Reinvestigation of the Thiazole Synthesis with Ethyl 3-Amino-2-[5-aryl-1,3,4-oxadiazol-2(*3H*)-ylidene]-3-thioxopropanoates and Related Reactions

Nico Paepke[a,b], Helmut Reinke[a], Klaus Peseke[a], and Christian Vogel[a]

[a] Department of Organic Chemistry, Institute of Chemistry, University of Rostock, Albert-Einstein-Straße 3a, 18059 Rostock, Germany
[b] Current address: Schreiner Group GmbH & Co. KG, Bruckmannring 22, 85764 Oberschleißheim, Germany

Reprint requests to Prof. Dr. Christian Vogel. Fax: +49-381-498-6412.
E-mail: christian.vogel@uni-rostock.de

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Dedicated with great appreciation to Professor Gerhard Maas on the occasion of his 60th birthday

Treatment of the 1,3,4-oxadiazoles **3a** and **3b** with 3-chloropentane-2,4-dione gave the thiazoles **4a** and **4b**, respectively, which were methylated to furnish compounds **5a** and **5b**. The formation of 1,3,4-oxadiazoles using the 1,3-dithietane **1** as starting material, and the consecutive reactions mentioned above were transferred into sugar chemistry to provide the corresponding derivatives **6** – **9** in good yields. The reaction of **5a** with benzyl amine, ethylene diamine and *o*-phenylene diamine afforded compounds **10**, **11**, and **12**, respectively, which possess better stabilized *push-pull* systems than **5a**. The structures of **3a**, **4a**, **5a**, **10**, **11**, and **12** were compared with the previously proposed structures **I** – **VI**, respectively. The structures of compounds **1**, **3b**, and **11** were confirmed by X-ray diffraction studies.

Key words: Diethyl (1,3-Dithietane-2,4-diylidene)bis(2-cyanoacetate), *Push-pull* Chemistry, Hydrogen Sulfide Migration, Consecutive Ring Closure Reaction, Structural Reinvestigation

Introduction

In previous papers published in the 1970ies we reported the smooth reaction of (2*E*,2′*E*)-diethyl 2,2′-(1,3-dithietane-2,4-diylidene)bis(2-cyanoacetate) (**1**) (Fig. 1) with carboxylic acid hydrazides (**2a**, **2b**) [1]. The state-of-the-art NMR and IR technique at that time gave only limited data which, for example, suggested the proposed structure **I** (Fig. 2) for the product of the reaction of **1** with benzohydrazide. In 1995, Neidlein *et al*. repeated this type of reaction, and their X-ray structure analysis has shown that instead of the dihydropyrazole **I** the oxadiazole **3a** was formed (Scheme 1), obviously by an unusual migration of hydrogen sulfide to the cyano group [2]. It is noteworthy that during the reaction no smell of hydrogen sulfide was observed.

The alleged dihydropyrazole **I** had been subjected to several secondary reactions, and it was feared now that the structures proposed for the resulting compounds **II** – **VI** are not correct. Therefore, we decided to repeat the formerly described reactions [3], and to reinvestigate the structures of these compounds. Furthermore, we report the extension of the 1,3-dithietane chemistry by using a sugar hydrazide instead of an aromatic hydrazide.

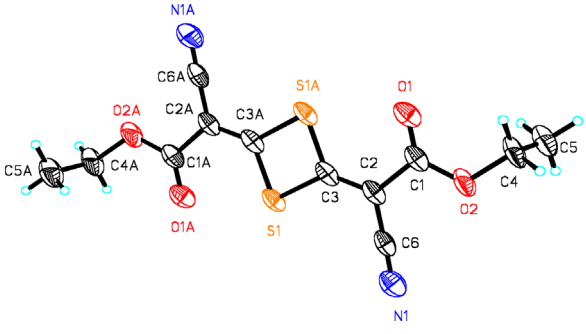


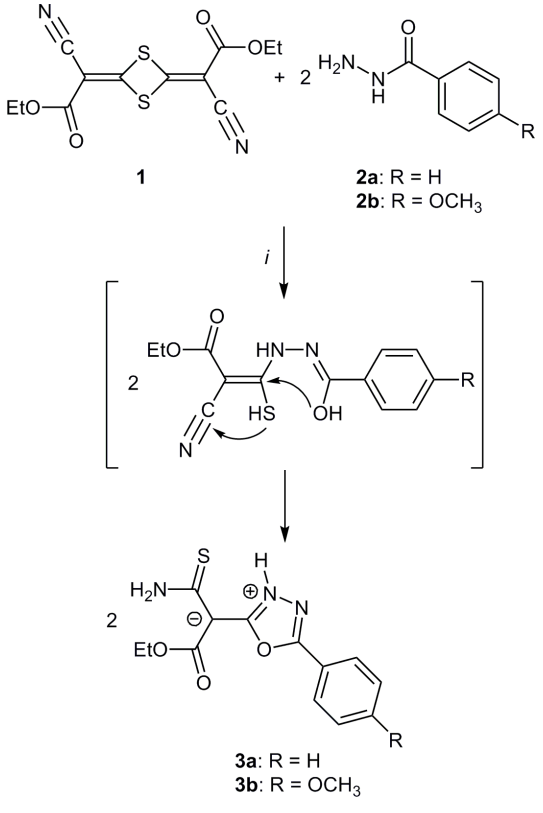
Fig. 1. Molecular structure of **1** in the crystal (ORTEP plot; displacement ellipsoids at the 50 % probability level; H atoms with arbitrary radii).

Results and Discussion

In a typical experiment the 1,3,4-oxadiazoles **3a** and **3b** were furnished by the reaction of 1,3-dithietane **1** with the aromatic hydrazides **2a** and **2b**, respectively [1].

The reaction was conducted in ethanol-chloroform solution at 60 °C, and after 30 min at r. t. the crystalline products were isolated. Analytical samples were obtained by crystallization from chloroform or ethanol. The constitution of the 1,3,4-oxadiazole **3b** was confirmed by X-ray diffraction studies (Fig. 3), and all the other analytical data of **3a** and **3b** confirmed the structural discussion of Neidlein *et al.* [2].

Now, it was interesting to examine the reaction of **3a** and **3b** with 3-chloropentane-2,4-dione as a 1,2-dielectrophile. As previously shown [4], the reaction under basic conditions gave a mixture of two products which were converted into the products **4a** and **4b**, respectively, by heating under reflux with acetic anhydride for 15 min (Scheme 2). On the basis of the structure



Scheme 1. Synthesis of the ethyl 3-amino-2-(5-aryl-1,3,4-oxadiazol-2-yl)-3-thioxopropanoates **3a** and **3b**. *Reagents and conditions:* (*i*) $CHCl_3$-EtOH, 60 °C, 30 min.

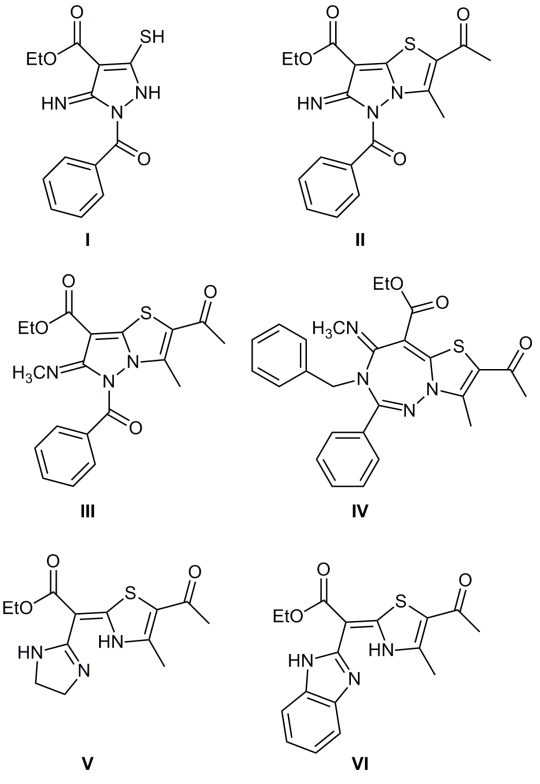


Fig. 2. Previously published, alleged structures of compounds **3a**, **4a**, **5a**, **10**, **11**, and **12**.

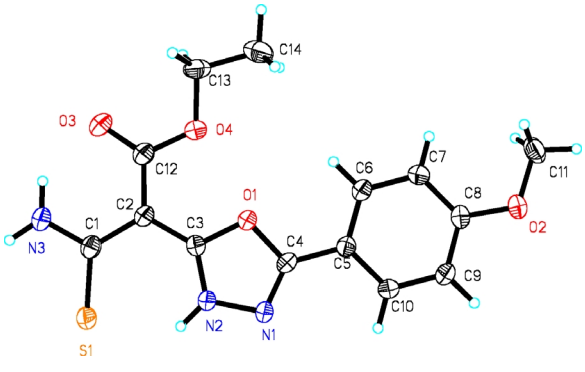
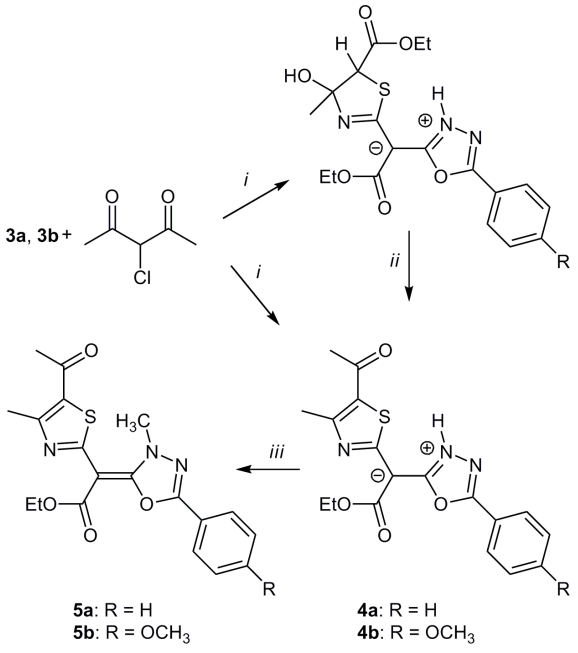
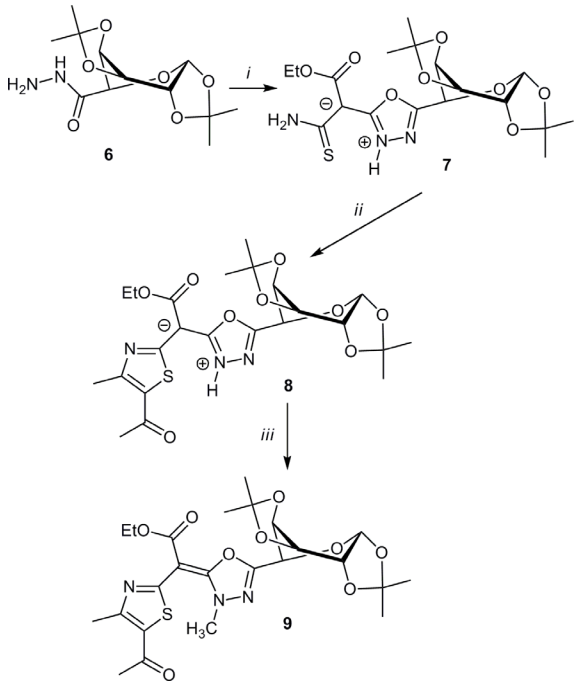


Fig. 3. Molecular structure of **3b** in the crystal (ORTEP plot; displacement ellipsoids at the 50 % probability level; H atoms with arbitrary radii). There are two intramolecular hydrogen bonds in the structure. While the NH_2 group at C1 has one H oriented towards O3 with a distance of 261.25(18) pm between N3 and O3, the distance between N2 and S1 is 288.99(12) pm.

of **3a** and **3b**, the previously described structure **II** can be discarded, as the ring closure of the thiocarbamoyl group obviously gave a 4-methylthiazolyl moiety as a structural element. Comparing both structural propos-



Scheme 2. Synthesis of the thiazole derivatives **4a** and **4b** by ring closure of compounds **3a** and **3b**, respectively, with 3-chloropentane-2,4-dione, and consecutive methylation. *Reagents and conditions:* (*i*) NaOEt, 20 °C, 2 h; (*ii*) $(AcO)_2O$, reflux, 15 min; (*iii*) ethereal CH_2N_2, $CHCl_3$, 20 °C, 10 min.



Scheme 3. Transfer of the reaction protocol described in Schemes 1 and 2 to the sugar hydrazide **6**. *Reagents and conditions:* (*i*) $CHCl_3$-EtOH, reflux, 10 min; (*ii*) NaOEt, 20 °C, 2 h; (*ii*) $(AcO)_2O$, reflux, 15 min; (*iii*) ethereal CH_2N_2, $CHCl_3$, 20 °C, 10 min.

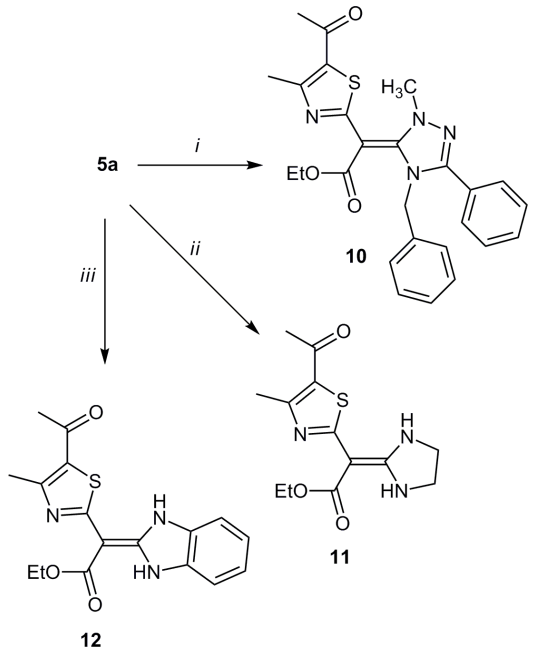
als **II** and **3a**, a remarkable similarity of all the functional groups is obvious.

The tautomeric structures of **3a** and **3b** discussed by Neidlein *et al*. [2] indicated the acidity of the proton predominantly located at 3-position of the oxadiazol ring. The ring closure to the thiazoles **4a** and **4b** should not have a strong influence on this tautomerism. This is demonstrated by the fact that in the ^{1}H NMR spectra of **4a** and **4b** a broad signal of an N-H proton appeared in the range of $\delta = 13.20$. Consequently, the reaction of **4a** and **4b** with an ethereal diazomethane solution provided the 3-methyl-oxadiazols **5a** and **5b**, respectively, in excellent yield (80 – 90 %). Again, the differences of functionalities between both structural proposals, **III** and **5a**, are small.

The protocol of the formation of 1,2,4-oxadiazoles by reaction of 1,3-dithietane **1** with aromatic hydrazides was now transferred to sugar hydrazides. For this reason, methyl 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranuronate [5] was treated with 85 % aq. hydrazine hydrate in EtOH, and the mixture was then heated under reflux for 2 h to provide the as yet unknown hydrazide **6** in nearly quantitative yield.

Fortunately, β-elimination which is a typical side-reaction of galacturonates under alkaline conditions was not observed. As expected, short heating under reflux of a solution of compounds **1** and **6** in chloroform gave the 1,3,4-oxadiazole **7** in 75 % yield. Under conditions described for the formation of the thiazoles **4a**, **4b** and **5a**, **5b**, the corresponding arabinoyl derivatives **8** and **9** were obtained in 73 % and 89 % yield, respectively (Scheme 3). Unfortunately, all attempts failed to get crystals of the two compounds for X-ray diffraction studies.

To examine the previously reported reaction of alleged compound **III** with primary amines [3], compound **5a** was heated under reflux with benzylamine in EtOH for 1 h. Instead of the originally discussed seven-membered ring **IV** we now proposed the formation of the 1,2,4-triazole **10** as the product of this reaction. It was found by ^{1}H and ^{13}C NMR investigations that neither the ester group nor the keto function of **5a** was attacked by the amine. Obviously, the oxygen atom of the 1,3,4-oxadiazole was replaced by a nitrogen atom providing the triazolylidene fragment which appears to lend improved stabilization to the *push-pull* system



Scheme 4. Reactions of thiazole **5a** with *N*-nucleophiles. *Reagents and conditions:* (*i*) benzyl amine, EtOH, reflux, 1 h; (*ii*) 50 % aq. ethylene diamine, EtOH, reflux, 10 min; (*iii*) phenylene diamine, EtOH, reflux, 5 h.

in compound **10** as compared to the oxadiazolylidene fragment in **5a**.

Finally, repetition of the reaction of **5a** with ethylene diamine and *o*-phenylene diamine afforded the crystalline imidazolidinylidenes **11** and **12** in 76 % and 58 % yield, respectively (Scheme 4). Again, the driving force of the reaction is the formation of a more stabilized *push-pull* system in **11** and **12** than in the starting material set up by ring closure of the vicinally constituted binucleophiles. However, the postulation of structures **V** and **VI** as a result of this reaction required a reductive N–N cleavage of the hydrazide fragment in compound **III** which is not very plausible [3]. On the other hand, **V** and **VI** are tautomeric structures of **11** and **12**, respectively. The X-ray structure analysis of compound **11** (Fig. 4) confirms the generation of the imidazolidin-2-ylidene and methylthiazolyl moieties instead of an imidazolyl and a thiazolin-2-ylidene residue in the alleged structure **V**.

Conclusion

The reaction of 1,3-dithietane **1** with benzohydrazide led to the 1,3,4-oxadiazole **3a** instead of the previously proposed pyrazoline **I**. The formation of

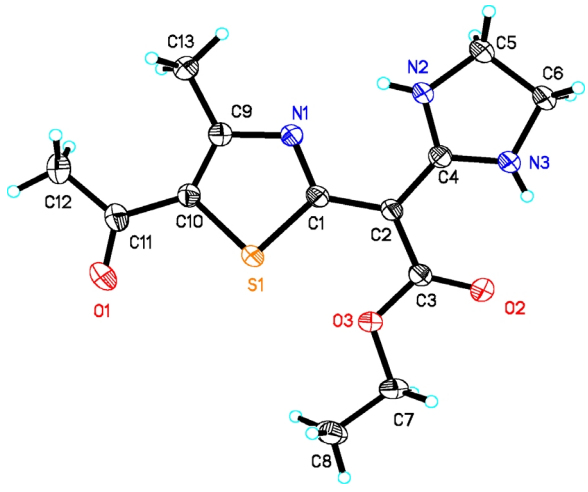


Fig. 4. Molecular structure of **11** in the crystal (ORTEP plot; displacement ellipsoids at the 50 % probability level; H atoms with arbitrary radii). Beside intramolecular hydrogen bonds between N2 and N1 with a distance of 264.33(18) pm and between N3 and O2 with a distance of 266.32(17) pm, there is an intermolecular interaction pattern with a center of inversion between two symmetry-equivalent molecules. Here the distance between the donor N3 and the acceptor O2 is 298.51(18) pm.

1,3,4-oxadiazoles described first by Neidlein *et al*. was confirmed by X-ray diffraction studies of compound **3b**. Subsequent reaction of **3a** with 3-chloropentane-2,4-dione afforded compound **4a**, in contrast to the earlier proposed structure **II**. Methylation of **4a** furnished **5a** instead of structure **III**. The reactions summarized here were successfully applied with the sugar hydrazide **6**, which itself was prepared for the first time, to afford the corresponding sugar derivatives **7** – **9**.

Finally, the nucleophilic attack of **5a** by benzylamine, ethylene diamine and *o*-phenylene diamine gave the stabilized *push-pull* structures **10**, **11**, and **12**, respectively, instead of the earlier postulated structures **IV**, **V**, and **VI**. Again, the structure of **11** was established by X-ray diffraction analysis.

Experimental Section

Melting points were determined with a Boetius microheating plate BHMK 05 (Rapido, Dresden) and are not corrected. Optical rotation was measured for solutions in a 2-cm cell with an automatic polarimeter GYROMAT (Dr. Kernchen Co.). ^{1}H NMR spectra (250.13 MHz, 300.13 MHz, and 500.13 MHz) and ^{13}C NMR spectra (62.89 MHz, 75.47 MHz, and 125.76 MHz) were recorded on Bruker instruments AC 250, ARX 300, and Avance 500, respectively,

with $CDCl_3$, CD_3OD or [D_6]DMSO as solvents. The calibration of spectra was carried out referring to solvent signals ($CDCl_3$: δ ^{1}H = 7.25, δ ^{13}C = 77.0; CD_3OD: δ ^{1}H = 4.78, δ ^{13}C = 49.0; [D_6]DMSO: δ ^{1}H = 2.50, δ ^{13}C = 39.7). ^{1}H and ^{13}C NMR signals were assigned by DEPT and two-dimensional ^{1}H,^{1}H COSY and ^{1}H,^{13}C correlation spectra (HMBC and HSQC). Mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analyses were performed on a CHNS-Flash-EA-1112 instrument (Thermoquest).

All washing solutions were cooled to ~5 °C. The $NaHCO_3$ solution was saturated. Reactions were monitored by thin-layer chromatography (TLC, Silica Gel 60, F_{254}, Merck KGaA). The followings solvents systems (v/v) were used: (A_1) 2 : 1, (A_2) 5 : 1, (A_3) 6 : 1, (A_4) 10 : 1, (A_5) 30 : 1, (A_6) 50 : 1, (A_7) 80 : 1, (A_8) 100 : 1 *n*-hexane-ethyl acetate; (B) 10 : 1 ethyl acetate-methanol. The spots were made visible by dipping the TLC plates into a methanolic 10 % H_2SO_4 solution and charring with a heat gun for 3 – 5 min. Preparative flash chromatography was performed by elution from columns of slurry-packed Silica Gel 60 (Merck, 63 – 200 μm). All solvents and reagents were purified and dried according to standard procedures [6]. After classical work-up of the reactions mixtures, the organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure (rotary evaporator).

*Reaction of oxadiazols **3a** and **3b** with 3-chloropentane-2,4-dione* [4]

Sodium (0.23 g, 10 mmol) and oxadiazole **3a** (2.91 g, 10 mmol) or **3b** (3.21 g, 10 mmol) [1] were dissolved in abs. EtOH (30 mL), and to the reaction mixture 3-chloropentane-2,4-dione (1.34 g, 10 mmol) was added. After shaking the mixture for 2 h at r. t., the released precipitate was filtered off and washed several times with water. The crude product was dried and then heated under reflux with 50 mL acetic anhydride for 15 min. The solution was chilled to r. t., and the formed crystals were isolated and crystallized from acetic acid to give compounds **4a** or **4b** as yellow needles.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[5-phenyl-1,3,4-oxadiazol-2(3H)-ylidene]acetate (**4a**)*

Yield 2.93 g (79 %). – M. p. 193 – 195 °C (acetic acid). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.48 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3), 2.46 (s, 3 H, $COCH_3$), 2.67 (s, 3 H, CH_3), 4.41 (q, 2 H, OCH_2CH_3), 7.50, 8.04 (2 m, 5 H, C_6H_5), 13.21 (br, 1 H, NH). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.5 (OCH_2CH_3), 14.8 (CH_3), 29.8 ($COCH_3$), 60.6 (OCH_2CH_3), 80.0 [O(NH)C=C(C_2)], 120.4, 124.0, 126.4, 128.9, 131.2 (NC=CS, C_6H_5, two signals are isochronic), 143.6 (NC=CS), 161.7, 162.2 (O(NH)C=C(C_2), O(N=)C-C_6H_5), 163.9, 165.6 (2 × C=O), 189.7 (C(S)=N). – $C_{18}H_{17}N_3O_4S$ (371.41): calcd. C 58.21, H 4.61, N 11.31, S 8.63; found C 58.13, H 4.68, N 11.07, S 8.74.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-ylidene]acetate (**4b**)*

Yield 2.89 g (72 %). – M. p. 203 – 205 °C (acetic acid). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.47 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3), 2.46 (s, 3 H, $COCH_3$), 2.66 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 4.39 (q, 2 H, OCH_2CH_3), 7.38, 7.97 (2 m, 4 H, C_6H_4), 13.20 (br, 1 H, NH). – ^{13}C NMR (75,5 MHz, $CDCl_3$): δ = 15.1 (OCH_2CH_3), 15.4 (CH_3), 30.4 ($COCH_3$), 55.9 (OCH_3), 61.1 (OCH_2CH_3), 80.6 [O(NH)C=C(C_2)], 114.9, 117.0, 120.8, 128.7 (NC=CS, C_6H_4, three signals are isochronic), 144.2 (NC=CS), 162.2, 162.6 (O(NH)C=C(C_2), O(N=)C-C_6H_5), 163.9, 166.1 (2 × C=O), 190.3 (C(S)=N). – $C_{19}H_{19}N_3O_5S$ (401.44): calcd. C 56.85, H 4.77, N 10.47, S 7.99; found C 56.73, H 4.76, N 10.22, S 7.91.

*Reaction of thiazols **4a** and **4b** with diazomethane* [3]

Thiazole **4a** (3.71 g, 10 mmol) or **4b** (4.01 g, 10 mmol) was dissolved in a minimum of chloroform and treated with an ethereal diazomethane solution. When the reaction was complete, indicated by a persisting yellow color of the solution, the reaction mixture was treated with acetic acid to destroy the excess of diazomethane. The solution was then diluted with the double volume of $CHCl_3$ and the organic layer washed with water, aq. $NaHCO_3$ (2×), and again water, dried, and concentrated. Crystallization from EtOH gave compounds **5a** or **5b** as yellow needles.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[3-methyl-5-phenyl-1,3,4-oxadiazol-2(3H)-ylidene]acetate (**5a**)*

Yield 3.51 g (91 %). – M. p. 180 – 181 °C (ethanol). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.38 (t, ^3J = 7.0 Hz, 3 H OCH_2CH_3), 2.50 (s, 3 H $COCH_3$), 2.66 (s, 3 H CH_3), 3.70 (s, 3 H NCH_3), 4.34 (q, 2 H OCH_2CH_3), 7.54, 7.96 (2 m, 5 H C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6 (OCH_2CH_3), 18.3 (CH_3), 30.7 ($COCH_3$), 40.1 (NCH_3), 60.0 (OCH_2CH_3), 74.6 [O(NCH_3)C=C(C_2)], 121.9, 126.1, 126.5, 129.2, 132.7 (NC=CS, C_6H_5, two signals are isochronic), 157.5 (NC=CS), 159.2, 163.6 (O(NCH_3)C=C(C_2), O(N=)C-C_6H_5), 165.6, 166.1 (2× C=O), 190.5 (C(S)=N). – $C_{19}H_{19}N_3O_4S$ (385.44): calcd. C 59.21, H 4.97, N 10.90, S 8.32; found C 58.93, H 5.13, N 10.68, S 8.29.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[3-methyl-5-(4-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-ylidene]acetate (**5b**)*

Yield 3.36 g (81 %). – M. p. 194 – 196 °C (ethanol). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.38 (t, ^3J = 7.0 Hz,

3 H OCH_2CH_3), 2.50 (s, 3 H $COCH_3$), 2.65 (s, 3 H CH_3), 3.60 (s, 3 H NCH_3) 3.89 (s, 3 H OCH_3), 4.34 (q, 2 H OCH_2CH_3), 7.02, 7.90 (2 m, 4 H C_6H_4). – ^{13}C NMR (75,5 MHz, $CDCl_3$): δ = 14.6 (OCH_2CH_3), 18.3 (CH_3), 30.7 ($COCH_3$), 40.0 (NCH_3), 55.5 (OCH_3), 59.9 (OCH_2CH_3), 74.2 [$O(NCH_3)C{=}C(C_2)$], 114.1, 114.8, 125.8, 128.3, 159.4 ($NC{=}CS$, C_6H_4, two signals are isochronic), 157.6 ($NC{=}CS$), 163.2, 163.4 ($O(NCH_3)C{=}C(C_2)$, $O(N{=})C$-C_6H_5), 165.6, 166.4 (2 × C=O), 190.4 ($C(S){=}N$). – $C_{20}H_{21}N_3O_4S$ (415.46): calcd. C 57.82, H 5.09, N 10.11, S 7.72; found C 58.11, H 5.32, N 9.97, S 7.26.

*(1,2;3,4-Di-O-isopropylidene-α-D-galactopyranose)uronhydrazide (**6**)*

Hydrazine hydrate (85 %, 0.77 g, 22 mmol) was added to a solution of methyl 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranuronate (2.88 g, 10 mmol) [4] dissolved in a minimum of EtOH with slight warming to give a clear reaction mixture. After heating under reflux for 2 h (monitored by TLC, solvent toluene : ethylacetate 2 : 1) the solution was chilled to r. t. and diluted with chloroform. The organic layer was washed several times with water, dried and concentrated. Traces of hydrazine were removed by coconcentration with toluene. After drying under high vacuum, compound **6** (2.74 g, 95 % yield) was received.

M. p. 150 – 152 °C. – $[\alpha]_D^{24}$ = −121.9 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.32 (s, 6 H $C(CH_3)_2$), 1.40, 1.50 (2 s, 6 H $C(CH_3)_2$), 4,35 (m, 2 H 2-H, 3-H), 4.64, 4.65 (2 s, 2 H 4-H, 5-H), 5.56 (d, 1 H ^3J = 4.9 Hz, 1-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 24.2, 24.8, 25.9, 26.0 (4 s, 4 × CH_3), 68.8 (C-5), 70.3 (C-2), 70.7 (C-4), 71.3 (C-3), 96.2 (C-1), 109.3, 109.6 (2 s, 2 × $C(CH_3)_2$), 168.7 (C=O). – $C_{12}H_{20}N_2O_6$ (288.30): calcd. C 49.99, H 6.99, N 9.72; found C 50.24, H 7.10, N 9.49.

*Ethyl 3-amino -2-[5-(1,2;3,4-di-O-isopropylidene-β-L-arabinopyranos-5-yl)-1,3,4-oxadiazol-2(3H)-ylidene]-3-thioxopropanoate (**7**)*

A hot solution of diethyl 2,2′-(1,3-dithietane-2,4-diylidene)bis(2-cyanoacetate) (**1**, 1.55 g, 5.0 mmol) [7] in $CHCl_3$ (5 mL) was added to a warm solution of hydrazide **6** (2.88 g, 10 mmol) in $CHCl_3$ (10 mL). The reaction mixture was heated under reflux for 10 min, then chilled to r. t. and evaporated. The residue was crystallized from ethyl acetate to provide compound **7** (3.32 g, 75 % yield) as colorless crystals.

M. p. 145 – 146 °C (ethyl acetate). – $[\alpha]_D^{22}$ = −55.7 (*c* = 1.03, $CHCl_3$). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.33, 1.37, 1.45, 1.57 (4 s, 12 H 2 × $C(CH_3)_2$), 1.34 (t, ^3J = 7.0 Hz, 3 H OCH_2CH_3), 4.25 (q, 2 H OCH_2CH_3), 4.46 (m, 1 H 2-H), 4.53 (dd, 1 H $^3J_{3,4}$ = 7.6 Hz, 3-H), 4.76 (dd, 1 H $^3J_{4,5}$ = 2.1 Hz, 4-H), 5.07 (d, 1 H 5-H), 5.67 (d, $^3J_{1,2}$ = 4.9 Hz, 1-H), 6.94, 10.25 (2 × br, 2 H NH_2), 7.76, 8.86 (1 H NH). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_3), 24.5, 24.7, 25.8, 26.1 (2 × $C(CH_3)_2$), 57.3 (OCH_2CH_3), 64.3 (C-5), 70.4 (C-2), 70.7 (C-4), 71.7 (C-3), 83.8 [$O(NH)C{=}C(C_2)$], 96.5 (C-1), 109.5, 110.8 (2 × $C(CH_3)_2$), 157.6, 166.5 ($O(NH)C{=}C(C_2)$, $O(N{=})C$-Ara), 166.7 (C=O), 190.4 ($C(S){=}N$). – MS (ESI): *m/z* (%) = 444 (100) $[M+H]^+$, 429 (95), 388 (19), 330 (14). – $C_{18}H_{25}N_3O_4S$ (443.47): calcd. C 48.75, H 5.68, N 9.48, S 7.23; found C 48.54, H 5.66, N 9.29, S 7.04.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[5-(1,2;3,4-di-O-isopropylidene-β-L-arabinopyranos-5-yl)1,3,4-oxadiazol-2(3H)-ylidene]acetate (**8**)*

Sodium (115 mg, 5 mmol) and compound **7** (2.22 g, 5 mmol) were dissolved in abs. EtOH (15 mL), and to the reaction mixture 3-chloropentane-2,4-dione (0.67 g, 5 mmol) was added. After shaking it for 2 h at r. t., the reaction mixture was concentrated, and the residue was dissolved in $CHCl_3$ (50 mL). The organic layer was washed with water (2 × 25 mL), dried and concentrated. The residue was dried under high vacuum and then heated under reflux with 25 mL acetic anhydride for 15 min. The solution was chilled to r. t. and poured into ice-water (150 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 25 mL), and the combined organic layers were washed with water (2 × 20 mL), dried and concentrated. The crude product was purified by column chromatography (chloroform : acetonitrile 5 : 1) to afford compound **8** (1.91 g, 73 % yield) as a colorless foam.

$[\alpha]_D^{23}$ = −123.8 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.37 (t, ^3J = 7.0 Hz, 3 H OCH_2CH_3), 1.33, 1.37, 1.48, 1.58 [4 s, 12 H 2 × $C(CH_3)_2$], 2.46 (s, 3 H $COCH_3$), 2.64 (s, 3 H CH_3), 4.34 (q, 2 H OCH_2CH_3), 4.45 (m, 1 H 2-H), 4.58 (dd, 1 H $^3J_{3,4}$ = 7.4 Hz, 3-H), 4.75 (dd, 1 H $^3J_{4,5}$ = 1.8 Hz, 4-H), 5.20 (d, 1 H 5-H), 5.70 (d, 1 H $^3J_{1,2}$ = 4.8 Hz, H-1). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.4 (OCH_2CH_3), 18.4 (CH_3), 24.6, 24.7, 25.9, 26.0 (2 × $C(CH_3)_2$), 29.8 ($COCH_3$), 60.5 (OCH_2CH_3), 64.3 (C-5), 70.5 (C-2), 70.7 (C-4), 72.2 (C-3), 80.0 [$O(NH)C{=}C(C_2)$], 96.5 (C-1), 109.2, 110.4 (2 × $C(CH_3)_2$), 120.2 ($NC{=}CS$), 143.6 ($NC{=}CS$), 159.9, 162.2 ($O(NH)C{=}C(C_2)$, $O(N{=})C$-Ara), 164.4, 165.6 (2 × C=O), 189.8 ($C(S){=}N$). – $C_{23}H_{29}N_3O_9S$ (523.56): calcd. C 52.76, H 5.58, N 8.03, S 6.12; found C 52.83, H 5.45, N 7.87, S 6.01.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[3-methyl-5-(1,2;3,4-di-O-isopropylidene-β-L-arabinopyranos-5-yl) 1,3,4-oxadiazol-2(3H)-ylidene]acetate (**9**)*

Compound **8** (524 mg, 1 mmol) was dissolved in a minimum of chloroform and treated with an ethereal diazomethane solution. When the reaction was complete, indicated by a persisting yellow color of the solution, the reaction mixture was treated with acetic acid to destroy the excess of diazomethane. The solution was then diluted with the double

volume of $CHCl_3$, and the organic layer washed with water, aq. $NaHCO_3$ (2×), and again water, dried, and concentrated. The desired compound **9** (479 mg, 89 %) was obtained analytically pure as a colorless foam.

$[\alpha]_D^{27}$ = −134.2 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.34 (t, ^3J = 7.0 Hz, 3 H OCH_2CH_3), 1.33, 1.36, 1.46, 1.55 (4 s, 12 H 2 × $C(CH_3)_2$), 2.47 (s, 3 H $COCH_3$), 2.62 (s, 3 H CH_3), 3.63 (s, 3 H NCH_3), 4.29 (q, 2 H OCH_2CH_3), 4.44 (m, 1 H 2-H), 4.56 (dd, 1 H $^3J_{3,4}$ = 7.6 Hz, 3-H), 4.75 (dd, 1 H $^3J_{4,5}$ = 1.8 Hz, 4-H), 5.06 (d, 1 H 5-H), 5.67 (d, 1 H $^3J_{1,2}$ = 4.9 Hz, H-1). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.4 (OCH_2CH_3), 18.3 (CH_3), 24.4, 24.6, 25.7, 26.0 (2 × $C(CH_3)_2$), 29.6 ($COCH_3$), 30.7 (NCH_3), 60.0 (OCH_2CH_3), 64.4 (C-5), 70.4 (C-2), 70.5 (C-4), 71.2 (C-3), 74.5 [O(NH)C=$C(C_2)$], 96.5 (C-1), 109.5, 110.7 (2 × $C(CH_3)_2$), 126.2 (N*C*=CS), 157.4 (NC=*C*S), 157.9, 164.0 (O(NH)*C*=$C(C_2)$, O(N=)*C*-Ara), 165.5, 166.0 (2 × C=O), 190.4 (*C*(S)=N). – $C_{24}H_{31}N_3O_9S$ (537.58): calcd. C 53.62, H 5.81, N 7.82, S 5.96; found C 53.37, H 6.01, N 7.87, S 5.71.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[4-benzyl-1-methyl-3-phenyl-1H-1,2,4-triazol-5(4H)-ylidene]acetate (**10**)* [3]

Benzylamine (643 mg, 6 mmol) was added to a solution of compound **5a** (1.16 g, 3 mmol) in EtOH (25 mL). The resulting reaction mixture was heated under reflux for 1 h, chilled to r. t., and evaporated. The residue was dissolved in chloroform (100 mL), and the organic layer was washed with water (50 mL), aq. 15 % $NaHSO_4$ (3 × 50 mL), water (50 mL), aq. $NaHCO_3$ (2 × 50 mL), and again water, (50 mL), dried, and evaporated. The yellow residue was purified by column chromatography (chloroform : acetonitrile 4 : 1) to furnish compound **10** (1.21 g, 85 %) as a syrup.

M. p. 89 – 91 °C (ethyl acetate–heptane). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.21 (m, 3 H OCH_2CH_3), 2.44 (s, 3 H $COCH_3$), 2.60 (s, 3 H CH_3), 3.86 (s, 3 H NCH_3), 4.16 (m, 2 H OCH_2CH_3), 5.21 (dd, 2 H ^2J = 18 Hz $H_2CC_6H_5$), 6.71, 7.12, 7.50 (3 m, 10 H $H_2CC_6H_5$, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.1 (OCH_2CH_3), 18.6 (CH_3), 30.7 ($COCH_3$), 38.3 (NCH_3), 50.6 ($H_2CC_6H_5$), 58.7 (OCH_2CH_3), 124.1, 126.9, 128.2, 128.5, 128.9, 129.1, 131.5, 133.6 (O(NCH_3)C=$C(C_2)$, (N*C*=CS), 2 × C_6H_5, six signals are isochronic), 153.0 (NC=*C*S), 155.0, 158.9 (N(NCH_3)*C*=$C(C_2)$, N(N=)*C*-C_6H_5), 164.9, 168.9 (2 × C=O), 190.0 (*C*(S)=N). – $C_{26}H_{26}N_4O_3S$ (474.57): calcd. C 65.80, H 5.52, N 11.81, S 6.76; found C 65.53, H 5.51, N 11.68, S 6.76.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-[imidazolidin-2-ylidene]acetate (**11**)* [3]

Ethylene diamine (50 % aqueous solution, 750 mg, 6 mmol) was added to a solution of compound **5a** (1.16 g, 3 mmol) in EtOH (30 mL), and the resulting reaction mixture was heated under reflux for 10 min. During heating crystallization started. After chilling the mixture to r. t. the crystals were filtered off and washed several times with cold EtOH. In such a way product **11** (673 mg, 76 %) was obtained in analytically pure form.

M. p. 184 – 185 °C (ethanol). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.0 Hz, 3 H OCH_2CH_3), 2.46 (s, 3 H $COCH_3$), 2.62 (s, 3 H CH_3), 3.78 (s, 4 H NCH_2CH_2N), 4.34 (q, 2 H OCH_2CH_3). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.7 (OCH_2CH_3), 18.3 (CH_3), 30.5 ($COCH_3$), 43.2 (NCH_2CH_2N, one signal is isochronic), 60.0 (OCH_2CH_3), 79.1 [NH(NH)C=$C(C_2)$], 124.4 (N*C*=CS), 156.3 (NC=*C*S), 164.5 [NH(NH)*C*=$C(C_2)$], 164.5, 168.9 (2 × C=O), 190.5 (*C*(S)=N). – $C_{13}H_{17}N_3O_3S$ (295.36): calcd. C 52.86, H 5.80, N 14.23, S 10.86; found C 52.93, H 5.92, N 13.98, S 10.87.

*Ethyl 2-(5-acetyl-4-methylthiazol-2-yl)-2-{1H-benzo[d] imidazol-2(3H)-ylidene}acetate (**12**)* [3]

Phenylene diamine (648 mg, 6 mmol) was added to a solution of compound **5a** (1.16 g, 3 mmol) in EtOH (30 mL), and the resulting reaction mixture was heated under reflux for 5 h. After chilling the mixture to r. t., the crystals were filtered off and washed several times with cold EtOH. Product **12** (721 mg, 70 %) was obtained as yellow needles.

M. p. 236 – 238 °C (acetonitrile). – ^{1}H NMR (250.13 MHz, [D_6]DMSO): δ = 1.37 (t, ^3J = 7.0 Hz, 3 H OCH_2CH_3), 2.45 (s, 3 H $COCH_3$), 2.74 (s, 3 H CH_3), 4.39 (q, 2 H OCH_2CH_3), 7.27, 7.68 (2 m, 4 H C_6H_4), 13.00 (br, 2H, NH). – ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 15.0 (OCH_2CH_3), 18.4 (CH_3), 30.3 ($COCH_3$), 59.7 (OCH_2CH_3), 78.4 [NH(NH)C=$C(C_2)$], 112.1, 123.0, 124.8, 130.3 (N*C*=CS, C_6H_4, three signals are isochronic), 150.0 [NH(NH)*C*=$C(C_2)$], 155.9 (NC=*C*S), 165.9, 167.8 (2 × C=O), 189.9 (*C*(S)=N). – $C_{17}H_{17}N_3O_3S$ (343.40): calcd. C 59.46, H 4.99, N 12.24, S 9.34; found C 59.18, H 5.08, N 12.00, S 9.47.

X-Ray structure determinations

Data collections were performed using an X8Apex diffractometer system with MoK_α radiation and a CCD area detector. The structures were solved with Direct Methods and refined against F^2 (program system used: Bruker SHELXTL [8]).

*Crystal structure data of **1**:* Crystal size: 0.025 × 0.21 × 0.6 mm^3, triclinic crystal system, space group $P\bar{1}$, a = 4.9450(2), b = 6.7471(3), c = 10.5470(5) Å, α = 82.926(3)°, β = 81.722(2)°, γ = 84.299(2)°, V = 344.38(3) Å^3, Z = 1, T = 293 K, μ(MoK_α) = 4.0 cm^{-1}, θ range for data collection 3.93 – 25.00°, index ranges (h, k, l) = ±5, ±8, ±12, 10317 measured reflections, 1201 independent reflections, R_{int} = 0.0301, GOF (F^2) = 1.135, $R1/wR2$ [$I \geq 2\sigma(I)$] = 0.0329/0.0871, $R1/wR2$ (all data) = 0.0376/0.0951, $\Delta\rho_{fin}$

(max/min) = 0.0304/−0.0244 e Å^{-3}. Remarks: All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were put into theoretical positions, and these positions were then refined with a riding model.

Crystal structure data of ***3b****:* Crystal size: 0.10 × 0.12 × 0.35 mm^3, triclinic crystal system, space group $P\bar{1}$, a = 7.3134(3), b = 9.1288(4), c = 11.5577(4) Å, α = 85.551(2)°, β = 83.651(2)°, γ = 69.2677(2)°, V = 718.52(5) Å^3, Z = 2, T = 173 K, μ(MoK_α) = 2.48 cm^{-1}, θ range for data collection 2.91 – 25.00°, index ranges (h, k, l) = ±8, ±10, ±13, 22641 measured reflections, 2512 independent reflections, R_{int} = 0.0295, GOF (F^2) = 1.086, $R1/wR2$ [$I \geq 2\sigma(I)$] = 0.0286/0.0816, $R1/wR2$ (all data) = 0.0345/0.085, $\Delta\rho_{\text{fin}}$ (max/min) = 0.197/−0.180 e Å^{-3}. Remarks: All non-hydrogen atoms were refined anisotropically. The hydrogen atoms at N2 and N3 were elucidated from a difference map, and their positions were refined freely. The other hydrogen atoms were put into theoretical positions, and these positions were then refined with a riding model.

Crystal structure data of ***11****:* Crystal size: 0.04 × 0.12 × 0.58 mm^3, monoclinic crystal system, space group $P2_1/n$, a = 10.1322(2), b = 7.3519(2), c = 19.1581(4) Å, β = 102.032(1)°, 3.45 – 27.50°, index ranges (h, k, l) = ±13, ±9, ±24, 27433 measured reflections, 3203 independent reflections, R_{int} = 0.0496, GOF (F^2) = 1.022, $R1/wR2$ [$I \geq 2\sigma(I)$] = 0.0345/0.0824, $R1/wR2$ (all data) = 0.0533/0.0912, $\Delta\rho_{\text{fin}}$ (max/min) = 0.283/−0.191 e Å^{-3}. Remarks: All non-hydrogen atoms were refined anisotropically. The hydrogen atoms at N2 and N3 were elucidated from a difference map, and their positions were refined freely. The other hydrogen atoms were put into theoretical positions, and these positions were then refined with a riding model.

CCDC 728522 (**1**), 728523 (**3b**), and 728524 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

[1] K. Peseke, *J. Prakt. Chem.* **1976**, *318*, 939 – 954.
[2] M. Jochheim, H. G. Krug, R. Neidlein, C. Krieger, *Heterocycles* **1995**, *41*, 1235 – 1250.
[3] K. Peseke, C. Vogel, *J. Prakt. Chem.* **1982**, *324*, 652 – 658.
[4] K. Peseke, C. Vogel, J. Blaesche, K.-H. Kollhof, *J. Prakt. Cem.* **1982**, *324*, 639 – 651.
[5] S. Kramer, B. Nolting, A.-J. Ott, C. Vogel, *J. Carbohydr. Chem.* **2000**, *19*, 891 – 921, and refs. cited therein.
[6] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1988**.
[7] K. Peseke, *Z. Chem.* **1975**, *15*, 19 – 20.
[8] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112 – 122.