A three-component reaction for rapid access to underexplored 1,3-thiazine-2-thiones†

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Driven by the shortage of known effective possibilities for the synthesis of 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones on the one hand and the promising potential of these structures as novel drug candidates on the other hand, synthetic access to 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones was developed. The desired products could be synthesized effectively and facilely starting from β-chlorovinyl aldehydes with the aid of a new MCR (multicomponent reaction). Furthermore, the 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones are shown to be appropriate substrates in the preparation of diverse annulated polycyclic systems.

Fig. 1 Known 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones.7

They were synthesized by the reaction of acetone with dimethylamine hydrochloride and paraformaldehyde in isopropanol. A subsequent treatment of the intermediate with carbon disulfide and an amine led to the formation of the desired 1,3-thiazine-2-thiones. It was shown that both examples are characterized by an inhibitory effect on the proliferation of different tumor cells and therefore are potential antitumor agents.7

In view of the pharmacological potential as well as the lack of efficient synthetic routes and our ongoing interest in developing practical methods for synthetic chemistry, we designed a facile synthesis of 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones 2 under mild reaction conditions.

In consideration of our experience in the use of β-chlorovinyl aldehydes 1 and the known preparation of 4-hydroxythiazolidine-2-thiones, we envisioned that the formation of 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones 2 could be realized by a new MCR, reacting a β-chlorovinyl aldehyde 1 with carbon disulfide and a primary amine (Fig. 2).

Combining a MCR employed to synthesize a relatively complex heterocyclic scaffold with a subsequent posttransformation has been abundantly highlighted as an advantageous method for the synthesis of heterocyclic compounds.8 Thus, we also investigated the conversion of the synthesized...
1,3-thiazine-2-thiones to annulated bicycles by exploiting the variable substituent at the nitrogen atom and the hydroxy group, which is formed during the synthesis of 1,3-thiazine-2-thiones.

Results and discussion

Synthesis of the substrates

Combining our previous published concept of synthesis of 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2\(\text{H}\)-1,3-thiazines\(^3\) and thiazolidinethiones\(^9\) the targeted 3,4-dihydro-2\(\text{H}\)-1,3-thiazine-2-thiones should be obtained in a MCR using \(\beta\)-chlorovinyl aldehydes, primary amines and carbon disulfide. The \(\beta\)-chlorovinyl aldehydes are received by the conversion of \(\alpha\)-methylene ketones with DMF and POCl\(_3\).\(^10\) We were able to synthesize (EZ)-3-chloro-2,3-diphenylacrylaldehyde\(^11\) (1a), (EZ)-3-chloro-3-(4-hydroxyphenyl)-2-phenylacrylaldehyde\(^3\) (1b), (EZ)-3-chloro-3-(4-chlorophenyl)-2-phenylacrylaldehyde\(^12\) (1c), (EZ)-3-chloro-2,3-bis(4-nitrophenyl)acrylaldehyde\(^3\) (1e), 2-chloro-1-cyclohexene-1-carboxaldehyde\(^13\) (1f), and (EZ)-3-chloro-3-methyl-2-phenylacrylaldehyde\(^14\) (1g).

Screening of reaction conditions

We started our investigation with (EZ)-3-chloro-2,3-diphenylacrylaldehyde (1a), allylamine, and carbon disulfide to investigate the optimal conditions for the preparation of 2\(\text{H}\)-1,3-thiazine-2-thione 2a (Table 1). Our previous research revealed the feasibility of using both isomers of the \(\beta\)-chlorovinyl aldehydes in a (EZ)-mixture as the substrate.\(^3\) Thus, we used the (EZ)-mixture of substrate 1 in all synthesis, with the exception of (E)-1d. The stoichiometry of the substrates was chosen as reported recently.\(^3\) As related to our previous studies, H\(_2\)O (in the case of thiazolidinethiones) and MeOH (in the case of 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2\(\text{H}\)-1,3-thiazines) are the solvents of choice. Thus, we tested H\(_2\)O as well as MeOH in combination with different bases—i.e. K\(_2\)CO\(_3\) and Et\(_3\)N—which are necessary to trap the liberated hydrogen chloride.

H\(_2\)O turned out to be an inappropriate solvent, whereas the use of MeOH led to the formation of the targeted 2\(\text{H}\)-1,3-thiazine-2-thione 2a in low yields (Table 1, entries 2 and 3). This may be reasoned by a (extremely) low solubility of 1a in H\(_2\)O and MeOH. For this reason, we screened further different solvents and bases. The highest yield so far was obtained using Et\(_3\)N in MeCN at r.t. (Table 1, entry 14).

Table 1 Optimization of the multicomponent reaction to prepare 2\(\text{H}\)-1,3-thiazine-2-thione\(^a\) 2a

| Entry | Solvent | Base   | Temperature | Reaction time [h] | Yield\(^b\) of 2a [%] |
|-------|---------|--------|-------------|-------------------|----------------------|
| 1     | H\(_2\)O | K\(_2\)CO\(_3\) | r.t.        | 24                | 0                    |
| 2     | MeOH    | K\(_2\)CO\(_3\) | r.t.        | 24                | 25                   |
| 3     | MeOH    | Et\(_3\)N | r.t.        | 24                | 22                   |
| 4     | MeOH/THF| K\(_2\)CO\(_3\) | r.t.        | 24                | 62                   |
| 5     | MeOH/THF| Et\(_3\)N | r.t.        | 24               | 46                   |
| 6     | THF     | K\(_2\)CO\(_3\) | r.t.        | 24                | 37                   |
| 7     | THF     | Et\(_3\)N | r.t.        | 24               | 45                   |
| 8     | DCM     | K\(_2\)CO\(_3\) | r.t.       | 24               | 10                   |
| 9     | DCM     | Pyridine | r.t.        | 24              | 2                   |
| 10    | DCM     | Et\(_3\)N | r.t.        | 24              | 64                   |
| 11    | DMF     | Et\(_3\)N | r.t.        | 24            | 58                   |
| 12    | MeCN    | K\(_2\)CO\(_3\) | r.t.       | 24          | 22                   |
| 13    | MeCN    | Pyridine | r.t.        | 24            | 6                   |
| 14    | MeCN    | Et\(_3\)N | r.t.        | 24            | 67\(^c\)             |
| 15    | MeCN    | Et\(_3\)N | r.t.        | 5             | 46                   |
| 16    | MeCN    | Et\(_3\)N | r.t.        | 15            | 55                   |
| 17    | MeCN    | Et\(_3\)N | r.t.        | 48            | 47                   |
| 18    | MeCN    | Et\(_3\)N | 0 °C         | 15           | 90\(^d\)             |
| 19    | MeCN    | Et\(_3\)N | 0 °C         | 24           | 90                   |

\(^a\) All reactions were performed using 1.00 mmol \(\beta\)-chlorovinyl aldehyde 1a, 1.50 mmol allylamine, 3.00 mmol carbon disulfide, and 0.50 mmol base in 5 mL solvent followed by column chromatography. \(^b\) All yields are isolated yields. \(^c\) The reaction was carried out two times using both 0.50 mmol and 1.00 mmol Et\(_3\)N, which led to identical yields in both cases. \(^d\) After completion of the reaction the solvent was removed by high-vacuum low-temperature distillation.
Next, we investigated the influence of the reaction time. A reaction time of 15 hours led to the highest yield of 2a (55%; Table 1, entry 16). Since an extended reaction time resulted in a lower yield, we had reason to suppose that a part of the already formed product decomposes under the tested conditions. Some NMR spectra suggested the assumption that enaminothiones are the products of decomposition. Thus, we performed the reaction in MeCN with Et₃N again, but this time for 15 hours at 0 °C. In this way, 2H-1,3-thiazine-2-thione 2a was isolated in 90% yield. For this reason the optimal reaction was performed at 0 °C for 15 hours using Et₃N in MeCN (Table 1, entry 18). It is worth mentioning that MeCN is distilled off via high-vacuum low-temperature distillation after the reaction is complete. Removal of the solvent at a rotary evaporator at 40 °C also causes partial decomposition.

The proposed mechanism for the formation of 2H-1,3-thiazine-2-thione 2 is shown in Scheme 1. First, the addition of the primary amine to the carbon disulfide leads to the N-monosubstituted carbamic acid A. The dithiocarbamate B is formed by the substitution of the chloride in the β-chlorovinyl aldehyde 1 with carbamic acid. The hydrogen chloride, which is formed as a co-product, is trapped by triethylamine. A subsequent ring-closure, occurring via a nucleophilic attack of the nitrogen atom of the dithiocarbamate group on the carbonyl group and a migration of a proton results in the formation of the product 2.

### Reaction scope

In order to explore the scope of the reaction under the optimized conditions, a number of β-chlorovinyl aldehydes 1a–g and primary amines were investigated. The results are summarized in Table 2. In almost all cases the performed reactions lead to the desired 2H-1,3-thiazine-2-thiones 2 in moderate to good yields. Referring to our model reaction with allylamine (Table 2, entry 1), we first investigated the influence of different unsaturated amines in the reaction with aldehyde 1a and carbon disulfide.

The products 2d and 2e designed from alkyne derivatives (Table 2, entries 4 and 5) are isolated in lower yields than

### Table 2 Preparation of 2H-1,3-thiazine-2-thiones **a**

| Entry | Aldehyde | Product | R¹ | R² | R³ | Yield[^b] [%] |
|-------|----------|---------|----|----|----|-------------|
| 1     | 1a       | 2a      | H  | H  | CH₂CH=CH₂ | 90          |
| 2     | 1a       | 2b      | H  | H  | CH₃(CH₂)₂=CH₂ | 79          |
| 3     | 1a       | 2c      | H  | H  | (CH₂)₂CH=CH₂ | 64          |
| 4     | 1a       | 2d      | H  | H  | (CH₂)₃C=CH   | 33          |
| 5     | 1a       | 2e      | H  | H  | (CH₂)₃C=CH   | 53          |
| 6     | 1a       | 2f      | H  | H  | (CH₂)₃CH₃   | 48          |
| 7     | 1a       | 2g      | H  | H  | Cy          | 70          |
| 8     | 1a       | 2h      | H  | H  | CH₃Ph       | 90          |
| 9     | 1a       | 2i      | H  | H  | CH₃(4-OMe-C₆H₄) | 53          |
| 10    | 1a       | 2j      | H  | H  | (CH₂)₂(2-Br-C₆H₄) | 89          |
| 11    | 1b       | 2k      | H  | OH | CH₃CH=CH₂ | 43          |
| 12    | 1e       | 2l      | H  | Cl | CH₃CH=CH₂ | 38          |
| 13    | 1d       | 2m      | OCH₃| OCH₃| CH₂CH=CH₂ | 78          |
| 14    | 1e       | 2n      | NO₂| NO₂| CH₃CH=CH₂ | 40          |
| 15    | 1d       | 2o      | OCH₃| OCH₃| CH₃(CH₂)=CH₂ | 67          |
| 16    | 1d       | 2p      | OCH₃| OCH₃| (CH₂)₂CH=CH₂ | 56          |
| 17    | 1d       | 2q      | OCH₃| OCH₃| CH(CH₃)₂ | 60          |
| 18    | 1d       | 2r      | OCH₃| OCH₃| C(CH₃)₃ | —           |
| 19    | 1d       | 2s      | OCH₃| OCH₃| CH₃CH₂OCH₃ | 81          |
| 20    | 1d       | 2t      | OCH₃| OCH₃| CH₃CH₂OPh | 65          |
| 21    | 1d       | 2u      | OCH₃| OCH₃| CH₃Ph     | 65          |
| 22    | 1d       | 2v      | OCH₃| OCH₃| 4-CH₃-C₆H₄ | —[^c]      |
| 23    | 1d       | 2w      | OCH₃| OCH₃| 4-NO₂-C₆H₄ | —           |

[^a]: All reactions were performed using 1.00 eq. β-chlorovinyl aldehyde 1, 1.50 eq. primary amine, 3.00 eq. carbon disulfide, and 0.50 eq. Et₃N in MeCN (5 ml per mmol β-chlorovinyl aldehyde) followed by high-vacuum low-temperature distillation to remove the solvent and column chromatography.

[^b]: All yields are isolated yields.

[^c]: The 2H-1,3-thiazine-2-thione 2v was observed in the NMR of the crude product, but could not be isolated.
those products synthesized from alkene derivatives (Table 2, entries 1–3).

Moreover, alkyl amines bearing a methylene group next to the nitrogen atom such as n-butylamine (Table 2, entry 6) and aliphatic amines with a methine group at this position—i.e. cyclohexyl amine and isopropyl amine (Table 2, entries 7 and 17)—were feasible substrates in the reaction, whereby n-butylamine seemed to react reluctantly. Only amines with a quaternary carbon atom next to the nitrogen atom—e.g. tert-butylamine (Table 2, entry 18)—seem to be not feasible substrates in this new multicomponent reaction. However, using p-toluidine as the substrate in the MCR the corresponding 2H-1,3-thiazine-2-thione 2v was generated. This could be confirmed by the NMR spectra of the crude product (see Fig. S3 in the ESI†). The isolation of 2v was attempted in different ways without success. This could probably be the result of a decomposition based on the instability of the resulting product 2v. In contrast to the conversion of p-toluidine, electron-poor aromatics did not even form the 2H-1,3-thiazine-2-thiones (Table 2, entry 23), with the result that only the educts of the reaction could be isolated.

But if aralkyl amines with a methylene group next to the nitrogen atom are used instead of aromatic amines the developed MCR successfully leads to 2H-1,3-thiazine-2-thiones 2 (Table 2, entries 8–10 and 21).

Noteworthily, amines with aromatics bearing functional groups such as bromine substituents (Table 2, entry 10) or with different kinds of aliphatic and aromatic ethers (Table 2, entries 9, 19 and 20) are also tolerated. The conversions of benzylamine with 1a and carbon disulfide to 2h (Table 2, entry 8) and the product 2a (Table 2, entry 1) of our model reaction, using allylamine, revealed the highest yield (90%).

The structure of 2a was confirmed by X-ray diffraction analysis (see Fig. S1 in the ESI†).16 Besides model substrate 1a, other β-chlorovinyl aldehydes were investigated likewise (Table 2, entries 11–23). Both substrates with electron-donating (Table 2, entries 11–13) and electron-withdrawing (Table 2, entry 14) groups at the para-position provided the desired thiones 2. Thus, the MCR tolerates the usage of aldehydes with different kinds of functional groups such as chlorine substituents, hydroxy, methoxy and nitro groups (Table 2, entries 11–14).

Analogous to our research results on synthesizing 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2H-1,3-thiazines3 the formation of 2H-1,3-thiazine-2-thiones 2 is also limited to 2,3-diaryl-β-chlorovinyl aldehydes 1a–e as substrates. The conversions of 2-chloro-1-cyclohexene-1-carboxaldehyde (1f) and 3-chloro-3-methyl-2-phenylacrylaldehyde (1g) each with allylamine and carbon disulfide did not lead to the corresponding products 2.

However, the presented results (Table 2) documented that the novel MCR allows the preparation of manifold 2H-1,3-thiazine-2-thiones 2 in moderate to excellent yields starting from readily accessible substrates.

In order to screen the reaction scope the applicability of various tryptamine derivatives, containing the pharmaceutically interesting indole, in the developed MCR was also examined (Fig. 3). Surprisingly, a product resulting from a twofold cyclization could be isolated after column chromatography.

At first, the formation of 2H-1,3-thiazine-2-thione occurred followed by an intramolecular electrophilic aromatic substitution (Pictet–Spengler-type reaction) at the heteroaromatic indole cycle and simultaneous substitution of the hydroxy group. The indole annulated 2H-1,3-thiazine-2-thiones 3 were obtained in moderate yields of up to 66% (Fig. 3). When 1-methyltryptamine was used as the substrate the second cyclization via the Pictet–Spengler-type reaction did not take place directly and 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thione 2x with an N-methylated indole could be isolated (Fig. 3). However, the cyclization of 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thione 2x to 2H-1,3-thiazine-2-thiones 3e can be realized by placing the substrate in DCM for 3 days at r.t. The transformation occurs quantitatively.

**Derivatization**

Based on the described results concerning 2H-1,3-thiazine-2-thiones 2 and our ongoing interest in using them as pre-
cursors in subsequent reactions (Scheme 2), we designed derivatives 2c and 2p to examine the conversion in a Lewis-acid mediated ring-closing reaction\textsuperscript{17} to pyridothiazinethiones 4. To the best of our knowledge this kind of ring-closing reaction was performed using InCl\textsubscript{3} for the first time. 2H-1,3-thiazine-2-thiones 2c and 2p were therefore stirred for 15 hours at r.t. in a DCM solution containing equimolar amounts of InCl\textsubscript{3}.

The mixtures of the racemic diastereomers of the targeted pyridothiazinethiones 4 were isolated in moderate yields (Scheme 2, products 4a and 4b).

Treatment of alcohols with catalytic amounts of InCl\textsubscript{3} and allyltrimethylsilane, allyl alcohol or allyl mercaptan, respectively, led to C–C, C–O or C–S bond formation by direct substitution of the hydroxy group.\textsuperscript{18} Using allylamine, which is the analogous nitrogen nucleophile, no C–N bond formation was observed. However, the products starting from allyltrimethylsilane could be obtained in good to excellent yields (Scheme 2, products 5a–d). Also the corresponding sulfur and oxygen containing dialkenes were synthesized in this way (Scheme 2, products 5e and 5f). Noteworthily, all generated products without a hydroxyl group (this extends to compound 3–6) were more stable than the 2H-1,3-thiazine-2-thiones 2. This may be reasoned with the low steadiness of N,O-hemiacetal in 2. Thus, a reaction temperature beyond 0 °C in subsequent reactions is allowed.

Due to their terminal alkene functional groups, compounds 5a–f are ideal substrates for ring-closing metathesis (RCM). Because of the positive outcome of previously reported similar procedures by our group we chose to employ the Ru catalyst A (Fig. 4).\textsuperscript{9}

The RCMs were performed in toluene using 5 mol% of Ru catalyst A to generate the six- and seven-membered annulated bicycles 6 in yields up to 83% (Scheme 2, products 6a–f).

Remarkably, the average yields of unsaturated pyridothiazinethiones 6a–d were higher than those of unsaturated azepinethiazinethiones 6.
nethiazinethiones 6e and 6f. For example, a comparison of the yield of the annulated bicycle 6d (83% yield) with the comparable oxygen containing seven membered bicycle 6f (50% yield) supports this observation. The structure of 6b was established by X-ray diffraction analysis (see Fig. S2 in the SI). Thus, several compounds containing the 2H-1,3-thiazine-2-thione substructures in addition to another biologically active structure could be formed based on the synthesized 2H-1,3-thiazine-2-thiones 2.

The subsequent conversions to annulated bicycles shown in Scheme 2 exemplify the feasibility to create a plethora of 2H-1,3-thiazine-2-thione-containing compounds starting from 2H-1,3-thiazine-2-thiones 2.

Conclusions

In conclusion, we developed a novel multicomponent reaction, which allows efficient and facile access to 4-hydroxy-3,4-dihydro-2H-1,3-thiazine-2-thiones. Starting from readily accessible β-chlorovinyl aldehydes, the targeted products can be prepared with the aid of primary amines and carbon disulfide under mild conditions. Moreover, the use of tryptamine derivatives as amine components leads to a cascade consisting of the 2H-1,3-thiazine-2-thione formation and a Pictet-Spengler-type cyclization. The shown potential of the 2H-1,3-thiazine-2-thiones in subsequent reactions provides the preparation of several compounds containing the 2H-1,3-thiazine-2-thione

Experimental

Synthesis of (RS)-3-allyl-4-hydroxy-5,6-diphenyl-3,4-dihydro-2H-1,3-thiazine-2-thione (2a) as a representative example for the synthesis of all 2H-1,3-thiazine-2-thiones

The aldehyde (EZ)-1a (243 mg, 1.00 mmol) was dissolved in 2 mL anhydrous MeCN. Allylamine (86 mg, 1.50 mmol), dissolved in 3 mL anhydrous MeCN, CS₂ (228 mg, 3.00 mmol) and anhydrous Et₃N (51 mg, 0.50 mmol) were added at 0 °C. After stirring overnight at 0 °C the solvent was removed via high-vacuum low-temperature distillation. Column chromatography (DCM; Rf = 0.23) afforded the desired thiazinethione 2a (304 mg, 90%) as a yellow solid, mp 110 °C (from DCM/n-hexane); IR (ATR): v = 3272, 2504, 3019, 2923, 1643, 1156, 1127, 760, 731 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 3.89–3.91 (1 H, m, OH), 4.68–4.72 (1 H, m, NCH₂), 5.18–5.22 (1 H, m, NCH₂), 5.26–5.28 (1 H, m, CH = CH₂), 5.30–5.33 (1 H, m, CH = CH₂), 5.75 (1 H, d, J = 9.2 Hz, NCH), 5.94–6.02 (1 H, m, CH = CH₂), 7.20–7.28 (10 H, m, 10 CH Ar) ppm; ¹³C NMR (125.8 MHz, CDCl₃): δ 55.41 (NCH₂), 84.72 (NCH), 119.51 (CH = CH₂), 127.41 (CHC = C), 127.91 (p-CH₃), 128.54, 128.65, 128.89 (6 CH Ar), 129.22 (p-CH₃), 130.05 (2 CH Ar), 131.49 (NCH₂CH), 134.08 (C ArCS), 135.79 (C ArCH), 137.09 (CHC = C), 189.48 (C=SQ ppm; MS (ESI): m/z 362.1 (M + Na⁺, 10%), 322.0 (M – OH, 100%), 279.0 (M – COS, 10%); HRMS (ESI): found 362.0660; calc. for C₁₉H₁₇N₃NaOS₂ [M + Na⁺] ³ 362.0649.

Single crystals of 2a obtained by crystallization from DCM and n-hexane were mounted in inert oil and transferred to the cold gas stream of the diffractometer.

Crystal structure determination of 2a

Crystal data. C₁₉H₁₇N₃OS₂, M = 339.45, monoclinic, a = 10.3443(5), b = 9.3521(4), c = 17.9838(8) Å, U = 1727.25(14) Å³; T = 150 K, space group P2₁/n, Z = 4, 90 499 reflections measured, 7596 unique (Rint = 0.0308), which were used in all calculations. The final wR2(F) was 0.1039 (all data).

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