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Communications

Unexpected Rearrangement of Dihydro-1,4-thiazine

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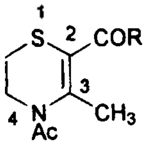
Dihydro-1,4-thiazine, an analogue of carboxin[1] used as an agrochemical fungicide, has an α,β-unsaturation to the carboxanilide group as well as sulfur and nitrogen atoms in a 1,4-thiazine skeleton. In our previous paper,[2] we reported the syntheses of 4-acetyl-5,6-dihydro-1,4-thiazine **1** and the isomeric 4-acetyl-5,6-dihydro-1,4-thiazine **2**, either by chlorinolysis of 1,3-thiazolidine or by an acid catalyzed ring expansion of 1,3-thiazolidine sulfoxides. We report herein, an unexpected rearrangement of dihydro-1,4-thiazine **3** by autoxidation involving molecular oxygen in aqueous media.



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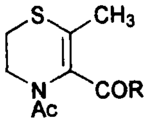

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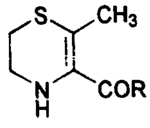

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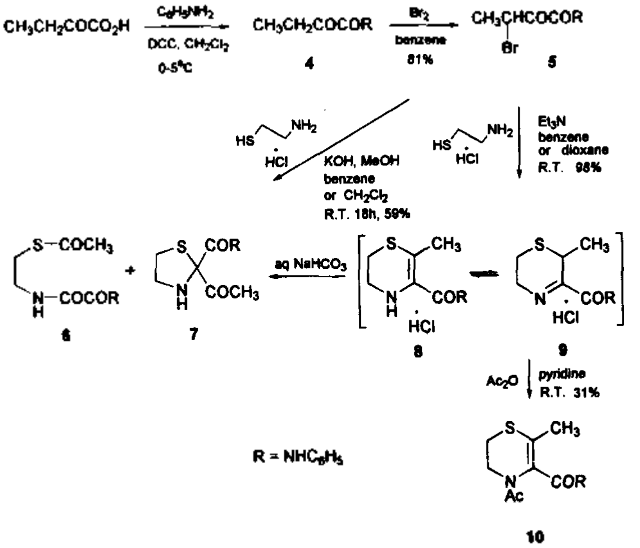
The starting α-keto anilide **4** was prepared through the previously reported methods.[3] Bromination of **4** in benzene at 60 °C gave the desired 2-bromide **5** (81%), the structure of which was confirmed by ^{1}H NMR.[4] Condensation of **5** with 2-aminoethanethiol hydrochloride in the presence of excess triethylamine (2 molar equivalents) in benzene or dioxane solution at room temperature gave white amorphous precipitates (98%). This solid was insoluble in deuterated chloroform and decomposed to a complex mixture in both dimethylsulfoxide-d_6 and deuterium oxide. This salt also slowly decomposed to a complex mixture at room temperature both in the neat state or in organic solvents. Treatment of this solid with acetic anhydride in the presence of pyridine at room temperature gave a 3-acetyl-5,6-dihydro-1,4-thiazine **10** as the major product (31%), which indicated **8** as the intermediate. Potentiometric analysis supported this solid as being a hydrochloric acid salt rather than that of hydrobromic acid.[5] We concluded that this unstable intermediate is a hydrochloric acid salt of dihydro-1,4-thiazine **8** which would be in equilibrium with imine **9**.

When aqueous saturated sodium bicarbonate solution was added to isolate the free amine, instead of the desired dihydro-1,4-thiazine **3**, we obtained an unexpected mixture of acetylthio **6** (60%) and 1,3-thiazolidine **7** (8%), as es-

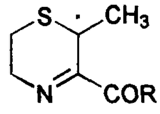


Scheme 1.

tablished by the various spectral data, and elemental analyses.[6] Similar results (whole mixture yield: 59%) were obtained with the 2-bromide **5** and 2-aminoethanethiol hydrochloride in the presence of potassium hydroxide in methanol at room temperature.

Surprisingly, a suspension of dihydro-1,4-thiazine hydrochloride **8** in methylene chloride was stable at room temperature in a nitrogen atmosphere for a few hours in the presence of water while the above mixture when subjected to air or oxygen afforded a mixture of acetylthio **6** and 1,3-thiazolidine **7** under the same conditions. Similar evidence was found in various aqueous solutions. As a result, we concluded that oxygen was involved in the rearrangement of dihydro-1,4-thiazine hydrochloride **8** in the presence of water.

Concerning the reaction mechanism, a free radical such as **11** could be considered as the reactive intermediate which is prone to autoxidation.[7] The stability of such a hybrid radical would arise from odd-electron delocalization into α/d-orbitals of sulfur as well as the possibility of an electron releasing effect, characteristic of the sulfur atom. Independent syntheses of **6** and **7** as well as mechanistic study related to the mechanism are in progress.



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2. (a) Lee, W. S.; Hahn, H.-G.; Mah, H. D. *J. Korean Chem. Soc.* **1989**, *33*, 247. (b) Lee, W. S.; Nam, K. D.; Hahn, H.-G. *J. Heterocyclic Chem.* **1993**, *30*, 1105.
3. Hahn, H.-G.; Chang, K. H.; Mah, H. D.; Lee, J. Y. *J. Korean Chem. Soc.* **1994**, *38*, 174.
4. mp 106-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (d, 3H, *J*=7.0 Hz, CH_3), 5.59 (q, 1H, *J*=7.0 Hz, CHBr), 7.18-7.68 (m, 5H, ArH), 8.71 (br. s, 1H, NH); ms: m/z 256 (M^+).
5. Martin, A. J. *Anal. Chem.* **1958**, *30*, 233.
6. For **6**: mp 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H, $COCH_3$), 3.10 (t, 2H, *J*=9.6 Hz, SCH_2), 3.56-3.59 (m, 2H, NCH_2), 7.31-7.67 (m, 5H ArH), 8.15 (br. s, 1H, NH), 9.48 (br. s, 1H, NHC_6H_5); ^{13}C NMR (78.5 MHz, $CDCl_3$) δ 29.09, 31.15, 40.30, 120.68, 125.99, 129.80, 137.17, 157.99, 159.66, 161.03; Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.13, H, 5.26, N, 10.53, S, 12.03. Found: C, 53.9, H, 5.25, N, 10.3.
   For **7**: mp 141.5-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 2H, 2-$COCH_3$), 2.73 (br. s, 1H, 3-NH), 3.00-3.10 (m, 2H, 5-CH_2), 3.74-3.80 (m, 2H, 4-CH_2), 7.09-7.61 (m, 5H, ArH), 9.50 (br. s, 1H, NHPh); ^{13}C NMR (78.5 MHz, $CDCl_3$) δ 26.06, 37.41, 53.77, 86.55, 119.60, 124.78, 129.08, 137.24, 167.20 167.20, 200.23; Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.57, H, 5.64, N, 11.19, S, 12.81, Found: C, 57.86, H, 5.47, N, 11.27.
7. Similar autoxidations of benzothiazines and cyclic pyrindene were reported. See Carelli, V.; Moracci, M. M.; Liberatore, F.; Cardellini, M.; Lucarelli, M. G.; Marchini, P.; Liso, G.; Reho, A. *Int. J. Sulfur Chem.* **1973**, *3*, 267. and Cohen, L. A.; Witkop, B. *J. Am. Chem. Soc.* **1955**, *77*, 6595.

Immobilization of Laccase onto the Gold Electrode Using β-Mercaptopropionate

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Immobilization of enzymes onto the electrode surfaces is very important in developing biosensors and enzyme reactors for industrial applications.[1] The immobilization is essential to reuse expensive enzymes and to facilitate the separation of reaction products without sacrificing the enzyme. In this communication, we report the immobilization of *Rhus vernicifera* laccase from Chinese lacquer tree onto the β-mercaptopropionate coated gold electrode. There have been several reports dealing with the immobilization of fungal laccases, and their uses for some catalytic reactions.[2] They were immobilized onto the graphite electrode by adsorption or in polymer films such as gelatin or polyurethane. Our effort in this paper is the first example of the immobilization of tree laccase onto the gold electrode using a self-assembly technique.[3]

Laccase (*p*-diphenol : O_2 oxidoreductase, EC 1.10.3.2) is a copper containing oxidase which is widely distributed in higher plants and fungi.[4] It belongs to multicopper oxidases

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