Efficacious Modification of the Procedure for the Aldehyde Release from 2-Substituted Thiazoles†

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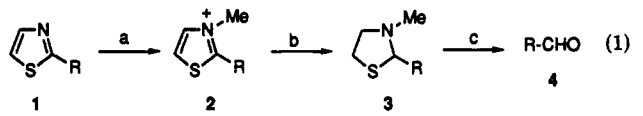
The key operation in the thiazole–aldehyde synthesis, i.e., the conversion of 2-substituted thiazoles 1 to aldehydes 4, is the hydrolytic ring scission to formyl group.[1] This operation involves a sequence of three-simple reactions: a, the N-methylation of the thiazole ring to the *N*-methylthiazolium salt 2; b, the exhaustive reduction of 2 to the thiazolidine 3; and c, the hydrolysis of 3 to the aldehyde 4 (eq 1).



The N-alkylation of 1 to 2 is needed to activate the quite inert thiazole ring[2] toward the reduction to the aldehyde oxidation state in 3. The original procedure of Altman and Richheimer[3] employed trimethyloxonium tetrafluoroborate in step a, sodium borohydride in step b, and mercury(II)-assisted hydrolysis in step c. A single example dealing with an achiral compound was described, and therefore the scope of this aldehyde release remained unexplored for years. Recently, we reexamined the Altman and Richheimer unmasking protocol and found it convenient to replace trimethyloxonium tetrafluoroborate with the less potent but easier to handle methyl iodide.[4] This modified procedure was applied to numerous 2-substituted thiazole 1 bearing a variety of chiral groups R, and it became the key process in new synthetic methodologies toward natural and unnatural carbohydrates.[1] The major advantage of the thiazole route over most of the other heterocycle–aldehyde syntheses[5] lies in the neutral method of aldehyde release from the thiazolidine intermediate 3 owing to the assistance of Hg(II) via coordination to sulfur.[6] Under this condition various hydroxy and amino protecting groups remain untouched as do stereocenters in the substituent R. However, as a rule the N-methylation of 1 requires long reaction times (12–24 h) in refluxing acetonitrile and 10–20 molar excess of CH_3I. Another inconvenience lies in the use of $HgCl_2$ which, although very efficient, brings about the problem of manipulation and disposal of the mercury containing byproducts. Looking for improved reaction conditions which could overcome the above drawbacks, we considered the Corey and Boger procedure[7] for the cleavage of the benzothiazole ring to carbonyl employing methyl fluorosulfonate ("Magic Methyl") for the N-methylation and silver(I) for catalysis of the final hydrolysis. However, this method did not appear to provide practical advantages since Magic Methyl is no longer commercially available[8] and silver salts are expensive. While a number of methyl esters of superacids are available for use as methylating agents,[9] we focused on the use[10] of methyl trifluoromethanesulfonate (methyl triflate) in step a. Moreover, Cu(II) was examined to replace Hg(II) as a $CuCl_2$–CuO mixture was successfully employed by Mukaiyama and co-workers to reveal aldehydes from the corresponding dithioacetals.[11]

The chiral aldehydes 4 shown in Table I were obtained from the corresponding 2-substituted thiazoles 1 by a new general one-pot procedure consisting of the N-methylation with a slight excess of methyl triflate, reduction with $NaBH_4$, and hydrolysis in the presence of $CuCl_2$ and CuO. In all cases the methylation was carried out at room temperature in anhydrous CH_3CN in the presence of powdered 4-Å molecular sieves and was complete in 5–10 min. The reduction with $NaBH_4$ and the copper(II)-mediated hydrolysis in acetonitrile–water occurred smoothly, so that the entire procedure, including the workup, requires approximately 2 h. The crude aldehyde was obtained as a brownish material which was transformed into a colorless product by filtration through a pad of Florisil. The yields of aldehydes isolated in this way were in the range 68–86%, and in most cases they are far superior to those resulting from our earlier method. The purity of the isolated compounds proved to be 95% or more by NMR analyses. Further purification by column chromatography on silica gel led to partial decomposition. Also, this new procedure appears to tolerate various hydroxy and amino protecting groups such as *O*-benzyl, *O*-silyl, dioxolane, and dioxane isopropylidenes, *N*-*tert*-butoxycarbonyl, and oxazolidine. On the other hand the presence of an unprotected hydroxy group appeared to interfere seriously as shown by the failure to isolate the α-hydroxy aldehyde **4c**. Epimerization of stereocenters occurred to a small extent (5–7% for the aldehydes **4a**, **4b**, and **4e**) or not at all as shown by close absolute optical rotation values of enantiomers **4f** and **4g** and by NMR analysis in the other cases.

In conclusion, this procedure efficiently converts chiral 2-substituted thiazoles to aldehydes in a short time, in good overall yields and with little epimerization. In addition to the aldehydes shown in Table I, this method has been applied to the synthesis of several other com-

† Dedicated to Professor A. I. Meyers on the occasion of his 60th birthday.

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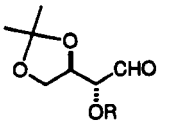
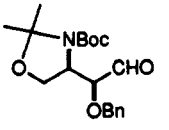
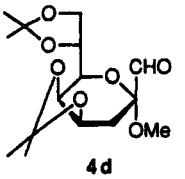
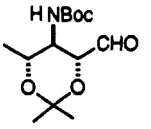
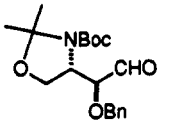
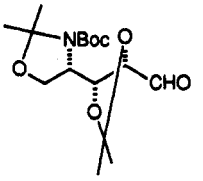
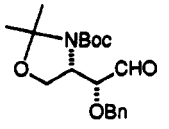
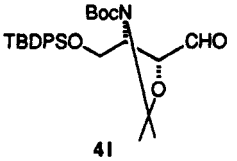
Table I. Aldehydes 4 Prepared from 2-Substituted Thiazoles 1

aldehyde 4	yield[a] (%)	aldehyde 4	yield[a] (%)
			86
4a R = Bn	75[b]	**4g**	
4b R = $SiMe_2Bu$-*t*	82[b]		
4c R = H	----		
	72		81
4d		**4h**	
	85[b]		78
4e		**4i**	
	86		80
4f		**4l**	

[a] Yields refer to isolated products. [b] Contaminated by 5–7% of the epimer at C-2 (see Experimental Section).

pounds with similar results and although routinely carried out on 0.5–2 mmol scales, it has proven to be equally applicable to large-scale preparations with 0.2 mol of 1.

Experimental Section

Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C for solutions in $CHCl_3$. ^1H NMR spectra were recorded with a 300-MHz spectrometer at the stated temperature. Flash column chromatography[12] was performed on silica gel 60 (230–400 mesh, Merck). Commercially available methyl triflate (Aldrich) was used without purification; it was stored under dry nitrogen and handled by standard syringe technique. The structures of the known compounds were verified by NMR spectroscopy.

(1*R*,2*S*)-1-*O*-Benzyl-2-[(*tert*-butoxycarbonyl)amino]-2,3-*N*,*O*-isopropylidene-1-(2-thiazolyl)-1,3-propanediol (1f). To a stirred, cooled (0 °C) solution of the corresponding alcohol[13] (0.95 g, 3.0 mmol) in dry DMF (15 mL) was added NaH as a 60% dispersion in oil (0.24 g, 6.0 mmol). Stirring was continued for an additional 15 min at rt, and then the mixture was cooled to 0 °C and treated with benzyl bromide (0.53 mL, 4.5 mmol). The suspension was stirred for 1 h at rt, and then MeOH was slowly added until a clear solution was obtained. After 15 min at rt the solution was concentrated to give a syrup which was treated with cold H_2O (30 mL) and extracted with CH_2Cl_2 (150 mL). The organic phase was concentrated and the residue eluted from a column of silica gel with 6:4 hexane–Et_2O to afford **1f** (1.17 g, 96%) as a syrup: $[\alpha]_D$ +4.2° (*c* 0.4); ^1H NMR (DMSO-d_6, 120 °C) δ 1.08 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 9 H), 3.97 (dd, 1 H, *J* = 6.5, 9.5 Hz), 4.19 (dd, 1 H, *J* = 1.9, 9.5 Hz), 4.31 (ddd, 1 H, *J* = 1.9, 5.8, 6.5 Hz), 4.50 (d, 1 H, *J* = 11.9 Hz), 4.63 (d, 1 H, *J* = 11.9 Hz), 5.14 (d, 1 H, *J* = 5.8 Hz), 7.26–7.38 (m, 5 H), 7.67 (d, 1 H, *J* = 3.2 Hz), 7.80 (d, 1 H, *J* = 3.2 Hz). Anal. Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.92. Found: C, 62.35; H, 7.10; N, 6.83.

(1*S*,2*R*)-1-*O*-Benzyl-2-[(*tert*-butoxycarbonyl)amino]-2,3-*N*,*O*-isopropylidene-1-(2-thiazolyl)-1,3-propanediol (1g). The corresponding alcohol[14] (1.11 g, 3.5 mmol) was benzylated as described for the preparation of **1f** to yield **1g** (1.36 g, 96%) as a syrup: $[\alpha]_D$ −5.8° (*c* 0.4). Anal. Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.92. Found: C, 62.36; H, 6.96; N, 6.46.

(1*R*,2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*-isopropylidene-3,4-*N*,*O*-isopropylidene-1-(2-thiazolyl)-1,2,4-butanetriol (1i). A solution of the 1,2 diol[15] (0.69 g, 2.0 mmol) and (±)-camphorsulfonic acid (20 mg) in C_6H_6 (40 mL) and 2,2-dimethoxypropane (20 mL) was refluxed for 15 min and then cooled to rt, neutralized with Et_3N, and concentrated. The residue was eluted from a column of silica gel with 97:3 CH_2Cl_2–$(CH_3)_2CO$ to give **1i** (0.72 g, 93%): mp 81–82 °C (from Et_2O–hexane); $[\alpha]_D$ −55.6° (*c* 0.5); ^1H NMR (DMSO-d_6, 120 °C) δ 1.34 (s, 9 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.46 (s, 3 H), 1.48 (s, 3 H), 4.00 (dd, 1 H, *J* = 5.0, 9.3 Hz), 4.03 (dd, 1 H, *J* = 2.8, 9.3 Hz), 4.19 (ddd, 1 H, *J* = 2.8, 5.0, 6.7 Hz), 4.48 (dd, 1 H, *J* = 6.7, 7.3 Hz), 5.36 (d, 1 H, *J* = 7.3 Hz), 7.65 (d, 1 H, *J* = 3.1 Hz), 7.75 (d, 1 H, *J* = 3.1 Hz). Anal. Calcd for $C_{18}H_{28}N_2O_5S$: C, 56.23; H, 7.34; N, 7.28. Found: C, 56.30; H, 7.25; N, 7.06.

2-*O*-Benzyl-3,4-*O*-isopropylidene-D-erythrose (4a). A mixture of the thiazole derivative **1a** (916 mg, 3.0 mmol), activated 4-Å powdered molecular sieves (6.0 g), and anhydrous CH_3CN (30 mL) was stirred at rt for 10 min, and then methyl triflate (0.44 mL, 3.9 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The residue was suspended in MeOH (30 mL), cooled to 0 °C, and treated with $NaBH_4$ (0.25 g, 6.6 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone (30 mL), filtered through Celite, and concentrated. To a solution of the residue in 10:1 CH_3CN–H_2O (30 mL) was added CuO (1.91 g, 24.0 mmol) and then, portionwise and under vigorous stirring, $CuCl_2 \cdot 2H_2O$ (0.51 g, 3.0 mmol). The mixture was stirred for 15 min and then filtered through Celite. Acetonitrile and most of the water were evaporated (bath temperature not exceeding 40 °C) to give a brown syrup. The residue was triturated with Et_2O (5 × 30 mL), and the liquid phase was pipetted and filtered through a pad (1 × 4 cm, h × d) of Florisil (100–200 mesh) to afford an almost colorless solution. After a further washing of Florisil with AcOEt (30 mL) the combined organic phases were concentrated to yield a mixture (563 mg) of **4a** (68%) together with its epimer (7%) calculated by NMR analysis. This mixture had $[\alpha]_D$ +28.8° (*c* 1.0) (lit.[16] $[\alpha]_D$ +36.8° (*c* 1.7)). Epimeric aldehyde[17] had $[\alpha]_D$ −14.6°.

2-*O*-(*tert*-Butyldimethylsilyl)-3,4-*O*-isopropylidene-D-erythrose (4b). Deblocking of **1b** (290 mg, 0.88 mmol) afforded a mixture (198 mg) of **4b** (77%) together with its epimer (5%). This mixture had $[\alpha]_D$ +8.1° (*c* 1.1) (lit.[17] $[\alpha]_D$ −1.5° (*c* 0.8)). Epimeric aldehyde[17] had $[\alpha]_D$ +187.1°.

Methyl 3-Deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-2-octosulo-2,6-pyranoside (4d). Deblocking of **1d** (295 mg, 0.79 mmol) afforded crude **4d** (181 mg, 72%) as a syrup: $[\alpha]_D$ +47.9° (*c* 0.9) (lit.[18] $[\alpha]_D$ +47.8° (*c* 0.5)).

2-*O*-Benzyl-3-[(*tert*-butoxycarbonyl)amino]-3-deoxy-3,4-*N*,*O*-isopropylidene-L-erythrose (4e). Deblocking of **1e**[19] (120 mg, 0.30 mmol) afforded a mixture (88 mg) of **4e** (80%) together with its epimer (5%); $[\alpha]_D$ −37° (*c* 0.7). An analytically pure sample of the mixture was obtained by column chromatography on silica gel (7:3 hexane–Et_2O): $[\alpha]_D$ −46° (*c* 0.6); ^1H NMR (DMSO-d_6, 100 °C) δ 1.41 (s, 9 H), 1.45 (s, 3 H), 1.50 (s 3 H), 3.86 (dd, 1 H, *J* = 2.1, 9.1 Hz), 3.94 (dd, 1 H, *J* = 5.7, 9.1 Hz), 3.95

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(dd, 1 H, J = 2.5, 6.7 Hz), 4.10 (ddd, 1 H, J = 2.1, 5.7, 6.7 Hz), 4.56 (d, 1 H, J = 11.7 Hz), 4.67 (d, 1 H, J = 11.7 Hz), 7.30–7.40 (m, 5 H), 9.62 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.76; H, 8.00; N, 3.99.

2-*O*-Benzyl-3-[(*tert*-butoxycarbonyl)amino]-3-deoxy-3,4-*N*,*O*-isopropylidene-L-threose (4f). Deblocking of **1f** (150 mg, 0.37 mmol) afforded crude **4f** (111 mg, 86%) as a syrup; $[\alpha]_D$ −4.8° (*c* 0.4). An analytical sample was obtained by column chromatography on silica gel (7:3 hexane–Et_2O): $[\alpha]_D$ −6.9° (*c* 0.6); ^1H NMR (DMSO-d_6, 100 °C) δ 1.41 (s, 9 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 4.00 (dd, 1 H, J = 3.3, 10.5 Hz), 4.03 (dd, 1 H, J = 3.8, 10.5 Hz), 4.08 (dd, 1 H, J = 2.1, 4.3 Hz), 4.20 (ddd, 1 H, J = 3.3, 3.8, 4.3 Hz), 4.57 (d, 1 H, J = 11.7 Hz), 4.69 (d, 1 H, J = 11.7 Hz), 7.26–7.38 (m, 5 H), 9.65 (d, 1 H, J = 2.1 Hz). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.40; H, 7.82; N, 3.88.

2-*O*-Benzyl-3-[(*tert*-butoxycarbonyl)amino]-3-deoxy-3,4-*N*,*O*-isopropylidene-D-threose (4g). Deblocking of **1g** (160 mg, 0.39 mmol) afforded crude **4g** (117 mg, 86%) as a syrup; $[\alpha]_D$ +7.1° (*c* 0.4). An analytical sample was obtained by column chromatography on silica gel (7:3 hexane–Et_2O); $[\alpha]_D$ +8.4° (*c* 0.6). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.53; H, 7.88; N, 3.92.

3-[(*tert*-Butoxycarbonyl)amino]-3,5-dideoxy-2,4-*O*-isopropylidene-D-ribose (4h). Deblocking of **1h** (130 mg, 0.40 mmol) afforded crude **4h** (88 mg, 81%) as a syrup; $[\alpha]_D$ −10.0° (*c* 0.5) (lit.[20] $[\alpha]_D$ −4.0° (*c* 1.2)).

4-[(*tert*-Butoxycarbonyl)amino]-4-deoxy-2,3-*O*-isopropylidene-4,5-*N*,*O*-isopropylidene-L-xylose (4i). Deblocking of **1i** (230 mg, 0.60 mmol) afforded crude **4i** (158 mg, 80%) as a syrup; $[\alpha]_D$ −26.4° (*c* 0.9). An analytical sample was obtained by column chromatography on silica gel (95:5 CH_2Cl_2–acetone): $[\alpha]_D$ −24.2° (*c* 0.7); ^1H NMR (DMSO-d_6, 100 °C) δ 1.35 (s, 3 H), 1.43 (s, 3 H), 1.44 (s, 9 H), 1.47 (s, 3 H), 1.49 (s, 3 H), 3.94 (dd, 1 H, J = 2.4, 9.3 Hz), 3.99 (dd, 1 H, J = 5.2, 9.3 Hz), 4.07 (ddd, 1 H, J = 2.4, 5.2, 7.2 Hz), 4.23 (dd, 1 H, J = 6.4, 7.2 Hz), 4.58 (dd, 1 H, J = 1.5, 6.4 Hz), 9.68 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.11; H, 8.64; N, 4.06.

3-[(*tert*-Butoxycarbonyl)amino]-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-2,3-*N*,*O*-isopropylidene-L-threose (4l). Deblocking of **1l** (990 mg, 1.79 mmol) afforded **4l** (713 mg, 80%) as a syrup; $[\alpha]_D$ +7.1° (*c* 1.1) (lit.[13] $[\alpha]_D$ +6.3° (*c* 1.2)).

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