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# Chemo- and regioselective synthesis of alkyl-3-thiazoline carboxylates

Xavier Fernandez, Roland Fellous, Louisette Lizzani-Cuvelier, Michel Loiseau and Elisabet Duñach*

*Laboratoire Arômes, Synthèse et Interactions, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice Cedex 2, France*

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**Abstract**—The synthesis of a series of allyl substituted 3-thiazoline-carboxylates was carried out from the corresponding thiazolidines, by a $MnO_2$-mediated oxidation reaction under mild conditions. The reaction was chemoselective towards the amine–imine oxidation and was also regioselective, affording the unsaturation at the 3-position of the heterocycle. © 2001 Published by Elsevier Science Ltd.

Thiazolines constitute a large family of heterocyclic compounds of which certain volatile derivatives are known for their applications in flavor and food chemistry.[1] More than 30 thiazoline structures have been up to now identified from natural sources and in food,[2] in particular in cooked meat[1,3] and in certain exotic fruits such as litchies.[4] 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, issued from the Strecker degradation of amino acids.[5] Their formation in processed foods involves interactions of α-dicarbonyl compounds, aldehydes, ammonia and hydrogen sulfide (Maillard reaction).[6] Thiazolines have also been studied for their pharmacological properties. Thus, some thiazoline derivatives present interesting anti-HIV[7] or anti-cancer[8] activities and can inhibit cell division.[9]

The chemical preparation of 3-thiazolines has generally been carried out through the reaction of an α-mercaptoketone, an aldehyde and ammonia at high temperature.[10] However, nonselective mixtures are generally obtained and this method does not allow the preparation of 3-thiazolines substituted by an ester group at position 4. Thiazolidines substituted in this way have been identified in exotic fruits such as guava and cupuaçu.[11]

We present here our results concerning a novel strategy for the synthesis of 4-ester substituted thiazolines, parallel to the biosynthetic route, in which thiazolidines are selectively oxidized to 3-thiazolines.

Thiazolidines, **1** were easily obtained in yields of 80–90% from the condensation of (*L*)-cysteine ethyl or methyl esters (or their ammonium salts) and an aldehyde derivative under slightly basic conditions.[12,13] The condensation afforded **1** 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 (2*R*,4*R*) in *cis*/*trans* ratios of 70/30 to 60/40 for the different derivatives **1a**–**g** in $CDCl_3$ at 20°C. This ratio corresponds to the equilibrium in solution; epimerization of thiazolidines with ring opening involving C-2 has been reported.[14]

The selectivity in the oxidation of thiazolidines has not been thoroughly studied. These substrates can undergo a nitrogen-centered oxidation to 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. We have recently proposed a selective synthesis of 2-thiazolines by a Ru-catalyzed/TBHP oxidation reaction under mild conditions.[15] In the case of the ester derivatives **1a**–**g**, the Ru/TBHP oxidation led to 2-thiazolines with good selectivities (>95%).

In order to obtain 3-thiazolines regioselectively other dehydrogenating agents such as manganese dioxide were tested. Various literature reports refer to the application of active manganese dioxide in dehydrogenation of nitrogen heterocycles.[16] This reagent has been suc-

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* Corresponding author. Fax: 33(0) 492076121; e-mail: dunach@unice.fr

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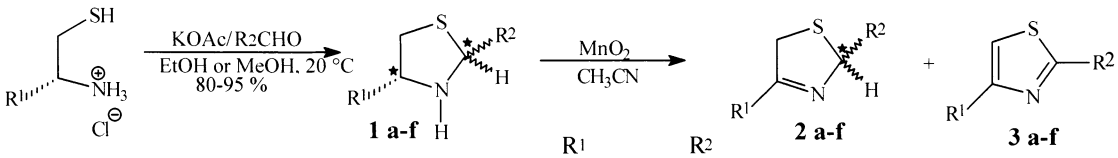
cessfully applied, for example, for the conversion of 2,3-dihydroindole into indole,[17] of indolines,[18] imidazolines[19] and pyrazolines[19] into the corresponding indoles, imidazoles and pyrazoles, respectively. However, in all these examples, the completely aromatized heterocyclic rings were obtained. In the particular case of thiazolidines, **1**, their oxidation by $MnO_2$ has been described to afford only thiazoles **3**[20,21] without any mention to 2- or 3-thiazoline formation.

In our aim to better control the partial oxidation reaction of 1,3-thiazolidines for the synthesis of 3-thiazolines, **2**, we examined the $MnO_2$-mediated oxidation of substrates **1a–g** under different reaction conditions (Scheme 1), and the main results are presented in Table 1.

In a typical experiment, the oxidation of methyl 2-isopropyl-thiazolidine-4(*R*)-carboxylate, **1a**, in the presence of excess $MnO_2$ (17 equiv.) in $CH_3CN$ at 50°C, afforded, after column purification, 64% isolated yield of methyl 2-isopropyl-3-thiazoline-4-carboxylate, **2a** (Table 1, entry 5). The conversion of **1a** was 100% and thiazole **3a** was formed as a by-product in 20% isolated yield. In all cases, the column separation between the oxidation products **2** and **3** was easy.

The influence of several factors was examined. Acetonitrile seemed to be the best solvent. Reactions could also be run in refluxing dichloromethane, but the oxidation led to lower yields of **2**. The use of 2 equiv. of $MnO_2$ led to a conversion of only 9% of **1a**. Good conversions were obtained with the use of 13 or more equivalents of $MnO_2$ (entries 1–4). Under these conditions, reaction times of 3–20 h were the most adequate for an optimal 3-thiazoline formation. Under the same conditions but longer reaction times, thiazoles **3** could be obtained with good yields (70–80%) and good selectivities (entries 13 and 14).

We could observe that the $MnO_2$ source had an important influence on the selectivity. Several $MnO_2$ qualities were tested. Precipitated $MnO_2$ hydrate (Prolabo) and $MnO_2$ suitable for use in batteries (Aldrich) gave the best results. $MnO_2$ obtained by a modified Attenburrow procedure[17] afforded lower yields of **2**, and the use of




| | R1 | R2 |
|---|---|---|
| **a** | COOMe | *i*-Pr |
| **b** | COOEt | Et |
| **c** | COOMe | *n*-Pr |
| **d** | COOEt | *n*-Bu |
| **e** | COOMe | Me |
| **f** | COOMe | *n*-Bu |
| **g** | COOEt | *n*-Pr |

**Scheme 1.**

**Table 1.** Oxidation of thiazolidines, **1**, to 3-thiazolines, **2**, by $MnO_2$[a]

| Entry | Starting | Equiv. $MnO_2$ | Reaction conditions | Ratio **1**:**2**:**3**[b] (%) | Isolated[c] yield of **2** (%) |
|---|---|---|---|---|---|
| 1 | **1a** | 2 | 50°C, 40 h | 82:9:0 | – |
| 2 | **1a** | 13 | 20°C, 20 h | 43:46:0 | 38 |
| 3 | **1a** | 20 | 60°C, 7 h | 0:58:41 | 50 |
| 4 | **1a** | 17 | 60°C, 5 h | 0:60:34 | 55 |
| 5 | **1a** | 17 | 50°C, 5 h | 0:72:27 | 64 |
| 6 | **1b** | 17 | 60°C, 3 h | 17:72:11 | 68 |
| 7 | **1b** | 12 | 55°C, 4 h | 29:65:5 | 55 |
| 8 | **1c** | 13 | 50°C, 8 h | 37:62:0 | 55 |
| 9 | **1d** | 20 | 50°C, 6 h | 0:70:28 | 60 |
| 10 | **1e** | 20 | 50°C, 6 h | 0:68:30 | 58 |
| 11 | **1f** | 20 | 50°C, 6 h | 0:68:30 | 60 |
| 12 | **1g** | 20 | 50°C, 7 h | 0:64:31 | 60 |
| 13 | **1a** | 20 | 60°C, 2 days | 0:0:90 | – |
| 14 | **1f** | 20 | 60°C, 2 days | 0:0:91 | – |

[a] General oxidation procedure: Product **1** (5 mmol) was stirred in $CH_3CN$ (50 ml) in the presence of $MnO_2$ (Prolabo, 2–20 equiv.). The reaction was followed by GC or TLC. The crude mixture was filtered over Celite. Solvent evaporation was followed by purification by column chromatography on silica gel, with hexane–ether (8:2) mixture as the eluent. The purified compounds were analyzed by $^1H$ and $^{13}C$ NMR and mass spectrometry and high resolution mass spectrometry.

[b] Ratio determined by GC.

[c] ee's Measured by $^1H$ NMR ($CDCl_3$, 20°C) in the presence of 10% $Eu(tfc)_3$[22]: **2a**: 14%, **2c**: 71%, **2e**: 74%, **2g**: 83%.

$MnO_2$ powder (Accros) led to very low oxidation efficiencies.

This procedure was applied to the oxidation of several substrates **1a**–**g** with isolated yields of 3-thiazolines in the range 38–68%. These series of compounds, **2a**–**g**, possessing an ester substituent at the 4-position have, to our knowledge, not yet been described. The enantiomeric excesses of compounds **2a**, **2c**, **2e** and **2g** have been measured to be in the range 14–83% (see footnote c, Table 1).

The formation of *N*-oxides, sulfoxides or sulfones was not observed, and the isomeric 2-thiazolines were obtained in only 1–3% yield.

The $MnO_2$-mediated oxidation was well adapted to the presence of the ester group at the 4 position. Thus, the $MnO_2$-mediated oxidation of thiazolidines with $R_1 = H$, obtained by the condensation of 2-mercaptoethylamine (cysteamine) with aldehydes, led to low yields and low selectivities: mixtures of 2- and 3-thiazolines (as determined by GC/MS) were obtained in less than 10% yield and important decomposition occurred.

In conclusion, we presented a new and practical synthesis of methyl or ethyl 3-thiazoline-4-carboxylates by an $MnO_2$-mediated oxidation of the corresponding thiazolidines. This oxidation leads to 3-thiazolines and thiazoles, and a careful kinetic control enables to obtain the desired 3-thiazolines in moderate to good yields. The enantioselectivity of this oxidation reaction is under current study.

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