A new multicomponent reaction: unexpected formation of derivatizable cyclic α-alkoxy isothioureas†

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An unexpected formation of cyclic α-alkoxy isothioureas has been achieved. As is known, the heterocyclic imines 2,5-dihydro-1,3-thiazoles are convertible to bisamides with the aid of a carboxylic acid and an isocyanide (Ugi reaction). Herein, it is shown that 2,5-dihydro-1,3-thiazole S-monoxides—the respective α-sulfinyl imines—are characterized by an altered reaction behavior. In a hitherto unknown multicomponent reaction the α-sulfinyl imines react with an isocyanide under acidic conditions in an alcoholic solution to the respective α-alkoxy isothioureas in good yields. In addition to the investigations on this unexpected synthesis the regioselectivity of the acylation of the synthesized compounds is described. A rearrangement, which is accelerated by EDC and HOBt, between both possible regioisomers was found.

Introduction

For more than 60 years the 2,5-dihydro-1,3-thiazole (3-thiazoline) scaffold has been an important industrial key element in the course of the preparation of pharmaceutically active molecules.1 Furthermore, other remarkable investigations on this family of heterocycles characterize fields of research in general.2 The synthesis of 3-thiazolines was first reported by F. Asinger in 1956.3 Following a modified protocol of the Asinger reaction the cyclic imines are preparable by a four-component reaction (A 4-CR) where an α-chloro aldehyde is reacted with a carbonyl compound, ammonia, and sodium hydrosulfide.4

3-Thiazolines could be converted into a large number of different products by functionalizing their reactive C=N double bond.5

One of the most important reactions involving imines is the Ugi three-component reaction (U 3-CR). In the U 3-CR an imine is treated with an isocyanide and a carboxylic acid to form the desired bisamide.6 As our earlier research had shown, 3-thiazolines are unproblematically employable as the imine component in the U 3-CR.7

In one of our recent studies, we had additionally investigated the chemoselective oxidation of 3-thiazolines.8 An oxidation of the sulfur atom leading to 3-thiazoline S-monoxides represents one possible and realizable reaction pathway of the oxidation of these substrates.

In order to examine the reaction behaviour of these new 3-thiazoline S-monoxides, we then tried to convert these compounds to the respective bisamides with the aid of the U 3-CR (Fig. 1). However, as presented in this paper, we observed that under the reaction conditions mentioned above, the 3-thiazoline S-monoxides react contrary to our expectations to cyclic isothioureas. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea. The products are characterized by an alkoxy moiety next to the endocyclic nitrogen atom of the isothiourea.
Results and discussion

Synthesis of the precursors

First, we synthesized four known 3-thiazolines \( \text{via} \) the A 4-CR. Treatment of the respective \( \alpha \)-chloro aldehyde with sodium hydrosulfide, an aqueous ammonia solution and acetone or cyclohexanone led to the cyclic imines 2,2,5,5-tetramethyl-2,5-dihydro-1,3-thiazole (1a)\(^5\), 5,5-diethyl-2,2-dimethyl-2,5-dihydro-1,3-thiazole (1b)\(^7\), 2,2-dimethyl-1-thia-3-azaspiro[4.5]-dec-3-ene (1c)\(^1\),\(^\text{10} \) and 2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-ene (1d)\(^5\).

The oxidation of 3-thiazolines 1 to sulfoxides 2 was described by us recently.\(^8\) In line with this, all four 3-thiazolines 1a-d were converted to the respective sulfoxides 2a-d with the aid of \textit{mCPBA} (Fig. 3).

Unexpected preparation of the cyclic isothioureas

On the basis of our earlier work,\(^7\) we wanted to examine the influence of the sulfoxide moiety on the reactivity of the cyclic imine by converting the 3-thiazoline \( \text{S}-\text{monoxides} \) 2 to bisamides. To validate the applicability of unoxidized 3-thiazolines 1 in the U 3-CR, we reacted the 3-thiazoline 1a with 1-chloro-4-isocyanobenzene and benzoic acid in MeOH. The bisamide 3 was found to be the most efficient acid to convert the 3-thiazoline \( S \)-monoxide 2a to bisamide with the aid of \textit{mCPBA} (Fig. 3).

Reaction scope

Next, we investigated the generality of this unexpected synthesis of cyclic \( \alpha \)-alkoxy isothioureas 4 by varying all three substrates (Table 2). First, the applicability of different isocyanides was studied. It was found that aryl, benzyl and alkyl isocyanides could be used for the conversion of 3-thiazolines 2. Substituents including aryl chlorides (Table 2, entries 1 and 10) and esters (Table 2, entries 5, 6, 9, and 13–15) were tolerated. Furthermore, it was determined that different alcohols, upon
the condition that they can be used as a solvent, are employ-
able reactants (Table 2, entries 7 and 8).

Besides model substrate 2a, three further 3-thiazoline
S-monoxides 2 were examined (Table 2, entries 9–16). It turned
out that compound 2e bearing a spiro-coupled cyclohexane
ring at the carbon C5 gave the highest yield (up to 87%;
Table 2, entry 13). Entry 16 proves that not only 3-thiazoline
S-monoxides 2a-c characterized by two methyl groups located at
the acetal carbon, but also 3-thiazoline S-monoxide 2d exhib-
ing a spiro-coupled cyclohexane ring at that carbon atom is an
appropriate substrate. When the substrate 2d is used, cyclohexa-
one instead of acetone is the co-product.

It would therefore appear that the unexpectedly observed
formation of the cyclic isothiourea 4a can be transferred to a
broad range of differently substituted substrates. Additionally,
the obtained products are suitable for further derivatizations.

Acylation of the synthesized isothioureas

They can be converted to N-acyl isothioureas by treating them
with the respective acid and EDC12 [1-ethyl-3-(3-dimethylami-
nopropyl)carbodiimide] as an activating agent in CH2Cl2. Follow-
ing this route, both possible regioisomers—products 5
acylated at the exocyclic nitrogen atom and products 6 acylated
at the endocyclic nitrogen atom—can be observed. Conversion
of isothiourea 4j bearing an aromatic substituent at the exo-
cyclic nitrogen atom with phenylacetic acid resulted in an excess
of product 5a, which is derivatized at the exocyclic nitrogen
atom (Table 3, entry 1), (5a : 6a 75 : 25) in the crude product.

Changing the solvent from CH2Cl2 to DMF or the reaction
temperature from room temperature to −20 °C did not have
any influence on the ratio between both regioisomers in the
crude product.

After isolation by column chromatography, the ratio was
shifted to 5a : 6a 27 : 73. To explain this shift of the ratio
between 5a and 6a during the isolation, we postulated that a
rearrangement of product 5, once formed by an exocyclic acyla-
tion, to 6 is possible. The existence of this rearrangement was
proven by a control experiment. Isolated 5a was kept in CDCl3
solution at room temperature without convection. As deter-
mined by 1H NMR analysis, the rearrangement to 6a was fully
completed after 24 d (Fig. S1, ESI†). In a repetition of this
experiment using additional EDC the rearrangement was
already completed after 9 d (Fig. S2, ESI†). Thus, the rearran-
gement between both regioisomers is accelerated by EDC.

### Table 1 Influence of the acid on the formation of the cyclic isothiourea 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BzOH (1.0 equiv.)</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>BzOH (0.5 equiv.)</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>BzOH (1.2 equiv.)</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>AcOH (1.0 equiv.)</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>TFA (1.0 equiv.)</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>H2SO4 (1.0 equiv.)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Reaction conditions: 2a (0.8 mmol), 1-chloro-4-isocyanobenzene (0.8 mmol), acid, in MeOH (5 mL), 72 h at r.t. *Isolated yield after chromatography on silica gel.
By using hydroxybenzotriazole (HOBt), which is mainly used as the additional activating agent to suppress the racemization of chiral substrates during peptide syntheses, in addition to EDC, we improved the outcome of the acylation reaction. Moreover, the use of HOBt in the conversion of 4\(j\) with phenylacetic acid led to the formation of only one regioisomer (6\(a\)) after 2 h (Table 3, entry 2). In line with this, the rearrangement of isolated 5\(a\) in CDCl\(_3\) under the addition of EDC and HOBt took less than 20 min (Fig. S3, ESI†). This clarifies that the rearrangement between both regioisomers is accelerated more strongly by a combination of EDC and HOBt than by the mere use of EDC. Entries 3 and 4 of Table 3 verify the regiospecific acylation of cyclic isothioureas 4 bearing an aromatic substrate at the exocyclic nitrogen atom within the reaction time, when HOBt is added to the reaction mixture.

A conversion of the isothiourea 4\(i\) characterized by an aliphatic substituent at the exocyclic nitrogen atom led mainly to product 6\(d\) (5\(d\) : 6\(d\) 40 : 60 in crude product; Table 3, entry 5; coupling agent: exclusive EDC). The rearrangement of 5\(d\) is very slow. Monitoring the rearrangement of isolated 5\(d\) in CDCl\(_3\) at room temperature without the influence of EDC and HOBt we ascertained that only half the amount of substrate 5\(d\) was rearranged to 6\(d\) after 115 d (Fig. S4, ESI†). In the conversion of 4\(l\), the addition of HOBt only had an influence on the overall yield (raised from 63% to 85%; Table 3, entry 6) and not on the product ratio. These observations were confirmed by the conversion of substrate 4\(n\), which is also characterized by an aliphatic substituent at the exocyclic nitrogen atom, with Fmoc-N\(\text{̃}\)-phenylglycine (Table 3, entries 7 and 8).

When a substrate is converted which bears an aromatic substituent at the exocyclic nitrogen atom the acylation at this exocyclic nitrogen atom is kinetically more preferred than the acylation at the endocyclic nitrogen atom. This is probably due to the mesomeric stabilization of the cationic intermediate stage. On the other hand, the thermodynamic stability of the product which is characterized by an exocyclic double bond and an acyl moiety at the endocyclic nitrogen atom in comparison to the regioisomer is enhanced by the aromatic substituent, because an exocyclic double bond results in a conjugated \(\pi\)-system. This results in the observed selectivities and speeds of rearrangements.

### Table 2 Substrate scope for the synthesis of cyclic isothioureas 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(R^4)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>4-Cl-Ph</td>
<td>Me</td>
<td>4a: 74</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>4b: 66</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>Bn</td>
<td>Me</td>
<td>4c: 69</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>Allyl</td>
<td>Me</td>
<td>4d: 55</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>CH(_2)COOMe</td>
<td>Me</td>
<td>4e: 73</td>
</tr>
<tr>
<td>6</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>(CH(_2))(_2)COOEt</td>
<td>Me</td>
<td>4f: 55</td>
</tr>
<tr>
<td>7</td>
<td>2a</td>
<td>Me</td>
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<td>4-Cl-Ph</td>
<td>Et</td>
<td>4g: 61</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>Me</td>
<td>Me</td>
<td>Allyl</td>
<td>Allyl</td>
<td>4h: 77</td>
</tr>
<tr>
<td>9</td>
<td>2b</td>
<td>Et</td>
<td>Et</td>
<td>CH(_2)COOMe</td>
<td>Me</td>
<td>4i: 63</td>
</tr>
<tr>
<td>10</td>
<td>2c</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
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<td>11</td>
<td>2c</td>
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<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>4k: 73</td>
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<tr>
<td>12</td>
<td>2c</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
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<td>4l: 71</td>
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<tr>
<td>13</td>
<td>2c</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>4m: 87</td>
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<td>14</td>
<td>2c</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
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<td>4n: 64</td>
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<td>15</td>
<td>2c</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
<td>-((CH(_2))(_2)\text{(-)}}</td>
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<td>16</td>
<td>2d</td>
<td>Me</td>
<td>Me</td>
<td>4-Cl-Ph</td>
<td>Et</td>
<td>4g: 34</td>
</tr>
</tbody>
</table>

\(\text{Reaction conditions: 2 (1.0 equiv.), carboxylic acid (1.0 equiv.), BzOH (1.0 equiv.), in R^4OH (6 mL per mmol 2), 72 h at r.t.}{\text{\textsuperscript{a}}}\text{\ isolated yield after chromatography on silica gel.}}\)
Conclusions

In summary, 3-thiazoline S-monoxides, which are easily preparable by an Asinger 4 CR and a subsequent oxidation, were converted to cyclic α-alkoxy isothioureas. The investigated conversion of the substrates with isocyanides and alcohols under acidic conditions opens unexpected access to the novel class of cyclic α-alkoxy isothioureas in good yields. This procedure may be useful for a general conversion of S,N-acetals to the corresponding N-acyl isothioureas.

The derivatization of the synthesized cyclic isothioureas by an acylation leads to two different regioisomeric products. The kinetic product, which is acylated at the exocyclic nitrogen atom, rearranges to the thermodynamic more stable second regioisomer, which is acylated at the endocyclic nitrogen atom. The selectivity and the speed of the rearrangement depend tremendously on the type of the substituent. EDC and HOBT were found to accelerate the rearrangement of N-acyl isothioureas.

Experimental

Synthesis of (RS)-2-(4-chlorophenylimino)-4-methoxy-5,5-dimethyl-1,3-thiazolidine (4a) as a representative example for the synthesis of all cyclic isothioureas

The sulfoxide 2a (717 mg, 4.50 mmol) was dissolved in 9 mL methanol. 1-Chloro-4-isocyanobenzene (619 mg, 4.50 mmol), dissolved in 9 mL methanol, and benzoic acid (550 mg, 4.50 mmol), dissolved in 9 mL methanol, were added dropwise. The reaction mixture was vigorously stirred for 72 h at r.t. The solvent was removed on a rotary evaporator. Purification of the crude product by column chromatography on silica gel (EtOAc, Rf = 0.63) afforded 4a (902 mg, 74%) as a colorless solid, mp 115–117 °C (from CH2Cl2–n-hexane); IR (ATR): v 3111, 3051, 2960, 2897, 2827, 1657, 1549, 1484, 1437, 1368, 1244, 1158, 1144, 1063, 843, 824 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ 1.39, 1.49 [6 H, 2s, C(CH3)2], 3.29 (3 H, s, OCH3), 5.50 [2 H, m, 2 0-CHAr(Cl)], 7.22–7.27 [2 H, 2 0-CHAr(Cl)], 7.19 (1 H, s, NCH), 7.43–7.65 [2 H, 2 0-CHAr(Cl)], 22.61, 30.66 (all data). 13C NMR (125.8 MHz, CDCl3): δ 22.61, 30.66 [C(CH3)2], 55.30 (OCH3), 57.04 [2CH2], 95.10 [CH2], 123.48 [2×CH2], 128.88 (CAr), 129.12 [2×CH2], 141.48 [2×CH2], 162.82 (C≡N) ppm; IC-MS (C–N): m/z 271.2 [M + H⁺, 100%]; HRMS (C–N): sector: found 271.0673; calc. for C12H16ClN2OS [M + H]+ 271.0672.

Single crystals of 4a were recrystallized from CH2Cl2 and n-hexane, mounted in inert oil and transferred to the cold gas stream of the diffractometer.

Crystal structure determination of 4a

Crystal data. C12H16ClN2OS, M = 270.77, triclinic, a = 6.1948(3), b = 10.9643(5), c = 11.2530(5) Å, U = 675.19(5) Å³, T = 120 K, space group P1, Z = 2, 6165 reflections measured, 6165 unique (Rint = 0.0000) which were used in all calculations. The final wR2 was 0.1262 (all data).

Acknowledgements

The authors gratefully acknowledge Marc Schmidtmann for X-ray crystallography.

Notes and references


11 The X-ray crystal structure is shown in the ESI.† CCDC 1037548 contains the supplementary crystallographic data.
