THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 14

JULY 11, 1975

2-Thiazolines in Organic Synthesis. A Synthesis of Mono-, Di-, and Trialkylacetaldehydes

A. I. Meyers* and James L. Durandetta

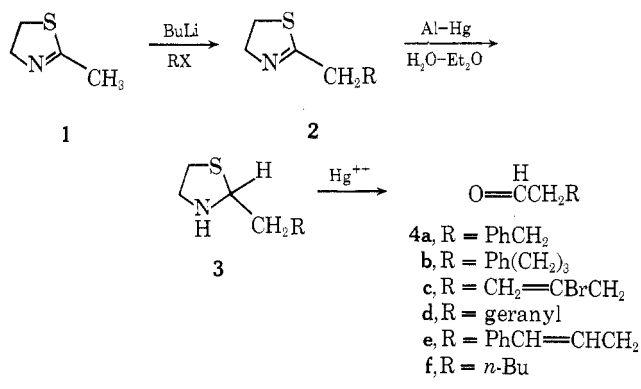
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received February 18, 1975

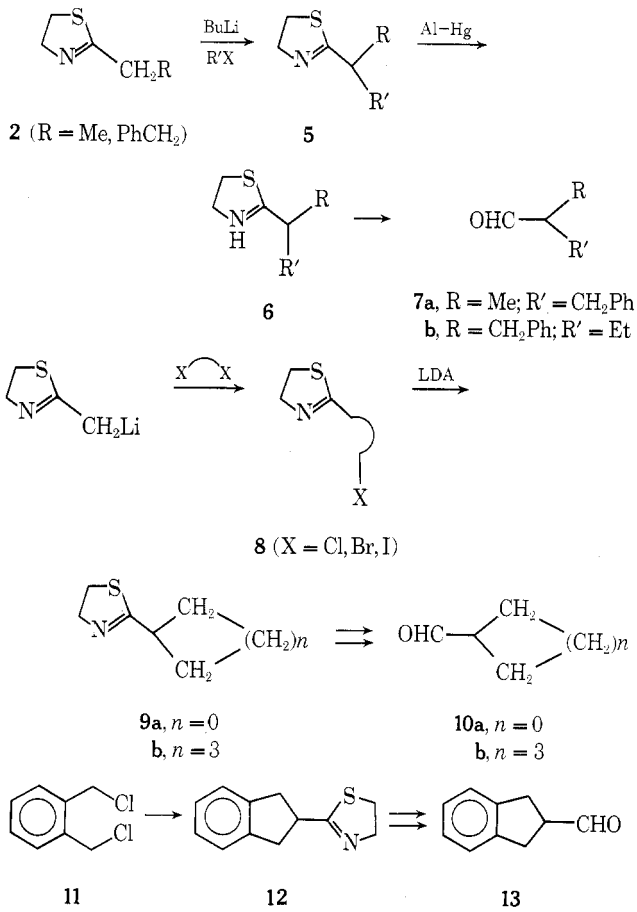
Metalation of 2-methyl-2-thiazoline (1) using *n*-butyllithium at low temperature furnishes a nucleophilic thiazoline anion which may be alkylated to *n*-(alkylmethyl)thiazolines (2). This process may be repeated to produce dialkylated (5 and 9) and trialkylated thiazolines 14. Reduction of the C=N link was readily accomplished using aluminum amalgam in wet ether affording the thiazolidines 3, 6, and 15, respectively. Release of the aldehydes 4, 7, 10, and 16 was then performed in aqueous acetonitrile containing mercuric chloride. Deuteration of C-1 of the aldehydes was also demonstrated by carrying out the aluminum amalgam reduction using ether moistened with deuterium oxide.

The use of heterocycles as precursors in the synthesis of functionalized aliphatic compounds has recently been discussed.[1] Several years ago we described in preliminary form[2] a synthesis of aldehydes from 2-methyl-2-thiazoline (7), a simple commercially available heterocycle. We wish to describe here more extensive studies which demonstrate the intrinsic value of this technique for preparing a variety of substituted acetaldehyde derivatives and their C-1 deuterated analogs. A major feature of this process rests in the fact that the immediate precursor to the elaborated acetaldehyde is the thiazolidine 3, which releases the product under neutral conditions. This circumvents the acidic conditions necessary to accomplish this same task in the Wittig[3] and oxazine[4] routes to aldehydes and thus avoids a variety of undesirable side reactions usually encountered with acid-sensitive aldehydes or their acid-sensitive substituents.

In the preparation of monoalkylated acetaldehydes, the scheme involves the metalation of 1 with *n*-butyllithium in THF at −78°. The resulting lithio salt was then treated with 1.0 equiv of various alkyl iodides or benzyl or allylic chlorides, furnishing the elaborated thiazolines 2 in 80–95% yield. A small amount (1–2%) of dialkylated material could be detected by GLC. The use of alkyl bromides gave somewhat lower yields (55–65%) whereas alkyl chlorides resulted in negligible alkylation (0–10%). The next step involved reduction of 2 to the thiazolidine 3 and this was readily accomplished using aluminum amalgam in moist ether, adapted from the procedure described by Cooper[5] for penicillins. For small-scale runs (<1 g), aluminum foil was utilized to make the amalgam, whereas it was more convenient to employ granular aluminum for larger scale reactions. In order to assess the feasibility of using other reducing agents it was found that sodium borohydride gave reasonable (45–53%) yields of thiazolidine but only under strict pH control (4–6) and the hydrochloride of 2 had to be initially prepared prior to reduction.[6a] Most other conditions involving sodium borohydride led to mixtures of thiazolidine and overreduced open-chain compounds unless *N*-alkyl quaternary salts were used.[6b] Reductions of 2 using aluminum amalgam consistently gave 90–97% yields of thiazolidines 3 and this was undoubtedly the method of choice. Cleavage to the aldehydes was performed using a slight excess of mercuric chloride in 80% aqueous acetonitrile at room temperature for 1–2 hr. Thus, the scheme led to monoalkyl acetaldehydes in 30–70% overall yield. The yields varied somewhat with the particular aldehyde prepared, being partly dependent upon the purity and stability of certain halides in the first step. For example, geranyl chloride was rather unstable and gave the corresponding thiazoline **2d** in only 48% yield. Furthermore, the intermediates 2 and 3 were purified (TLC, distillation, or column) in some cases which resulted in loss of material. Alkylation of the lithio thiazoline was also accomplished with 2-iodopropane and 2-iodohexane, giving 2 (R = *i*-Pr) and 2 (R = 2-hexyl) in 78 and 50% yield, respectively. Although these products were not brought forward to the corresponding aldehydes, the results indicate that secondary halides are also useful electrophiles in this process.



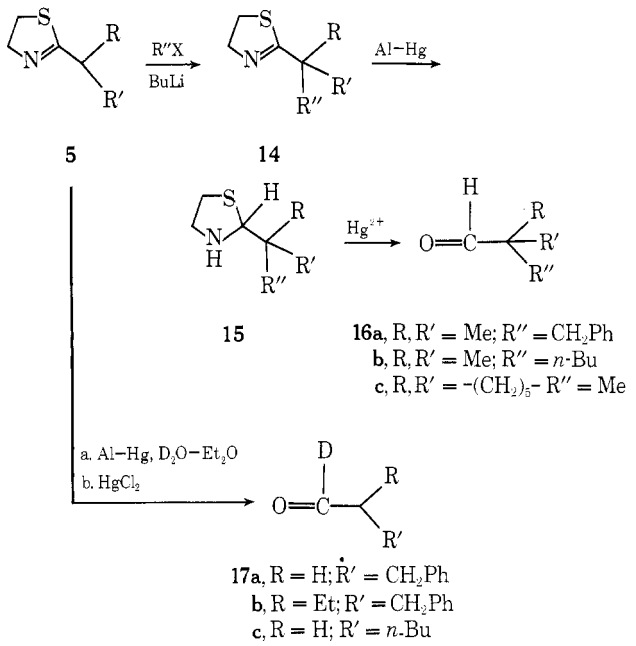
The scheme was further studied with respect to prepar-



ing dialkylacetaldehydes. Thus 2-ethyl and 2-phenethyl thiazolines (**2**) were subjected to low-temperature metalation with butyllithium and treated with benzyl chloride and ethyl iodide, respectively. This furnished **5** (R = Me; R′ = $PhCH_2$) and **5** (R = $PhCH_2$; R′ = Et) in good yield. In order to obtain aldehydic products completely free from monoalkyl derivatives, it was necessary to purify **5** prior to reduction and cleavage. This was accomplished merely by distillation which provided the dialkylated thiazolines **5** in high purity (>98% via GLC). Reduction of the latter using aluminum amalgam gave the thiazolidines **6** (90–94%), which were cleaved by mercuric chloride as mentioned earlier, affording 2-methyl-3-phenylpropionaldehyde (**7a,** 95%) and 2-ethyl-3-phenylpropionaldehyde (**7b,** 88%).

α,ω-Dihalides could be sequentially alkylated by first forming the haloalkyl thiazolines **8,** which were then metalated (with or without prior purification) to the cycloalkyl thiazolines **9.** In this manner, the 2-(cyclopropyl) **9a** and 2-(cyclohexyl) **9b** were prepared in 61 and 60% yields, respectively. Reduction and cleavage led to cyclopropane- and cyclohexanecarboxaldehydes (**10a** and **10b**). The synthesis of 2-indancarboxaldehyde (**13**) was also accomplished starting from *o*-xylenyl dichloride (**11**). The cyclic thiazoline **12,** however, was formed in lower yield (30%) owing to competing side reactions during the cyclization step. The acidity of the chlorobenzyl protons was assumed to be competing with proton removal from the α position of the thiazoline side chain. Furthermore, if **8** contained a bromo or iodo atom, the cyclization was best carried out using lithium diisopropylamide (LDA) to avoid halogen–metal interchange when butyllithium was employed. To form the cyclopropyl thiazoline, 1-chloro-2-bromoethane was used, since 1,2-dibromoethane undergoes rapid elimination to ethylene.[4]

Trialkylated acetaldehydes **16** were also prepared by metalation of dialkylthiazolines **5.** It was found that although butyllithium performed satisfactorily as the base, LDA



gave cleaner products and somewhat higher yields of alkylation (90–95%) to the trialkylated thiazolines **14.** Once again, in order to eliminate troublesome side products such as the dialkylated starting materials **5,** the trialkylated thiazolines were distilled prior to reduction. The purification could be made convenient by appropriate choice of alkyl group introduction. For example, if 2-ethylthiazoline (**5,** R = Me; R′ = H) is alkylated sequentially with 1,5-dibromopentane giving the 1-methyl-1-cyclohexylthiazoline **14** [R = Me; R′ and R″ = $-(CH_2)_5-$], distillative separation is simple. On the other hand, if this trisubstituted thiazoline is prepared from 2-(cyclohexyl)thiazoline [**5,** R = R′ = $-(CH_2)_5-$] and methyl iodide, the separation becomes more difficult owing to the closeness of the boiling points of the starting and final products. Reduction of **14** in the usual fashion gave the corresponding trisubstituted thiazolidines **15,** which were cleaved without purification to the trialkylacetaldehydes in good yield.

Finally, several representative examples of C-1 deuterated aldehydes were prepared. Thus, by reduction of dialkyl thiazolines **5** in ether saturated with deuterium oxide, the aluminum amalgam furnished the appropriate thiazolidines, which were readily cleaved with mercuric chloride in aqueous acetonitrile to produce the deuterated aldehydes **17a–c.** The deuterium content was determined by mass and NMR spectra and found to be 94 ± 3%. This technique compares favorably with the deuterated aldehydes prepared from the dihydro-1,3-oxazine route[4] while utilizing deuterium oxide rather than the more expensive sodium borodeuteride.

In summary, the 2-thiazoline **1** provides a useful template on which to construct mono-, di-, or trialkylacetaldehydes. This overcomes the limitation in the oxazine–aldehyde synthesis wherein no dialkylation or trialkylation could be performed owing to the competing reactions observed for secondary or tertiary oxazine carbanions.[4] In the following article the use of the mild neutral cleavage to release the aldehyde from the thiazolidine allows the preparation of protected β-hydroxy aldehydes and products derived therefrom.

Experimental Section[7]

Monoalkylation of 2-Methyl-2-thiazoline to 2. A dry 250-ml flask fitted with rubber septums, three-way stopcock, and magnetic stirrer was evacuated and flushed with nitrogen. A 0.8 *M* solution (10.0 g/90 ml) of 2-methyl-2-thiazoline (Aldrich) in THF was

syringed into the flask and cooled to −78° with Dry Ice–acetone. After 15 min, a hexane solution of *n*-butyllithium (1.05 equiv) was added over a 20-min period via a syringe. A precipitate formed within 15 min after the complete addition of the lithium reagent. The mixture was stirred for 1.5 hr at −78°, the alkyl halide (1.03–1.05 equiv) in 20 ml of THF was added dropwise via a syringe (5–10 min), and the clear resulting solution was stirred for an additional 1 hr at −78°. The mixture was slowly allowed to come to room temperature (2–3 hr) or allowed to stir overnight, prior to quenching in 150 ml of ice–water. The aqueous mixture was adjusted to pH 2–3 with dilute hydrochloric acid. The organic layer (hexane–THF) was separated and the aqueous layer was extracted with 100 ml of *n*-pentane. The organic extracts were discarded. The aqueous solution was neutralized with 20% potassium hydroxide (pH 10), saturated with salt, and extracted with ether. Concentration of the dried ethereal extracts (K_2CO_3) gave the crude alkylated thiazolines **2** in 90–95% yield (88–92% purity by GLC, UCW-98). Further purification was accomplished by distillation.

2-(2-Phenethyl)-2-thiazoline (2a) was prepared from benzyl chloride: bp 127–130° (2.4 Torr); 86% yield; ir (film) 1625, 1610, 1503, 1460, 760, 710 cm^{-1}; NMR (CCl_4) δ 2.6–3.3 (m, 6), 4.1 (t, 2), 7.3 (br s, 5).

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.92; H, 6.92; N, 7.59.

2-(4-Phenylbutyl)-2-thiazoline (2b) was prepared from 3-phenylpropyl iodide: bp 153–156° (2.4 Torr); 74% yield; ir (film) 1625, 1608, 1500, 1200, 987, 755, 710 cm^{-1}; NMR (CCl_4) δ 1.6 (m, 4), 2.2–2.8 (m, 4), 3.02 (t, 2), 4.05 (t, 2), 7.18 (m, 5).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39. Found: C, 70.99; H, 7.80; N, 6.44.

2-(3-Bromo-3-butenyl)-2-thiazoline (2c) was prepared from 2,3-dibromopropene: bp 80–82° (0.45 Torr); 68% yield; ir (film) 2940, 2855, 1630, 1435, 1425, 1200, 1092, 1033, 975, 912, 887 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (br s, 4), 3.3 (t, 2), 4.25 (t, 2), 5.45 (d, 1), 5.65 (d, 1).

Anal. Calcd for $C_7H_{10}NSBr$: C, 38.19; H, 4.58; N, 6.36. Found: C, 37.95; H, 9.76; N, 6.25.

2-(Geranylmethyl)-2-thiazoline (2d) was prepared from geranyl chloride, which in turn was prepared from geraniol according to Collington and Meyers.[8] The geranyl chloride used here was ~80% pure and contained ~20% mesylate from the homoallylic alcohol present in geraniol. Bulb-to-bulb distillation of crude **2d** gave 50% yield: ir (film) 1628, 1605, 1592, 1493, 1452, 1379, 994, 981, 745, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (m, 9), 2.02 (m, 4), 2.5 (m, 4), 3.3 (t, 2), 4.2 (t, 2), 5.2 (m, 2).

Anal. Calcd for $C_{14}H_{23}NS$: C, 70.83; H, 9.76; N, 5.90. Found: C, 71.03; H, 9.71; N, 5.85.

***trans*-2-(4-Phenyl-3-butenyl)-2-thiazoline (2e)** was prepared from cinnamyl chloride (crude) used in 20% excess in the alkylation. Bulb-to-bulb distillation gave **2e:** 55% yield; ir (film) 1626, 1596, 1575, 1492, 962, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 2.6 (m, 4), 3.2 (m, 4), 4.2 (t, 2), 5.9–6.6 (m, 2), 7.1–7.5 (m, 5).

Anal. Calcd for $C_{13}H_{15}NS$: C, 71.84; H, 6.96; N, 6.45. Found: 71.21; H, 7.10; N, 6.40.

2-(*n*-Pentyl)-2-thiazoline (2f) was prepared from *n*-butyl iodide: 88% yield after bulb-to-bulb distillations; ir (film) 1627, 1460, 995, 915 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, 3), 1.0–2.1 (m, 6), 2.55 (t, 2), 3.3 (t, 2), 4.2 (t, 2).

Anal. Calcd for $C_8H_{15}NS$: C, 61.09; H, 9.61; N, 8.91. Found: C, 60.89; H, 9.80; N, 9.13.

n-Butyl bromide gave **2f** in 66% yield; *n*-butyl chloride gave no product.

2-(2-Methylpropyl)-2-thiazoline (2, R = *i*-Pr) was prepared from **1** and isopropyl iodide: bp 70–73° (10 Torr); 78% yield; ir (film) 1625, 1462, 1383, 1366, 1150, 984 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (d, 6), 1.84–2.4 (heptet, 1), 2.4 (d, 2), 3.2 (t, 2), 4.2 (t, 2).

Anal. Calcd for $C_7H_{13}NS$: C, 58.69; H, 9.15. Found: C, 58.55; H, 9.78.

Isopropyl bromide gave only ~10% alkylation product.

2-(Dialkyl)-2-thiazolines. 2-(1-benzylethyl)-2-thiazoline (5, R = Me; R′ = CH_2Ph). A solution of 2-ethyl-2-thiazoline (**2**, R = Me, 4.00 g, 34.8 mmol) in 40 ml of dry THF was placed in the previously described apparatus and cooled to −78°. *n*-Butyllithium (22 ml, 35.0 mmol) was added dropwise over 10 min and the suspension was stirred at −78° for 1.5 hr, after which 6.2 g (4.3 ml) of benzyl bromide was added. Stirring was continued for 30 min, and the solution was allowed to warm to ambient and poured into 40 ml of ice–water. The pH was adjusted to 2–3 and the organic layer was separated and discarded. The aqueous layer was extracted with pentane and the latter layer was also discarded. The aqueous solution was neutralized (10% KOH) to pH 10 and then extracted with ether. The ethereal solution was dried (K_2CO_3) and concentrated, leaving 6.01 g of crude product. Distillation, bp 97–99° (0.25 Torr), gave 4.95 g (70%) of **5** (R = Me; R′ = CH_2Ph): ir (film) 1624, 1495, 1450, 970, 920 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (d, 3), 2.6–3.3 (m, 5), 4.2 (t, 2), 7.2 (m, 5); mass spectrum *m/e* 205 (M^+).

2-(1-Benzylpropyl)-2-thiazoline (5, R = CH_2Ph; R′ = Et) was prepared from 12.1 g of 2-phenethyl-2-thiazoline (**2**, R = CH_2Ph) and 17.1 g of ethyl iodide in a manner identical with above. The ethereal residue gave 12.7 g of crude product which was distilled, bp 137–140 (2.2 Torr), to give 11.1 g (79%) of pure product: ir (film) 1627, 1500, 1410, 990, 755, 710 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3), 1.3–1.8 (m, 2), 2.8–3.2 (m, 5), 4.1 (t, 2), 7.2 (m, 5).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39. Found: C, 70.89; H, 7.81; N, 6.56.

2-(Cyclopropyl)-2-thiazoline (9a, *n* = 0). In the usual apparatus 8.12 g (80.4 mmol) of 2-methyl-2-thiazoline was dissolved in 105 ml of dry THF and cooled to −78°. *n*-Butyllithium (51.1 ml, 82.4 mmol) was added dropwise over a 20-min period and the suspension was stirred at −78° for 1.5 hr. A solution of 1-bromo-2-chloroethane (11.5 g, 80.5 mmol) in 20 ml of THF was added over 5 min and the solution was stirred for 1.5 hr. A second portion of *n*-butyllithium (51.5 ml) was then added over a 20-min period and the solution again was allowed to stir for 40 min at −78°. After this period the mixture was slowly warmed to ambient and stirring was continued overnight. The reaction mixture was quenched in ice–water, and the work-up proceeded as described for **2** or **5**. Distillation of the ethereal residue gave 6.5 g (62%) of pure cyclopropylthiazoline: bp 51–54° (0.5 Torr); ir (film) 1622, 1380, 1228, 1205, 1183 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (d, 4), 1.85 (q, 1), 3.25 (t, 2), 4.2 (t, 2).

Anal. Calcd for C_6H_9NS: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.50, H, 7.25; N, 10.84.

2-(Cyclohexyl)-2-thiazoline (9b, *n* = 3). The lithio salt of 2-methyl-2-thiazoline was prepared as described above, and quickly transferred (via syringe) to a flask containing 3 equiv of 1,5-dibromopentane in 50 ml of THF, previously cooled to −78°. After stirring for 1.5 hr, the mixture was warmed to −30° and kept at this temperature for an additional 1 hr, after which it was quenched in ice–water. The solution was acidified to pH 2 with 6 *N* hydrochloric acid, and then the organic layer was separated and discarded. The aqueous acidic solution was extracted once with pentane and the latter was also discarded. The aqueous solution was made alkaline with 10% sodium hydroxide and the organic material was removed by ether extraction. The ethereal solution was dried (K_2CO_3) and concentrated at or below room temperature. The residue, 2-(6-bromohexyl)-2-thiazoline, was dried further by dissolving it in 20 ml of THF and adding Linde molecular sieves, 4A. The drying agent was removed by filtration (after 2 hr) and the 0.1 *M* THF solution containing the bromoalkylthiazoline was introduced into a reaction flask, cooled to −78°, and treated with 1.1 equiv of lithium diisopropylamide (prepared just prior to use from *n*-butyllithium and diisopropylamine, THF, 0°). The reaction was stirred for 5 hr at −78° and then allowed to warm to 0–5°, quenched in 25–35 ml of ice water, and worked up as in **2** or **5**. Bulb-to-bulb distillation of the ethereal residue gave 0.91 g (62%) of 2-(cyclohexyl)-2-thiazoline: ir (film) 1625, 1450, 990 cm^{-1}; NMR ($CDCl_3$) δ 4.2 (t, 2), 3.2 (t, 2), 2.8–0.7 (m, 11); mass spectrum *m/e* 169 (M^+), 114 (base).

The formation of **9b** (*n* = 3) was also accomplished by sequential addition of *n*-butyllithium and lithium diisopropylamide (1.0 equiv), each of which eliminated the need to isolate the intermediate bromoalkylthiazoline. If *n*-butyllithium was used in the cyclization step in place of LDA, various yields (10–30%) of 2-(*n*-hexyl)-2-thiazoline were formed arising from halogen–metal interchange. A small amount of 1,6-(dithiazolinyl)hexane was also detected in these reactions.

2-(2-Indanyl)-2-thiazoline (12) was prepared from α,α'-dichloro-*o*-xylene (10.7 g, 62 mmol) and 2-methyl-2-thiazoline (1.1 g, 11 mmol) according to the above detailed procedure for **9b:** yield 25% of an oil, 0.53 g from bulb-to-bulb distillation; mass spectrum *m/e* 203 (M^+), 115, 116; ir (film) 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.0–3.7 (overlapping multiplet, triplet, 7), 4.2 (t, 2), 7.2 (m, 4).

2-(Trialkyl)-2-thiazoline (14). General Procedure. The dialkylmethylthiazolines **5** (2–11 mmol) were dissolved in sufficient dry THF to make the solutions 0.7–0.8 *M*. The solution was cooled in the previously described apparatus to −78° and *n*-butyllithium (1.1 equiv)[9] was added dropwise over 5–10 min. The reaction mixture was stirred at −78° for 2–3 hr and the alkyl halide (1.1 equiv) in THF was added over 10–20 min. Stirring was continued for 2–3 hr and the clear solution was allowed to warm to room temperature

and poured into 100 ml of ice–water, and 20–30 ml of ether was then added. The two-phase solution was made acidic with 6 *M* hydrochloric acid and the aqueous layers were combined. The aqueous solution was rendered alkaline by addition of 20% sodium hydroxide, saturated with sodium chloride, and then extracted with four 25-ml portions of ether. The dried (K_2CO_3) ethereal extracts were concentrated and the residues were distilled in the Kugelrohr apparatus. Specific data for trialkylthiazolines follow.

2-(1,1-Dimethylphenethyl)-2-thiazoline (14, R, R′ = Me; R″ = CH_2Ph) was prepared from 0.57 g (4.4 mmol) of 2-(isopropyl)-2-thiazoline and benzyl chloride: yield 0.58 g (65%); ir (film) 1620, 1495, 1458, 1454, 1385, 1365, 1030, 989, 744, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (s, 6), 2.9 (s, 2), 3.2 (t, 2), 4.2 (t, 2), 7.2 (m, 5).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81. Found: C, 70.91; H, 7.78.

2-(1,1-Dimethyl-*n*-pentyl)-2-thiazoline (14, R, R′ = Me; R″ = *n*-Bu). Using lithium diisopropylamide as the base, 0.88 g (6.8 mmol) of 2-(isopropyl)-2-thiazoline and *n*-butyl iodide (1.05 equiv) gave 1.06 g (84%) of product: ir (film) 1621, 1470, 1460, 1386, 1365, 1035, 990, 925 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3), 1.2 (s, 6), 1.1–1.8 (m, 6), 3.2 (t, 2), 4.2 (t, 2).

Anal. Calcd for $C_{10}H_{19}NS$: C, 64.81; N, 10.32. Found: C, 64.54; H, 10.22.

2-(1-Methylcyclohexyl)-2-thiazoline [14, R, R′ = $-(CH_2)_5-$; R″ = Me] was prepared from 2-ethyl-2-thiazoline (**2**, R = Me, 1.32 g, 11.5 mmol) and 1,5-dibromopentane (13.4 g) according to the cyclization procedure for **9**: yield 1.19 g (57%); mass spectrum *m/e* 183 (M^+), 128, 40 (base).

Anal. Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35. Found: C, 64.82; H, 9.17.

Aluminum Amalgam Reduction of 2-Thiazolines. General Procedure. Aluminum foil (1.0–1.3 g, 10–12 g-atoms excess) was roughed with sandpaper, cut into 0.5-in. squares, and weighed in the reaction flask. The aluminum was etched with 5% potassium hydroxide solution until vigorous evolution of hydrogen occurred. The basic solution was removed by decantation and the aluminum was rinsed once with water and covered with 0.5% mercuric chloride solution for 1.5–2.0 min. The mercuric chloride solution was poured off, the aluminum was washed with water, and the mercuric chloride solution was reintroduced for 1.5–2.0 min. Once again the mercuric chloride solution was decanted away, and water was added to rinse the aluminum, followed by successive rinsing with absolute ethanol and ether. A solution of the 2-thiazoline to be reduced (1.0–2.0 g in 75 ml of ether previously shaken with water) was added to the freshly prepared amalgam and the mixture was heated to reflux for 1–2 hr. The progress of the reduction was followed by examining aliquots on TLC plates. The reductions were usually complete in less than 1 hr of reflux. Alternatively, the reductions were carried out at room temperature and were usually complete in 4 hr. Isolation of the thiazolidines was accomplished by filtering the reaction mixture to remove the hydroxides and drying the ethereal solution (K_2CO_3) prior to concentration. The residue (usually amounted to 90–95% material of 90–95% purity) was determined by ir (loss of C=N band at 1620–1630 cm^{-1}) and NMR (exchangeable proton when D_2O was added; position varied with concentration but found mainly between 1.0 and 2.0 ppm). No further purification of the thiazolidines **3**, **6**, and **15** was performed prior to cleavage to aldehydes. It was found convenient to use granular aluminum (8–20 mesh) on larger scale reductions and this was performed as follows. Granular aluminum (7.5–8.5 g) was used for reduction of 4–5 g of thiazoline and the amalgam was prepared in the same manner as the foil by successive treatment of KOH, $HgCl_2$, water, etc. As before, the amalgam prepared was used immediately for reduction of the thiazolines.

Cleavage of Thiazolidines 3, 6, and 15. General Procedure. A solution of thiazolidines (3.8–4.2 g) in the minimum amount of acetonitrile was added dropwise to 7.5–8.3 g of mercuric chloride in 30 ml of acetonitrile–water (4:1) over a 15-min period. A precipitate formed immediately and the mixture was stirred at room temperature for 2 hr. Water (25 ml) was added and the mixture was filtered. The filtrate was extracted with pentane or pentane–ether (1:1) and the organic extract was dried over sodium or potassium carbonate. Concentration of the solution gave the crude aldehydes, which were 90–95% pure (via GLC and NMR). The following aldehydes were all obtained using this procedure and the yields of cleavage are given.

3-Phenylpropionaldehyde: 64.5%; 2,4-DNP, mp 152–153° (lit.[4] mp 153–154°)

5-Phenylvaleraldehyde: 71.1%; *p*-nitrophenylhydrazone, mp 81–83° (lit.[10] mp 82–84°)

4-Bromo-4-pentenal (4c): 57%; oil; ir (film) 2818, 2730, 1726, 1687, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (br s, 4), 5.5 (d, 1), 5.7 (d, 1), 9.8 (t, 1) (purity >95% via NMR); mass spectrum *m/e* 163 (M^+).

Anal. Calcd for C_5H_7BrO: C, 36.31; H, 4.29. Found: C, 36.77; H, 4.31.

Geranylacetaldehyde (4d): 74.4% crude, 61% after bulb-to-bulb distillation; ir (film) 2710, 1728, 1675, 1450, 1384, 1375, 1110, 1055, 830 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (m, 9), 2.02 (m, 4), 2.42 (m, 4), 5.15 (m, 2), 9.7 (t, 1); mass spectrum *m/e* 180 (M^+), 137, 69 (base); 4-phenylsemicarbazone, mp 57–59° (lit.[11] mp 58°).

***trans*-5-Phenyl-4-pentenal (4e):** 54% oil; ir (film) 3030, 2830, 2725, 1725, 1653, 1600, 1580, 965, 745, 692 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (br s, 4), 5.8–6.5 (m, 2), 7.25 (m, 5), 9.67 (t, 1); mass spectrum *m/e* 160 (M^+), 132, 131, 129, 117, 116, 115, 104 (base), 91; semicarbazone, mp 132–133°.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.05, H, 7.37.

***n*-Hexaldehyde (4f):** 88%; 2,4-DNP mp 104–105° (lit.[12] mp 104°).

2-Methyl-3-phenylpropionaldehyde (7a): 83%; bp 44–45° (0.2 Torr), identical with authentic sample.[4]

2-Benzylbutyraldehyde (7b): 79%; 2,4-DNP mp 112–113.5° (lit.[13] mp 114–115°)

Cyclopropanecarboxaldehyde (10a): 64%; 2,4-DNP mp 182–183° (lit.[4] mp 184–185°). $CaCO_3$ (0.3 g) was added to the mercuric chloride in aqueous acetonitrile to neutralize slight traces of acid formed during the cleavage. The aldehyde and acetonitrile codistilled, making purification difficult. Yield was determined by GLC and NMR spectrum.

Cyclohexanecarboxyaldehyde (10b): 66%; unstable and partially decomposes upon distillation; bp 80–82° (25 mm), semicarbazone mp 172–174° (lit.[12] mp 173).

2-Indancarboxaldehyde (13): 84.7%; purified by column chromatography (silica gel, 9:1 hexane–benzene), oil, purity 95%; mass spectrum *m/e* 146 (M^+), 116, 115, 89, 92, 91; ir (film) 3050, 2920, 2820, 2710, 1725, 740 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 1), 3.2 (s, 4), 7.2 (br s, 4), 9.7 (d, 1).

2,2-Dimethyl-3-phenylpropionaldehyde (16a): 83.3%; 2,4-DNP mp 151–152° (lit.[14] mp 154–155°).

2,2-Dimethylhexanal (16b): 80.8%; semicarbazone mp 130–131° (lit.[15] mp 134–135°).

1-Methylcyclohexanecarboxaldehyde (16c): 71.4%; 2,4-DNP mp 152–153° (lit.[16] mp 154–155°). The product was air sensitive and decomposed slightly during molecular distillation at atmospheric pressure.

Formation of C-1 Deuterated Aldehydes 17a–c. Reduction of 2-thiazolines was performed in the following manner. The procedure for preparing the aluminum amalgam given above was followed exactly through the second treatment with 0.5% mercuric chloride. The amalgam was then washed once with distilled water, twice with absolute ethanol, three times with reagent-grade acetone, and three times with anhydrous THF. The thiazoline was dissolved in ether saturated with D_2O (98.5%) (anhydrous ether was employed) and added to the freshly prepared amalgam in an oven-dried flask containing a drying tube. The reaction mixture was stirred for 1–1.5 hr, filtered, and worked up in the manner used for protioaldehydes. Cleavage to the deuterioaldehydes was also performed in the usual manner. Distillation gave the following.

3-Phenylpropionaldehyde-d_1 (17a), 91 ± 2% deuterium (NMR and *m/e*).

2-Ethyl-3-phenylprionaldehyde-d_1 (17b), 94 ± 3% deuterium (NMR).

***n*-Hexanal-d_1 (17c),** 90 ± 3% deuterium (NMR).

Acknowledgment. Financial assistance by the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No.—**1**, 2346-00-1; **2a**, 25478-36-8; **2b**, 55089-11-7; **2c**, 55089-12-8; **2d**, 55089-13-9; **2e**, 55089-14-0; **2f**, 21226-52-8; **2** (R = *i*-Pr), 26851-79-6; **2** (R = Me), 16982-46-0; **3a**, 55089-15-1; **3b**, 55089-16-2; **3c**, 55781-93-6; **3d**, 55089-18-4; **3e**, 55089-19-5; **3f**, 41204-65-3; **4a**, 104-53-0; **4b**, 36884-28-3; **4c**, 36884-29-4; **4d**, 55089-20-8; **4e**, 36884-75-0; **4e** semicarbazone, 55089-21-9; **4f**, 66-25-1; **5** (R = Me; R′ = CH_2Ph), 55089-22-0; **5** (R = CH_2Ph; R′ = Et), 37873-55-5; **5** (R, R′ = Me), 45533-49-1; **6a**, 55089-23-1; **6b**, 55089-24-2; **7a**, 5445-77-2; **7b**, 24569-60-6; **9a**, 55089-25-3; **9b**, 55089-26-4; **10a**, 1489-69-6; **10b**, 2043-61-1; **11**, 612-12-4; **12**,

55089-27-5; **13**, 37414-44-1; **14a**, 55089-28-6; **14b**, 55089-29-7; **14c**, 55089-30-0; **15a**, 55089-31-1; **15b**, 55089-32-2; **15c**, 55089-33-3; **16a**, 1009-62-7; **16b**, 996-12-3; **16c**, 6140-64-3; benzyl chloride, 100-44-7; 3-phenylpropyl iodide, 4119-41-9; 2,3-dibromopropene, 513-31-5; geranyl chloride, 5389-87-7; cinnamyl chloride, 2687-12-9; *n*-butyl iodide, 542-69-8; *n*-butyl bromide, 109-65-9; isopropyl iodide, 75-30-9; benzyl bromide, 100-39-0; ethyl iodide, 75-03-6; 1-bromo-2-chloroethane, 107-04-0; 1,5-dibromopentane, 111-24-0; 2-(6-bromohexyl)-2-thiazoline, 55089-34-4.

References and Notes

(1) A. I. Meyers, "Heterocycles in Organic Synthesis", Wiley-Interscience, New York, N.Y., 1974.
(2) A. I. Meyers, R. Munavu, and J. Durandetta, *Tetrahedron Lett.*, 3929 (1972).
(3) G. Wittig and H. Rieff, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968).
(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(5) R. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **94**, 1021 (1972).
(6) (a) Sodium cyanoborohydride was also investigated with regard to its reduction efficiency and although 80–85% reduction was observed in many cases (0°, pH 4–5, MeOH, HCl), there were instances where the reagent caused overreduction. (b) G. M. Clarke and P. Sykes, *Chem. Commun.*, 370 (1965); E. L. Eliel, E. W. Della, and M. M. Rogic, *J. Org. Chem.*, **27**, 4712 (1962); J. C. Getson, J. M. Greene, and A. I. Meyers, *J. Heterocycl. Chem.*, **1**, 300 (1964); L. J. Altman and S. L. Richheimer, *Tetrahedron Lett.*, 4709 (1971).
(7) Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind. Butyllithium was purchased from Alfa-Ventron, Beverly, Mass. All solvents were dried using a recirculating still and refluxing over sodium benzophenone ketyl.
(8) E. W. Collington and A. I. Meyers, *J. Org. Chem.*, **36**, 3044 (1971).
(9) In recent experiments, it was found that lithium diisopropylamide in place of butyllithium leads to slightly higher yields of alkylation (10–15%).
(10) I. Heilbron, "Dictionary of Organic Compounds", Oxford University Press, London, 1965.
(11) Belgian Patent 634,738; *Chem. Abstr.*, **62**, P3941e (1965).
(12) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1956.
(13) A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 1783 (1969).
(14) G. Opitz, H. Wellman, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 3657 (1961).
(15) M. Bruzau, *Ann. Chim. (Paris)*, **7**, 257 (1934).
(16) W. Parker and R. A. Raphael, *J. Chem. Soc.*, 1723 (1955).

2-Thiazolines in Organic Synthesis. Formation of β-Hydroxy Aldehydes with Protected Hydroxy Groups. A Synthesis of Homoallylic Alcohols

A. I. Meyers,* James L. Durandetta, and Raphael Munavu

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received February 18, 1975

The addition of lithiothiazoline to carbonyl compounds provides an adduct which may be transformed into β-hydroxy aldehydes. The latter are rather labile compounds and may be stabilized by temporarily masking the β-hydroxy group to avoid retro-aldol condensation. The use of chloromethyl methyl ether to trap the thiazoline–carbonyl adduct **12** proved to be synthetically useful with respect to the preparation of β-oxy aldehydes. This masking group was stable to all the conditions necessary to construct β-hydroxy aldehydes. Wittig olefin condensations were employed to convert the β-hydroxy aldehydes to homoallylic alcohols, after release of the hydroxy protecting group.

In the previous article[1] we described the preparation of mono-, di-, and trialkylated acetaldehydes by sequential metalation–alkylation of 2-methyl-2-thiazoline (**1**). We wish to further exemplify the utility of **1** with respect to forming β-hydroxy aldehydes, **4**, the elusive primary adducts of aldol condensations,[2] and derivatives containing a temporarily masked hydroxy function **13**. The latter are useful precursors to homoallylic alcohols **16** by the usual Wittig condensations.

Metalation of **1** with *n*-butyllithium (THF, −78°) followed by addition of an aldehyde or ketone gave, after hydrolytic work-up, the hydroxy thiazoline in 80–95% yield. Attempts to purify **2**, when they were oils, by distillation resulted in thermal reversal to the original carbonyl component and **1**. Alternatively, attempts to pass the hydroxy thiazolines through silica gel columns resulted in considerable reversal to starting materials. However, this was not a major deterrent, since the crude hydroxy thiazolines were of sufficient purity (88–94% via NMR and TLC) to proceed further. Reduction to the thiazolidine derivative **3** was accomplished in 80–90% yield using aluminum amalgam in moist ether as previously described.[1] In some instances, the pure thiazolidine was isolated and completely characterized (Experimental Section), whereas in most cases the crude material (85–95% purity via NMR and TLC) was treated directly with mercuric chloride in aqueous acetonitrile. The β-hydroxy aldehydes **4** released in this mild fashion were obtained in good yield and the crude material was of 90–95% purity. Herein lies the major feature of this technique. The neutral conditions employed for the cleavage of **3** allow for the isolation of the usually labile β-hydroxy aldehydes. However, the extreme lability of these substances was consistently observed when more complex structures were involved. For example, 3-phenyl-3-hydroxypropional-