Pergamon

Tetrahedron Letters 41 (2000) 3381–3384

TETRAHEDRON LETTERS

Novel synthesis of 2-thiazolines

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Received 10 February 2000; accepted 10 March 2000

Abstract

The synthesis of a series of 2-thiazolines was carried out under mild conditions from the corresponding thiazolidines, by a Ru-catalyzed/TBHP oxidation reaction conditions. The reaction was chemoselective towards the amine-imine oxidation and was also regioselective, affording the unsaturation at the 2-position of the heterocycle, even with thiazolidine substrates bearing ester groups at the 4-position. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: thiazolines; thiazolidines; oxidation; ruthenium-catalyzed; TBHP.

Thiazolines constitute a family of compounds known for their application in flavor chemistry.[1] More than 30 thiazoline structures have been up to now identified from natural sources,[2] in particular in cooked meat,[1] and in certain exotic fruits such as litchis.[3] The biosynthesis of thiazolines (in fruits and vegetables) seems to involve the enzymatic oxidation of thiazolidine intermediates, formed from the coupling reaction of cysteine or cysteamine with aldehydes.[4] Thiazolines have also been studied for their pharmacological properties. Thus, some thiazoline derivatives present interesting anti-HIV[5] or anti-cancer[6,7] activities and can inhibit cell division.[8]

The chemical preparation of 2-thiazolines is generally carried out by the condensation of 2-aminothiols such as cysteine (or a cysteine derivative) with either a nitrile,[9] a carboxylic acid[10] or an ester.[11] 2-Thiazolines can also be obtained from the dehydration of β-hydroxythioamides under the Mitsunobu conditions[12,13] or with the Burgess reagent.[14] A multistep synthesis from oxazolidines or oxazolines has also been reported.[15] However, these reactions generally require drastic reaction conditions, such as the use of triisobutyl aluminum.

We present here our results concerning a new strategy, parallel to the biosynthetic route, in which thiazolidines are catalytically and selectively oxidized to 2-thiazolines.

Thiazolidines, **1**, are easily obtained in 60–90% yields by the condensation of a 2-aminothiol (or its ammonium salt) and an aldehyde derivative under slightly basic conditions.[16,17] The use of (L)-cysteine esters afforded **1f**–**h** as a mixture of (2*R*,4*R*) and (2*S*,4*R*) diastereomers. 2D-NOESY NMR experiments indicated the preferential formation of the *cis* isomer in *cis/trans* ratios of about 65/35. Epimerization

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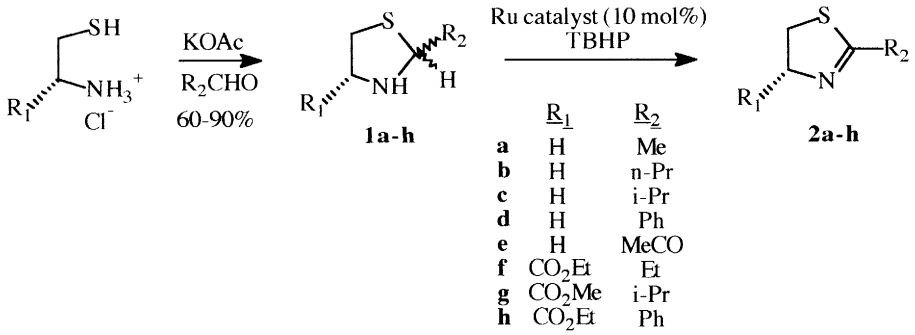
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00419-6

of thiazolidines with ring opening involving C-2 has been reported.[18] Under strong acidic or basic conditions, or at high temperature, 1,3-thiazolidines undergo epimerization followed by decomposition.[19]

The selectivity in the oxidation of thiazolidines has not been thoroughly studied. These substrates present several sites of reactivity: a nitrogen-centered oxidation can afford either *N*-oxides or 2- or 3-thiazolines, and further oxidation to thiazoles. Oxidation can also occur at sulfur, to afford sulfoxide or sulfone derivatives.

In particular, for the desired oxidation of thiazolidines to 2-thiazolines, the related oxidations of amines to imines include the use of oxidants such as the di-*t*-butyliminoxyl radical,[20] the bis(trifluoroacetate) of diphenylselenium[21] and iodosyl benzene[22] or *t*-butylhydroperoxide[23] in the presence of a ruthenium catalyst. However, these methods have only been applied to simple and acyclic amines, generally benzylic (to afford the conjugated imines or nitriles) and without other oxidable functional groups present.

We examined the Ru-catalyzed oxidation of thiazolidines (Scheme 1) under different reaction conditions, and the main results are presented in Table 1.



Scheme 1.

In a typical experiment the $RuCl_2(PPh_3)_3$-catalyzed (10 mol%) oxidation of 2-isopropyl-1,3-thiazolidine, **1c**, in the presence of 1 equiv. of TBHP in CH_2Cl_2 at room temperature, afforded a 67% isolated yield of 2-isopropyl 2-thiazoline, **2c** (after column purification), in a selective reaction, with a conversion of 90% (entry 1). No reaction occurred under the same conditions in the absence of the Ru catalyst. The selectivity of **2c** among the other possible oxidation compounds was of 98%.

This Ru-catalyzed procedure was applied to the oxidation of several substrates **1** with isolated yields of 2-thiazolines in the range of 36 to 86%. The formation of *N*-oxide, sulfoxide or sulfone was not observed, and the isomeric 3-thiazoline was obtained in only 1–4% yield.

Several ligands on $RuCl_2$ or $RuCl_3$ complexes were tested; phosphine ligands such as PPh_3 and amine ligands such as TMEDA or cyclam (1,4,8,11-tetraazacyclotetradecane). The comparison between the catalytic activities of the three systems was evaluated in the oxidations of **1c** and **1f** (entries 1, 3–6). Ru/PPh_3 and Ru/TMEDA systems were more active and afforded better yields of **2** than the Ru/cyclam system.

The influence of several factors was examined. The use of toluene instead of CH_2Cl_2 led to emulsion problems upon isolation (entry 2). However, good results were obtained in acetonitrile (entries 3, 5, 6 10, 12). The use of two equiv. of TBHP led to further decomposition of the thiazoline with $RuCl_2(PPh_3)_2$, and to an increase of the corresponding thiazole with the use of $RuCl_3$/TMEDA or $RuCl_3$/cyclam. No reaction occurred when using molecular oxygen or PHIO as the oxidants.

The oxidation to 2-thiazolines was very selective. It afforded better yields and selectivities in the case of 4-unsubstituted thiazolidines, **1a**–**e** (95–100%) as compared to the 4-substituted analogs, **1f**–**h** (80–96%).

Table 1
Ru-catalyzed oxidation of thiazolidines, **1**, to 2-thiazolines, **2**, by TBHP[a]

Entry	Starting **1**	Catalyst [b]	Reaction conditions	Conversion of **1** (%)	% Isolated yield of **2**[c] (%)	Reaction selectivity[d] (%)
1	**1c**	**A**	CH_2Cl_2, rt, 4 h	90	67	98
2	"	"	toluene, rt, 4 h	70	36	97
3	"	**B**	MeCN, 45 °C, 7 h	90	61	96
4	**1f**	**A**	CH_2Cl_2, rt, 6 h	55	45	96
5	"	**B**	MeCN, 45 °C, 7 h	75	67	82
6	"	**C**	"	40	48	92
7	**1a**	**A**	CH_2Cl_2, rt, 4 h	100	40	100
8	**1b**	"	"	70	86	95
9	**1d**	"	"	100	55	90
10	**1e**	**B**	MeCN, rt, 4 h	100	70	98
11	**1g**	**A**	CH_2Cl_2, rt, 6 h	50	64	97
12	"	**C**	MeCN, 45 °C, 7 h	40	45	92
13	**1h**	**A**	CH_2Cl_2, rt, 4 h	94	53	80

a) General oxidation procedure: Product **1** (4 mmol) was stirred in the corresponding solvent (8 ml) in the presence of the Ru catalyst (0.4 mmol). TBHP (1 equiv.) in 10 ml solvent was slowly added into the solution and the reaction was followed by GC. The crude mixture was filtered over alumina with CH_2Cl_2 and washed with an aqueous Na_2SO_4, and aqueous KI. Solvent evaporation was followed by purification by column chromatography with silica gel, with cyclohexane-ethyl acetate (8:2) mixture as the eluent. The purified compounds **2a-h** were analyzed by ^1H and ^{13}C-NMR and mass spectrometry, and their spectra compared to those of authentic samples.
b) Catalyst A: $RuCl_2(PPh_3)_2$. Catalyst B: $RuCl_3$/TMEDA (1/3). Catalyst C: $RuCl_3$/cyclam (1:1.5).
c) Yields of **2** were calculated as a function of the converted **1**.
d) The % selectivity refers to the GC ratio of 2-thiazoline, **2** with respect to sum of all the other possible oxidation compounds: 3-thiazoline, thiazole, N-oxide, sulfoxide and sulfone at the end of the reaction.

Among the 2-thiazolines prepared, some of them such as **2e** and **2a** constitute interesting compounds from the point of view of their flavor and perfume properties. Thus, 2-acetyl-2-thiazoline, **2e**, presents some popcorn aroma properties,[24,25] and **2a** the flavor of cooked beef.[5]

In conclusion, the selective synthesis of 2-thiazolines has been achieved via the easy preparation of thiazolidines followed by their mild Ru/PPh_3 or Ru/TMEDA-catalyzed oxidation with TBHP. This new access to 2-thiazolines is parallel to the biosynthetic way for these compounds in plants.

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