Unsymmetric Peptide Trichalcogenides –SSS–/–SSSe– Bond Formation by Rhodium-catalyzed Exchange Reaction

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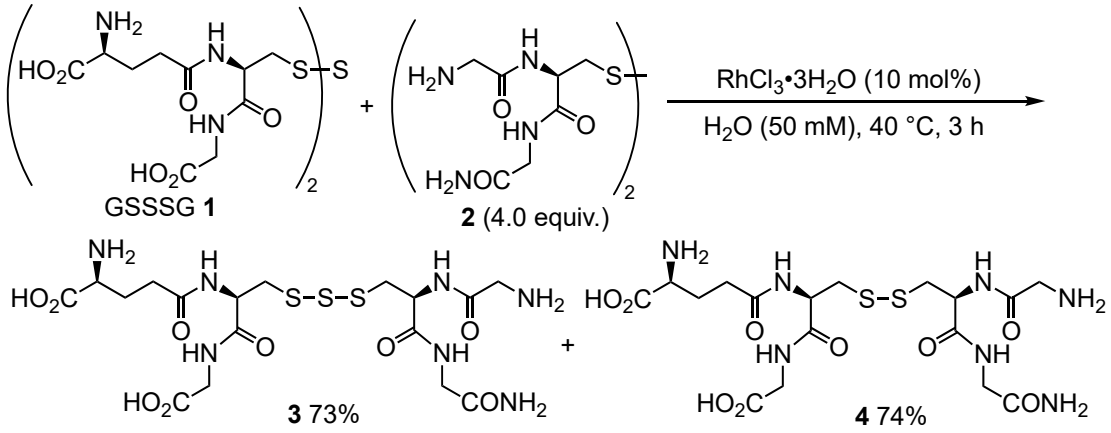
Peptide polysulfides, which have various functions such as strong antioxidant and signal transduction activity, have recently attracting considerable interest. Previously, we reported rhodium-catalyzed synthesis of peptide polysulfides by insertion of sulfur into unprotected peptide disulfides.[1] Rhodium-catalyzed synthesis of unsymmetric trichalcogenides containing –S–S–S–/–S–S–Se– bonds using exchange reaction between peptide trisulfide and disulfides/diselenides was found.

Glutathione trisulfide (GSSSG) **1** (0.1 mmol) was reacted with a disulfide derivative of Gly-Cys-Gly **2**[2] (4.0 equiv.) in the presence of $RhCl_3 \cdot 3H_2O$ (10 mol%) in water (50 mM) at 40 °C for 3 h. Then, unsymmetric trisulfide **3** (0.073 mmol, 73%) and the disulfide **4** (0.074 mmol, 74%) were obtained with the recovery of **1** (0.024 mmol, 24%) and **2** (0.32 mmol, 80%). **3** and **4** were isolated by reverse-phase HPLC, and structures were determined by NMR, IR, Raman, and MS. By using diselenide derivatives instead of disulfide **2**, unsymmetric trichalcogenide compounds with an –S–S–Se– bond can be obtained. Selenium is larger in size, more polarizable, and more nucleophilic than sulfur. These peptide trichalcogenide compounds containing selenium are expected to have a higher bioaffinity with biomacromolecules and exhibit slightly different and interesting biological activities. The reaction smoothly proceeded in wide ranges of pH (1–8) using various unprotected peptides, and formed new unsymmetric trichalcogenide compounds containing –S–S–S–/–S–S–Se– bonds.



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2) Arisawa, M.; Fukumoto, K.; Yamaguchi, M. *ACS Catal.*, **2020**, *10*, 15060.