$, $C_{\alpha,Thia}H$), 3.68 (3H, s, CO_2CH_3), 3.40–3.18 (2H, d, m, $C_{\beta,Thia}H$), 3.15–2.99 (2H, m, $C_{\beta,Phe}H$),1.64–1.43 (3H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$), 1.43 (9H, s, Boc), 0.82 (6H, dd, $^3J_{H,H}$ = 6.2 Hz, $^2J_{H,H}$ = 9.3 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 171.9 (CO_{Thia}), 171.6 (CO_2CH_3), 171.2 (CO_{Leu}), 155.6 ($C_{q,Thia}$), 153.2 (CO_{Boc}), 152.8 (N=CH-S), 136.1 ($C_{q,Ar,Phe}$), 129.3 ($C_{Ar,Phe}$), 128.6 ($C_{Ar,Phe}$), 127.1 ($C_{Ar,Phe}$), 125.5 (N-C=CH-S), 80.1 ($C_{q,Boc}$), 54.3 ($C_{\alpha,Thia}$), 53.5 ($C_{\alpha,Phe}$), 52.3 (CO_2CH_3), 51.6 ($C_{\alpha,Leu}$), 40.8 ($C_{\beta,Leu}$), 37.7 ($C_{\beta,Phe}$), 33.2 ($C_{\beta,Thia}$), 28.3 (C_{Boc}), 24.5, 23.0 ($C_{\delta,Leu}$), 21.8 ($C_{\gamma,Leu}$). – MS (ESI^+): 547.28 $[M + H]^+$, 569.29 $[M + Na]^+$. – $C_{27}H_{38}N_4O_6S$ calc. C, 59.32; H, 7.01; N, 10.25; S, 5.87; found C, 57.6; H, 7.14; N, 9.7; S, 5.44.

1.2.5. ***5***

To a screw-top Schlenk tube was given **3** (228 mg, 0.57 mmol), dissolved in dry acetonitrile (2 mL) and excess ethylbromide (4 mL). The tube was sealed and the mixture was stirred for 60 h at 90 °C and was then directly loaded to a flash chromatography column (SiO_2, EtOAc/pentane 1:1 → ethylbromide, CH_2Cl_2/MeOH 9:1 → educt and product (R_f (CH_2Cl_2/MeOH, 9:1) = 0.10). **5** was received as an oil which was lyophilised from acetonitrile/water to yield a yellow-white solid (97 mg, 33%). ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 10.61 (1H, d, $^3J_{H,H}$ = 2.3 Hz, N=C*H*-S), 8.84 (1H, d, $^3J_{H,H}$ = 6.6 Hz, NH_{Leu}), 8.16 (1H, d, $^3J_{H,H}$ = 2.3 Hz, C=C*H*-S) 5.91 (d, $^3J_{H,H}$ = 6.7 Hz, NH_{Thia}), 4.90–4.72 (3H, m, $C_{\alpha,Leu}H$, N-CH_2-CH_3), 4.48–4.28 ($C_{\alpha,Thia}H$), 3.68 (3H, s, CO_2CH_3), 3.39–3.25 (2H, m, $C_{\beta,Thia}H$), 1.83–1.45 (6 H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$, N-CH_2-CH_3), 1.35 (9H, s, Boc), 0.75 (6H, pseudo-tr, $^3J_{H,H}$ = 5.9 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 173.6 (CO_{Thia}), 170.1 (CO_2CH_3), 159.0 ($C_{q,Thia}$), 155.3 (CO_{Boc}), 145.7 (N=CH-S), 124.2 (C=CH-S), 80.4 ($C_{q,Boc}$), 52.4 ($C_{\alpha,Thia}$), 51.9 (N-CH_2-CH_3), 50.7 (CO_2CH_3), 49.5 ($C_{\alpha,Leu}$), 39.8 ($C_{\beta,Leu}$), 31.2 ($C_{\beta,Thia}$), 28.5 (C_{Boc}), 25.0, 22.9 ($C_{\delta,Leu}$), 21.5 ($C_{\gamma,Leu}$), 15.8 (N-CH_2-CH_3). – MS (ESI^+): 428.21 $[M - Br]^+$. – $C_{20}H_{34}BrN_3O_5S$ calc. C, 47.24; H, 6.74; N, 8.26; S, 6.31; found C, 45.99; H, 6.55; N, 7.94; S, 6.07.

1.2.6. ***6***

To a screw-top Schlenk tube was given **4** (245 mg, 0.45 mmol), dissolved in dry acetonitrile (2 mL) and excess ethylbromide (4 mL). The tube was sealed and the mixture was stirred for 60 h at 90 °C and was then directly loaded to a flash chromatography column (SiO_2, EtOAc/pentane 1:1 → ethylbromide, CH_2Cl_2/MeOH 9:1 → educt and product (R_f (CH_2Cl_2/MeOH, 9:1) = 0.13). **6** was received as an oil which was lyophilised from acetonitrile/water to yield a yellow-white solid (95 mg, 31%). ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 10.20 (1H, d, $^3J_{H,H}$ = 2.5 Hz, N=C*H*-S), 8.66 (1H, d, $^3J_{H,H}$ = 7.7 Hz, NH_{Phe}), 8.00 (1H, d, $^3J_{H,H}$ = 2.5 Hz, C=C*H*-S) 7.77 (1H, $^3J_{H,H}$ = 7.7 Hz, NH_{Leu}), 7.31–7.09 (5H, m, $H_{Ar,Phe}$), 6.14 (d, $^3J_{H,H}$ = 7.7 Hz, NH_{Thia}), 4.85–4.64 (4H, m, $C_{\alpha,Phe}H$, $C_{\alpha,Leu}H$, N-CH_2-CH_3), 4.37–4.26 (1H, m, $C_{\alpha,Thia}H$), 3.39 (3H, s, CO_2CH_3), 3.34–3.26 (2H, m, $C_{\beta,Phe}H$), 3.12 (2H, d, $^3J_{H,H}$ = 7.2 Hz, $C_{\beta,Thia}H$), 1.60 (3H, t, $^3J_{H,H}$ = 7.2 Hz, N-CH_2-CH_3), 1.49–1.34 (3H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$), 1.30 (9H, s, Boc), 0.78 (6H, dd, $^3J_{H,H}$ = 5.7 Hz, $^2J_{H,H}$ = 16.3 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 173.1 (CO_{Thia}), 172.8 (CO_2CH_3), 170.0 (CO_{Leu}), 157.8 ($C_{q,Thia}$), 155.5 (CO_{Boc}), 146.1 (N=CH-S), 136.8 ($C_{q,Ar,Phe}$), 129.6 ($C_{Ar,Phe}$), 128.6 ($C_{Ar,Phe}$), 127.0 ($C_{Ar,Phe}$), 124.4 (N-C=CH-S), 80.3 ($C_{q,Boc}$), 54.1($C_{\alpha,Thia}$, N-CH_2-CH_3), 52.4 ($C_{\alpha,Phe}$), 50.6 (CO_2CH_3), 49.5 ($C_{\alpha,Leu}$), 40.8 ($C_{\beta,Leu}$), 37.6 ($C_{\beta,Phe}$), 31.0 ($C_{\beta,Thia}$), 28.4(C_{Boc}), 24.8 22.7 ($C_{\delta,Leu}$), 22.0 $C_{\gamma,Leu}$), 15.7 (N-CH_2-CH_3). – (ESI^+): 575.29 $[M - Br]^+$. – $C_{29}H_{43}BrN_4O_6S$ calc. C, 53.12; H, 6.61; N, 8.5; S, 4.89; found C, 50.21; H, 6.74; N, 7.83; S, 4.56.

1.2.7. ***7***

To a dried Schlenk tube charged with molecular sieves (4 Å, 50 mg) were added **5** (97 mg, 0.19 mmol) and Ag_2O (22 mg, 0.10 mmol). The mixture was flushed three times with N_2 and then dry CH_2Cl_2 was added (15 mL). The flask was closed and shaken overnight in the dark. $[Ru(p\text{-cymene})Cl_2]_2$ (59 mg, 0.10 mmol) was added and the reaction was allowed to shake for another 24 h. The solution was filtered through celite and the solvent was removed under reduced pressure. The orange residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) and was then recrystallized from CH_2Cl_2/pentane (10 mL/30 mL) at −20 °C to yield **7** as an orange powder (40 mg, 28%). ^{1}H NMR (acetonitrile-d_3, 250 MHz, 25 °C) δ = 7.38 (1H, s, C=C*H*-S), 6.00 (1H, d, $^3J_{H,H}$ = 8.1 Hz, NH_{Leu}), 5.66–5.45 (1H, m, NH_{Thia}), 5.42 (2H, dd, *AA′XX′*, *N* = 8.0 Hz, 6.0 Hz, $H_{Ar,p-cymene}$), 5.23 (2H, dd, *AA′XX′*, *N* = 13.1 Hz, 5.9 Hz, $H_{Ar,p-cymene}$), 4.83–4.64 (2H, m, $C_{\alpha,Leu}H$, N-CH_2-CH_3), 4.50–4.31 (2H, m, $C_{\alpha,Thia}H$, N-CH_2-CH_3), 3.66 (3H, s, CO_2CH_3), 3.51–3.30 (1H, m, $C_{\beta,Thia}H$), 3.26–3.06 (1H, m, $C_{\beta,Thia}H$), 2.82–2.63 (1H, m, C$H(CH_3)_2$-$Ar_{p-cymene}$), 1.98 (3H, s, $H_{Methyl,p-cymene}$), 1.76–1.46 (6H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$, N-CH_2-CH_3), 1.39 (9H, s, Boc), 1.21 (6H, dd, $^3J_{H,H}$ = 6.9 Hz, $^2J_{H,H}$ = 2.7 Hz, (CH(CH_3)$_2$-$Ar_{p-cymene}$), 0.92 (6H, dd, $^3J_{H,H}$ = 8.0 Hz, $^2J_{H,H}$ = 6.4 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR (acetonitrile-d_3, 63 MHz, 25 °C): δ = 174.2 (CO_{Thia}), 171.9 (CO_2CH_3), 171.9 (NCS), 156.8 ($C_{q,Thia}$), 147.2 (CO_{Boc}), 124.3 (C=CH-S), 107.6, 101.5 ($C_{q,Ar,p-cymene}$), 87.9, 87.5, 86.7, 85.7 ($C_{Ar,p-cymene}$), 80.8 ($C_{q,Boc}$), 54.7 ($C_{\alpha,Thia}$), 53.2 (N-CH_2-CH_3), 52.2 (CO_2CH_3), 50.8 ($C_{\alpha,Leu}$), 41.4 ($C_{\beta,Leu}$), 31.8 ($C_{\beta,Thia}$), 28.7 (C_{Boc}), 25.5 ($C_{Methyl,p-cymene}$), 22.8, 22.0 ($C_{\delta,Leu}$), 21.8 ($C_{\gamma,Leu}$), 18.9, 18.7 (CH(CH_3)$_2$-$Ar_{p-cymene}$), 17.1 (CH(CH_3)$_2$-$Ar_{p-cymene}$), 15.8 (N-CH_2-CH_3). – MS (ESI^+): 698.14 $[M - Cl]^+$.– $C_{30}H_{47}Cl_2N_3O_5RuS$ calc. C, 49.11; H, 6.46; N, 5.73; S, 4.37; found C, 46.43; H, 5.84; N, 5.65; S, 3.90.

1.2.8. ***8***

To a dried Schlenk tube charged with molecular sieves (4 Å, 50 mg) were added **6** (95 mg, 0.14 mmol) and Ag_2O (17 mg, 0.07 mmol). The mixture was flushed three times with N_2 and then dry CH_2Cl_2 was added (15 mL). The flask was closed and shaken overnight in the dark. $[Ru(p\text{-cymene})Cl_2]_2$ (44.4 mg, 0.07 mmol) was added and the reaction was allowed to shake for another 24 h. The solution was filtered through celite and the solvent was removed under reduced pressure. The orange residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) and was then recrystallized from CH_2Cl_2/pentane (10 mL/30 mL) at −20 °C to yield **8** as an orange powder (30 mg, 24%). ^{1}H NMR (acetonitrile-d_3, 250 MHz, 25 °C) δ = 7.53 (1H, s, C=C*H*-S), 7.43 (1H, d, $^3J_{H,H}$ = 7.1 Hz, NH_{Leu}), 7.41–7.16 (6H, m, $H_{Ar,Phe}$, NH_{Phe}), 5.96–5.87 (1H, m, NH_{Thia}), 5.42 (2H, pseudo-tr, AA'XX', *N* = 6.5 Hz, $H_{Ar,p-cymene}$), 5.23 (2H, dd, AA'XX', *N* = 11.7 Hz, 6.0 Hz, $H_{Ar,p-cymene}$), 4.86–4.53 (4H, m, $C_{\alpha,Leu}H$, $C_{\alpha,Phe}H$, N-CH_2-CH_3), 4.34–4.24 (1H, m, $C_{\alpha,Thia}H$), 3.64 (3H, s, CO_2CH_3), 3.24–2.94 (4H, m, $C_{\beta,Thia}H$, $C_{\beta,Phe}H$), 2.83–2.61 (1H, m, CH (CH_3)$_2$-$Ar_{p-cymene}$), 1.98 (3H, s, $H_{Methyl,p-cymene}$), 1.76–1.40 (6H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$, N-CH_2-CH_3), 1.39 (9H, s, Boc), 1.26–1.19 (6H, m, CH (CH_3)$_2$-$Ar_{p-cymene}$), 0.88 (6H, dd, $^3J_{H,H}$ = 6.4 Hz, $^2J_{H,H}$ = 10.8 Hz,

$C_{\delta,Leu}H$). – ^{13}C NMR (acetonitrile-d$_3$, 63 MHz, 25 °C): δ = 173.6 (CO_{Thia}), 173.3 (CO_2CH_3), 171.9 (CO_{Leu}), 171.7 (NCS), 156.9 ($C_{q,Thia}$), 148.4 (CO_{Boc}), 138.7 ($C_{q,Ar,Phe}$), 130.7 ($C_{Ar,Phe}$), 129.7 ($C_{Ar,Phe}$), 128.0 ($C_{Ar,Phe}$), 124.2 (C=CH-S), 107.6, 101.5 ($C_{q,Ar,p-cymene}$), 90.0, 87.8, 87.3, 85.9 ($C_{Ar,p-cymene}$), 80.9 ($C_{q,Boc}$), 55.2 ($C_{\alpha,Thia}$), 55.0 (N-CH_2-CH_3), 53.4 (CO_2CH_3), 53.2 ($C_{\alpha,Phe}$), 50.9 ($C_{\alpha,Leu}$), 42.2 ($C_{\beta,Leu}$), 38.4 ($C_{\beta,Phe}$), 32.2 ($C_{\beta,Thia}$), 28.9 (C_{Boc}), 25.7 ($C_{Methyl,p-cymene}$), 23.6, 22.8 ($C_{\delta,Leu}$), 22.3 ($C_{\gamma,Leu}$), 18.9, 18.7 ($CH(CH_3)_2$-$Ar_{p-cymene}$), 18.2 ($CH(CH_3)_2$-$Ar_{p-cymene}$), 17.8 (N-CH_2-CH_3). – MS (ESI$^+$): 845.17 [M – Cl]$^+$. – $C_{39}H_{56}Cl_2N_4O_6RuS$ calc. C, 53.17; H, 6.41; N, 6.36; S, 3.64; found C, 50.33; H, 5.94; N, 6.33; S, 3.25.

1.2.9. **9**

To a dried Schlenk tube charged with molecular sieves (4 Å, 50 mg) were added **5** (62 mg, 0.12 mmol) and Ag_2O (14 mg, 0.06 mmol). The mixture was flushed three times with N_2 and then dry CH_2Cl_2 was added (15 mL). The flask was closed and shaken overnight in the dark. $[RhCp^*Cl_2]_2$ (37.2 mg, 0.06 mmol) was added and the reaction was allowed to shake for another 24 h. The solution was filtered through celite and the solvent was removed under reduced pressure. The orange residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) and was then recrystallized from CH_2Cl_2/pentane (10 mL/30 mL) at −20 °C to yield **9** as an orange powder (25 mg, 28%). ^{1}H NMR (DMSO-d$_6$, 400 MHz, 25 °C) δ = 8.36 (1H, d, $^3J_{H,H}$ = 7.9 Hz, NH_{Leu}), 7.63 (1H, s, C=CH-S), 4.6–4.57 (1H, m, $C_{\alpha,Leu}H$), 7.20 (d, $^3J_{H,H}$ = 8.7 Hz, NH_{Thia}), 4.52–4.43 (2H, $C_{\alpha,Leu}H$, N-CH_2-CH_3), 4.40–4.28 (1H, m, N-CH_2-CH_3, $C_{\alpha,Thia}H$), 3.61 (3H, s, CO_2CH_3), 3.17–2.99 (2H, m, $C_{\beta,Thia}H$), 1.71–1.44 (21, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$, N-CH_2-CH_3, Cp(CH_3)$_5$), 1.35 (9H, s, Boc), 0.88 (6H, dd, $^3J_{H,H}$ = 6.4 Hz, $^2J_{H,H}$ = 20.7 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR (DMSO-d$_6$, 100 MHz) : δ = 172.7 (CO_{Thia}), 171.0 (CO_2CH_3), 170.7 (NCS), 155.2 ($C_{q,Thia}$), 147.7 (CO_{Boc}), 124.2 (C=CH-S), 96.3 (“d”, $J_{Rh,H}$ = 6.8 Hz, C_{q,Cp^*}), 78.3 ($C_{q,Boc}$), 52.8 ($C_{\alpha,Thia}$), 51.9 (CO_2CH_3), 51.8 (N-CH_2-CH_3), 50.2 ($C_{\alpha,Leu}$), omitted by solvent ($C_{\beta,Leu}$), 29.8 ($C_{\beta,Thia}$), 28.0 (C_{Boc}), 24.1 ($C_{\gamma,Leu}$), 22.7, 21.1 ($C_{\delta,Leu}$), 17.0 (N-CH_2-CH_3), 8.3 ($C_{Cp,Me}$). – MS (ESI$^+$): 700.21 [M – Cl]$^+$, 744.0, 746.10 [M-Et-H+K]$^+$. – $C_{30}H_{48}Cl_2N_3O_5RhS$ calc. C, 48.92; H, 6.57; N, 5.70; S, 4.35; found C, 46.3; H, 6.53; N, 5.63; S, 4.66.

1.2.10. **10**

To a dried Schlenk tube charged with molecular sieves (4 Å, 50 mg) were added **6** (83 mg, 0.13 mmol) and Ag_2O (15 mg, 0.06 mmol). The mixture was flushed three times with N_2 and then dry CH_2Cl_2 was added (15 mL). The flask was closed and shaken overnight in the dark. $[RhCp^*Cl_2]_2$ (38.7 mg, 0.06 mmol) was added and the reaction was allowed to shake for another 24 h. The solution was filtered through celite and the solvent was removed under reduced pressure. The orange residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) and was then recrystallized from CH_2Cl_2/pentane (10 mL/30 mL) at −20 °C to yield **10** as an orange powder (30 mg, 27%). ^{1}H NMR (DMSO-d$_6$, 400 MHz, 25 °C) δ = 8.40 (1H, d, $^3J_{H,H}$ = 7.6 Hz, NH_{Leu}), 7.94 (d, $^3J_{H,H}$ = 8.4 Hz, NH_{Phe}), 7.58 (1H, s, C=CH-S), 7.28–7.16 (6H, m, $H_{Ar,Phe}$, NH_{Thia}), 4.6–4.57 (1H, m, $C_{\alpha,Leu}H$),4.52–4.43 (3H, m, $C_{\alpha,Phe}H$, N-CH_2-CH_3), 4.40–4.28 (1H, m, $C_{\alpha,Thia}H$), 3.58 (3H, s, CO_2CH_3), 3.13–2.88 (4H, m, $C_{\beta,Thia}H$, $C_{\beta,Phe}H$), 1.76–1.42 (21H, m, $C_{\beta,Leu}H$, $C_{\gamma,Leu}H$, N-CH_2-CH_3, Cp(CH_3)$_5$), 1.34 (9H, s, Boc), 0.86 (6H, dd, $^3J_{H,H}$ = 6.5 Hz, $^2J_{H,H}$ = 14.0 Hz, $C_{\delta,Leu}H$). – ^{13}C NMR (DMSO-d$_6$, 100 MHz, 25 °C): δ = 171.9 (CO_{Thia}), 171.8 (CO_2CH_3), 171.7 (CO_{Leu}), 170.0 (NCS), 155.4 ($C_{q,Thia}$), 146.5 (CO_{Boc}), 137.0 ($C_{q,Ar,Phe}$), 129.0 ($C_{Ar,Phe}$), 128.1 ($C_{Ar,Phe}$), 126.5 (C=CH-S), 96.8, 96.5, 96.3 (“td”, $J_{Rh,H}$ = 6.4 Hz, C_{q,Cp^*}), 78.4 ($C_{q,Boc}$), 53.5 ($C_{\alpha,Thia}$), 51.8 (CO_2CH_3, NCH_3), 53.2 ($C_{\alpha,Phe}$), 50.8 ($C_{\alpha,Leu}$), 41.2 ($C_{\beta,Leu}$), 36.5 ($C_{\beta,Phe}$), 29.7 ($C_{\beta,Thia}$), 28.0 (C_{Boc}), 23.9 ($C_{\gamma,Leu}$), 22.9, 21.6 ($C_{\delta,Leu}$), 17.0 (N-CH_2-CH_3), 8.5 (“t”, $J_{Rh,C}$ = 22.6 Hz, $C_{Cp,Me}$). – MS (ESI$^+$): 847.29 [M – Cl]$^+$, 891.20, 893.17 [M-Et-H+K]$^+$. – $C_{39}H_{57}Cl_2N_4O_6RhS$ calc. C, 53.00; H, 6.50; N, 6.34; S, 3.63; found C, 53.64; H, 7.31; N, 7.31; S, 3.97.

Acknowledgments

We thank the Ruhr-University Research School and the German Science Foundation DFG (FOR 630) for funding.

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