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.

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

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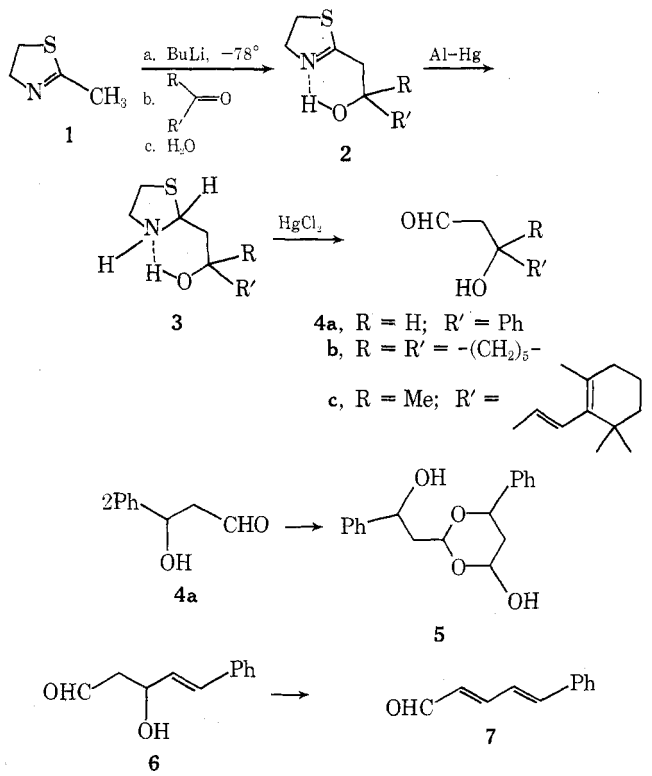
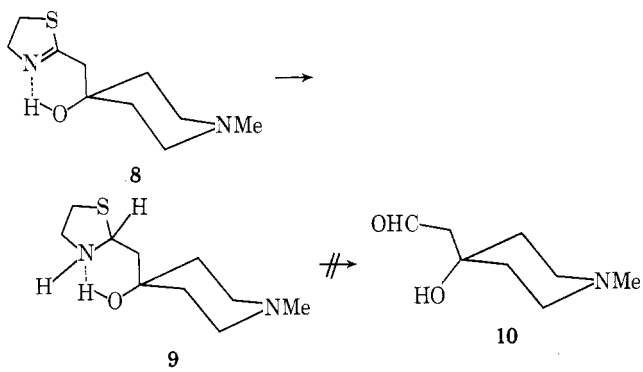
The addition of lithiothiazoline to carbonyl compounds provides an adduct which may be transformed into β-hydroxy aldehydes. The latter are rather labile compounds and may be stabilized by temporarily masking the β-hydroxy group to avoid retro-aldol condensation. The use of chloromethyl methyl ether 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-

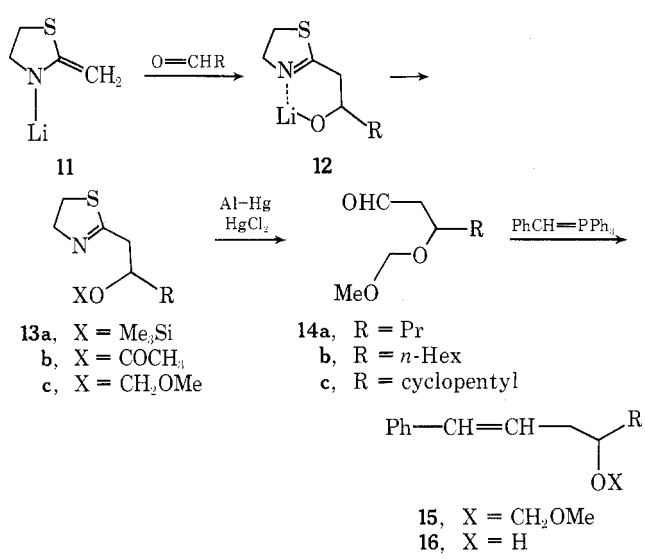


dehyde (**4a**) was isolated as its condensed dimer **5**, which when treated with 2,4-dinitrophenylhydrazine gave the 2,4-DNP of cinnamaldehyde. Reaction of the lithio salt of **1** with cinnamaldehyde gave good yields of the expected adduct **2** (R = H; R′ = CHC=CHPh) as well as the corresponding thiazolidine **3**. However, upon mercuric chloride cleavage of the latter, a mixture (~2.5:1) of the hydroxy aldehyde **6** and the diene aldehyde **7** was obtained. Thus, even this mild cleavage step caused dehydration. The use of buffers during the mercuric chloride step failed to change this result. The ease of dehydration to the dienal was demonstrated further when the mixture of **6** and **7** was passed through an alumina column providing pure **7**. When β-ionone was alkylated with the lithio salt of **1**, good yields of the adduct **2** were also obtained. The reduction to **3** and the cleavage to the β-hydroxy aldehyde **4c** also proceeded without event. However, the latter (90–95% purity) upon attempts at dehydration to the unsaturated aldehyde in a manner similar to that used for **7**, gave only retro-aldol products (β-ionone recovered quantitatively). The generality of the thiazoline alkylation and reduction was further demonstrated by use of 1-methyl-4-piperidone, which furnished **8** and **9**, respectively. Cleavage with mercuric chloride, however, gave only 1-methyl-4-piperidone and none of the hydroxy aldehyde **10** was isolated. These results suggested that a hydroxyl protecting group would be necessary to avoid the retro-aldol process.



8 **9** **10**

We, therefore, investigated the feasibility of introducing a hydroxyl protecting group during the sequence which would withstand all the conditions encountered along the route to the aldehyde. The most obvious point in which to introduce a masking group appears in the acylation of **11** to the lithio adduct **12**. Without isolation, **12** could be treated with an appropriate electrophile, furnishing **13**. When acetyl chloride was introduced to the solution of **12**, a poor (10–20%) yield of **13b** was obtained, the major product being elimination. Use of trimethylsilyl chloride gave **13a** in 70–75% yield, but subsequent treatment with mercuric chloride to free the protected aldehyde resulted in loss of the trimethylsilyl group. The mercuric ion was found to be responsible for the aqueous instability of the *O*-trimethylsilyl group and therefore this route was abandoned. On the other hand, introduction of a slight excess of chloromethyl methyl ether to the solution of **12** gave the methoxymethyl ethers **13c** in 63–72% distilled yield. The crude thiazoline product **13c** was always contaminated with 5–10% of the hydroxy thiazoline **13** (X = H) and attempts to use a larger excess of chloromethyl methyl ether resulted in poor yields of **13c**. It was shown that excess chloromethyl methyl ether slowly forms a highly colored, unstable quaternary salt with the thiazoline in THF solution. Reduction of **13c** using aluminum amalgam in moist ether proceeded in 80–88% yield to furnish the corresponding thiazolidines, which were then cleaved, using mercuric chloride, to the β-methoxymethyleneoxy aldehydes **14**. The protecting group survived the two previous steps without incident and the pure aldehydes were isolated in 42–53% yield.



11 **12**

13a, X = Me_3Si
b, X = $COCH_3$
c, X = CH_2OMe

14a, R = Pr
b, R = *n*-Hex
c, R = cyclopentyl

15, X = CH_2OMe
16, X = H

Several additional experiments were performed using ketones in place of aldehydes. The in situ methoxymethylation proceeded in 40–50% yield (as estimated by NMR spectra), which presumably was a result of increased steric interaction. Further experimentation will be needed before tertiary alkoxides can be adequately protected.

In order to demonstrate that these β-alkoxy aldehydes were suitable for further synthetic transformations, we elected to carry out typical Wittig couplings with benzyltriphenylphosphoranes. The couplings proceeded smoothly (71–84% yields) giving rise to the olefinic acetals **15** as mixtures of cis and trans isomers with the latter predominating by 2–4:1 (GLC). Geometrically pure materials could be collected from the GLC instrument although this was only done in one case.

Hydrolysis to the homoallylic alcohols **16** was accomplished in 95–98% yield by treatment with dilute hydrochloric acid in aqueous tetrahydrofuran. The reaction proceeded with no discernible dehydration to the corresponding dienes nor with any change in the cis:trans ratio present in the olefinic acetals.

In summary, this and the previous article demonstrate rather convincingly that a route to alkylated acetaldehydes and their β-hydroxy derivatives is indeed feasible and that homoallylic alcohols can be prepared with a wide variety of structural features whose architecture is compatible with the schemes described. This method should take its place among other routes to homoallylic alcohols which involve (a) addition of allylic metallics to carbonyl compounds, (b) reaction of formaldehyde with olefins,[3] (c) allylic ether rearrangements,[4] and (d) ring cleavage of THF derivatives.[5,6]

Experimental Section[7]

Condensation of Carbonyl Compounds with 2-Methyl-2-thiazoline (1). General Procedure. The lithio salt of 2-methyl-2-thiazoline was prepared as described previously.[1] A solution of 1.05 equiv of the carbonyl compound in 20 ml of dry THF was added at −78° over 5–10 min, resulting in the disappearance of the suspension of the lithiothiazoline. The mixture was allowed (2–3 hr) to warm to room temperature and then poured into 150 ml of ice–water, acidified to pH 2–3 with 6 *N* hydrochloric acid, and extracted with pentane–ether (1:1). The latter extracts containing only unreacted carbonyl compounds were discarded and the aqueous layer was rendered alkaline by slow addition of 20% sodium hydroxide. The resulting oil was removed by extraction with ether (three times) and the combined ether extracts were dried (K_2CO_3)

and concentrated to give 85–97% of crude hydroxy thiazoline **2**. Purification procedures varied for each compound; however, the purity (85–95%) of the crude material was sufficient to proceed further. Distillation of **2** could not be performed for purification since reversal to starting materials occurred for all compounds above 120–140°. The following were prepared according to this method.

2-(2-Hydroxy-2-phenethyl)-2-thiazoline (2, R = H; R′ = Ph) was obtained from 3.39 g (33 mmol) of **1**, 21.0 ml (34 mmol) of *n*-butyllithium in hexane, and 4.20 g (38 mmol) of benzaldehyde. The yield of product was 5.91 g (87%) of a viscous yellow oil: ir (neat) 3300, 1625 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5), 2.6–2.8 (d, 2), 3.0–3.3 (t, 2), 4.0–4.3 (t, 2), 3.7 (br s, 1, exchangeable with D_2O), 4.8–5.2 (t, 1). The product was 93 ± 2% pure as determined by the NMR spectrum. Attempts to assess purity by GLC led to varying amounts of starting materials which depended on the temperature of both the injection port and column.

2-(1-Hydroxycyclohexylmethyl)-2-thiazoline [2, R, R′ = $-(CH_2)_5-$] was prepared on the same scale as the previous product, giving 94% crude material (95% purity) which was recrystallized from hexane: mp 92–94°; ir (KBr) 3600–3000, 1615, 1170, 1018 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.0 (m, 10), 2.6 (t, 2), 3.3 (t, 2), 4.4 (m, 3, one proton exchanges with D_2O leaving this signal as a triplet).

Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03; S, 16.08. Found: C, 60.50; H, 8.43; N, 6.96; S, 16.30.

2-[(2-Hydroxy-4-phenyl)-*trans*-3-butenyl]-2-thiazoline (2, R = H; R′ = CH=CHPh) was obtained from 10 g of **1** and 10.35 g of cinnamaldehyde in 95% crude yield (18.8 g). Recrystallization from benzene–hexane (1:1) gave pure material: mp 81–83°; ir (KBr) 3600–3000, 1625, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (broad d, 2, long-range coupling through the C=N to C-4), 3.2 (t, m, 2), 4.2 (t, 2), 4.4–4.9 (m, 2, one proton exchanges with D_2O), 6.2 (d of d, J = 5, 16 Hz, 1), 6.7 (d, 1), 7.3 (m, 5); *m/e* 233 (M^+).

Anal. Calcd for $C_{13}H_{15}NSO$: C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found: C, 66.84; H, 6.44; N, 5.84; S, 13.98.

β-Ionone Adduct 2 (R = Me; R′ = β-iononyl) was prepared from 3.7 g of **1** and 7.13 g of β-ionone to give 10.9 g (97%) of crude product (~95% purity) as an oil: TLC (ether) gave one major spot (R_f 0.48) and several minor spots; ir (film) 3600–3610, 1623 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 6), 1.37 (s, 3), 1.63 (s, 3), 1.4–2.3 (m, 6), 2.7 (t, 2), 3.2 (t, 2), 4.2 (t, 2), 5.1 (m, 1, exchangeable with D_2O), 5.5 (d, J = 16 Hz, 1), 6.2 (d, J = 16 Hz, 1).

2-(4-Hydroxy-1-methylpiperdinylmethyl)-2-thiazoline (8) was prepared from 1.87 g (18 mmol) of **1** and 1.92 g (17 mmol) of 1-methyl-4-piperidone, giving 3.25 g (90%) of **8**: mp 88–89.5° (hexane); ir (KBr) 3600–3100, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.5 (m, 4), 2.3 (s, 1), 2.3–2.8 (m, 7), 3.2 (t, 2), 4.3 (m, 3, one proton exchangeable with D_2O leaving a triplet of two protons).

Anal. Calcd for $C_{10}H_{18}N_2OS$: C, 56.01; H, 8.46; N, 13.08. Found: C, 56.14; H, 8.61; N, 12.84.

Reduction to 2-(2-Hydroxy-2-alkylethyl)-2-thiazolidines (3). General Procedure. The aluminum amalgam was prepared as previously described[1] from either aluminum foil or granular aluminum (8–20 mesh) and the reductions were carried out in ether which had been previously saturated with water (or deuterium oxide). The thiazolines **2** or **8** dissolved (0.05–0.1 *M*) in moist ether were treated with the freshly prepared amalgam (10–12 g-atoms excess) and the mixture was heated to reflux gently for 2 hr. The solids were removed by filtration and washed with small portions of ether. The combined ethereal solutions were dried (K_2CO_3) and concentrated to leave the crude thiazolidines. Purification was only performed on crystalline products although the spectral data indicated that all reduced materials were at least 90% pure and could be carried on to produce the aldehydes.

2-(2-Hydroxy-2-phenethyl)-1,3-thiazolidine (3, R = H; R′ = Ph) was obtained in 86% yield: mp 81–82.5; ir (KBr) 3250, the peaks at 1630 (C=N) and 2350 cm^{-1} (SH) were absent, indicating complete reduction and no ring cleavage to mercapto amines; NMR ($CDCl_3$) δ 4.4–5.1 (m, 2), 2.7–3.6 (m, 6, two protons were exchangeable with D_2O), 1.8–2.3 (m, 2).

Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.09; H, 7.15; N, 6.50.

2-(1-Hydroxycyclohexylmethyl)-1,3-thiazolidine [3, R, R′ = $-(CH_2)_5-$] was prepared in 97% yield: mp 81–82° (from silica gel chromatography); ir (KBr) 3200, 1445, 1200, 973, 945, 920, 905 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.1 (m, 10), 2.4–3.6 (m, 2, exchanges with D_2O), 3.0 (m, 2), 3.3 (m, 2), 4.8 (d of d, 1); MS *m/e* 201 (M^+), 183, 158, 155, 154, 103, 99, 88 (base).

2-[(2-Hydroxy-4-phenyl)-*trans*-3-butenyl]-1,3-thiazolidine (3, R = H; R′ = CH=CHPh) was prepared in 94% crude yield: mp 79–81° [benzene–hexane (1:1)]; ir (KBr) 3240, 3140, 1595, 1490 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.2 (m, 2), 2.6–3.5 (m, 6, two protons exchange with D_2O), 4.6 (m, 2), 6.1 (d of d, J = 4, 16 Hz, 1), 6.6 (d of d, J = 2, 16 Hz, 1), 7.2 (m, 5); *m/e* 235 (M^+).

β-Ionyl-1,3-thiazolidine (3, R = Me; R′ = β-iononyl) gave 82.4% of crude product (>90% purity) which was recrystallized from hexane: mp 90–91°; ir (KBr) 3600–3100, 1460–1430, 1370, 1360, 1215, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (s, 6), 1.25 (s, 3), 1.7 (s, 3), 1.3–2.2 (m, 8), 2.5–3.5 (m, 4, two protons exchange with D_2O), 4.8 (t, 2), 5.5 (d, J = 16 Hz, 1), 6.3 (d, J = 16 Hz, 1); MS *m/e* 295 (M^+), 281, 262, 237, 193, 192, 177 (base), 143, 88.

2-(4-Hydroxy-1-methylpiperdinylmethyl)-1,3-thiazolidine (9) was obtained in 83% yield as a viscous oil: ir (film) 3600–3000 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.0 (m), 2.25 (s, 3), 2.2–3.5 (m), 4.9 (t, 1); *m/e* 216 (M^+). Cleavage to the corresponding aldehyde **4** [R, R′ = $-(CH_2)_4NMe$] proceeded only to return 1-methyl-4-pyridone and no aldehydic product could be isolated.

Cleavage to β-Hydroxy Aldehydes 4. General Procedure. The thiazolidine (1.5 g) was dissolved in 3 ml of acetonitrile and slowly added to a solution of mercuric chloride (2.5 g) in 30 ml of 80% acetonitrile–water which resulted in a suspension. The mixture was stirred for 1.5 hr and then diluted with 25 ml of water and filtered. The filtrate was extracted several times with ether–pentane (1:1) and the organic layer was dried (K_2CO_3 or $MgSO_4$) prior to concentration. The crude aldehydes were generally 90+% pure. The following were prepared in this manner.

3-Phenyl-3-hydroxypropionaldehyde dimer (5) was obtained in 75% yield as a viscous oil: ir (neat) 3400 cm^{-1}, no C=O absorption; NMR ($CDCl_3$) δ 7.0–7.4 (m, 10), 4.1–4.8 (m, 4), 1.0–2.7 (m, 6). Treatment of the dimer with 2,4-dinitrophenylhydrazine solution gave the 2,4-DNP derivative of cinnamaldehyde, mp 251–252° (lit.[8] mp 252°).

2-(1-Hydroxycyclohexyl)acetaldehyde [4b, R, R′ = $-(CH_2)_5-$] was prepared in 94% yield: mp 92–94° (hexane); ir (KBr) 3440, 2740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (br s, 10), 2.6 (d, J = 1.5 Hz, 2), 3.5 (br s, 1, exchangeable with D_2O), 10.0 (t, J = 1.5 Hz, 1). On standing at room temperature for several hours, the product slowly dehydrates to the α,β- and β,γ-unsaturated aldehyde as seen by vinyl absorptions appearing in the 5–6-ppm region. The hydroxy aldehyde is stable for long periods of time when stored in the freezer (−20°). A 2,4-DNP derivative gave mp 194–195° and when admixed with an authentic sample of the 2,4-DNP of cyclohexylidineacetaldehyde[9] produced no melting point depression.

Aldol of β-ionone and acetaldehyde 4c (R = Me; R′ = β-iononyl) was obtained in 64% yield (>90% purity) from the mercuric chloride cleavage as a viscous oil: ir (film) 3430, 2730, 1721, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (s, 6), 1.4 (s, 3), 1.63 (s, 3), 1.0–2.4 (m, 6), 2.65 (d, J = 2 Hz, 2), 3.4 (br s, 1, exchangeable with D_2O), 5.5 (d, J = 16 Hz, 1), 6.2 (br d, 1), 10.0 (t, J = 2 Hz, 1). Attempts to dehydrate **4c** to the unsaturated aldehyde by passing through neutral alumina (activity 1) gave only β-ionone by a retro-aldol reaction.

5-Phenyl-2,4-pentadienal (7). Mercuric chloride cleavage of the corresponding thiazolidine **3** gave, after work-up, a mixture of the β-hydroxy aldehyde **6** and the dienal **7**. Passage through acid-washed alumina (hexane–ether) furnished **7**, mp 37–39° (lit.[9] mp 37–39°).

2-(2-Cyclopentyl-2-methoxymethyloxyethyl)-2-thiazoline (13c, R = Cyclopentyl). A solution of 2-methyl-2-thiazoline (**1**, 9.76 g, 96.6 mmol) in 95 ml of dry THF was cooled to −78°. *n*-Butyllithium (44.5 ml, 97.8 mmol) in hexane was added dropwise over 35–40 min. The resulting suspension was stirred for 30 min after *n*-butyllithium addition and 11.1 ml (106 mmol) of cyclopentanecarboxaldehyde was added over 30 min at −78°. The clear solution was stirred for 30 min and then allowed to warm to ambient temperature (2–3 hr). Chloromethyl methyl ether (7.5 ml, 2–3% excess) was added and the solution was stirred overnight, after which it was poured into 100 ml of ice–water. The pH of the aqueous mixture was adjusted to 2–3 with 6 *N* hydrochloric acid while kept at 0–5° and extracted with 100 ml of hexane. The organic layer was discarded and the aqueous layer was neutralized to pH 10 using 20% sodium hydroxide, saturated with sodium chloride, and extracted with 4 × 100 ml of ether. The dried extracts (K_2CO_3) were concentrated, giving 21.9 g of an oil which was distilled (bulb-to-bulb) furnishing 16.6 g (72%) of **13c**: ir (film) 1625, 1450, 1210, 1145 cm^{-1}; NMR ($CDCl_3$) δ 4.75 (AB quartet, $-OCH_2O$), 4.2 (t, 2), 3.8 (q, −CHO), 3.4 (s, 3), 3.2 (t, 2), 2.8 (d, 2), 1.1–2.2 (m, 9); *m/e* 243 (M^+).

2-(2-Methoxymethyloxyoctyl)-2-thiazoline (13c, R = *n*-Hexyl). Under the same reaction conditions, 9.48 g of **1**, 43.5 ml of

n-butyllithium, 13.8 ml (1.1 equiv) of *n*-heptaldehyde, 7.25 ml (1.03 equiv) of chloromethyl methyl ether, and 95 ml of THF were used. Bulb-to-bulb distillation gave 15.3 g (64%) of product: ir (film) 1625, 1150, 1095, 1035 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 13), 2.8 (d, 2), 3.3 (t, 2), 3.4 (s, 3), 4.0 (q, 1), 4.3 (t, 2), 4.75 (s, 2).

Anal. Calcd for $C_{13}H_{25}NO_2S$: C, 60.19; H, 9.71. Found: C, 60.26; H, 9.87.

2-(2-Methoxymethyloxypentyl)-2-thiazoline (13c, R = *n*-Propyl). Under the same reaction conditions, 5.2 g of **1**, 24.0 ml of *n*-butyllithium, 4.95 ml of butyraldehyde, 3.95 ml of chloromethyl methyl ether, and 65 ml of THF were used. Purification of the crude reaction product on 15 g of silica gel (hexane–benzene) gave 7.05 g (72%) of pure product: ir (film) 1622, 1150, 1095, 1035, 910, 673 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (m, 3), 1.2–1.8 (m, 4), 2.75 (d of d, J = 7, 2 Hz, 2), 3.3 (t of d, J = 7, 2 Hz, 2), 3.4 (s, 3), 4.0 (p, 1), 4.2 (t, 2), 4.7 (s, 2).

2-(2-Methoxymethyloxyphenethyl)-2-thiazoline (13c, R = Ph). Under the same reaction conditions, 1.81 g of **1**, 8.4 ml of *n*-butyllithium, 2.0 ml of benzaldehyde, 1.36 ml of chloromethyl methyl ether, and 35 ml of THF were used. Bulb-to-bulb distillation furnished 3.42 g (75%) of product: ir (film) 1620, 1145, 1095, 1060, 1020 cm^{-1}; NMR ($CDCl_3$) δ 2.9 (d, 2), 3.2 (t, 2), 3.3 (s, 3), 4.2 (t, 2), 4.5 (s, 2), 5.0 (d of d, 1), 7.3 (m, 5).

Reduction of 13c to Thiazolidines. General. The previously described preparation of aluminum amalgam was employed. A tenfold excess of aluminum foil was used. Approximately 100 ml of moist ether was used for each 2.0–2.5 g of thiazoline **13c**. This solution was added to the amalgam immediately after its preparation and the mixture was stirred vigorously. Spontaneous reflux usually occurred; however, if it did not, heat was applied to the flask to bring about gentle reflux. Progress of the reduction was followed by TLC and the complete absence of starting material was noted after 2–4 hr. Isolation of the thiazolidines was identical with that described for **3**. No attempts were made to purify the products, although cursory examination by NMR and ir spectroscopy indicated that the products were 85–95% pure, with crude yields of 87–94%.

3-(Methoxymethyloxy)alkylacetaldehydes (14). General Procedure. The crude thiazolidines from above were dissolved in 30–40 ml of acetonitrile–water (4:1). Solid sodium bicarbonate (100–200 mg to neutralize any hydrochloric acid that might form) was added followed by 2.5–3.0 g of mercuric chloride. The immediately formed precipitate, which often became pasty and required mechanical separation, was stirred or manually agitated for 1–2 hr. Saturated brine was added (30–40 ml) and the solids were removed by suction filtration. Extraction and washing of the aqueous solution and the solids, respectively, with *n*-hexane gave a combined *n*-hexane extract which was washed once with cold 2 *N* hydrochloric acid followed by 5% aqueous bicarbonate. Drying (K_2CO_3) and concentration gave the protected aldehydes **14** listed below.

3-(Methoxymethyloxy)hexaldehyde (14a) was obtained in 55% distilled yield: bp 78–80° (20 Torr); ir (film) 2710, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.9–1.8 (m, 7), 2.6 (d of d, 2), 3.4 (s, 3), 4.1 (p, 1), 4.7 (s, 2), 9.8 (t, 1); *m/e* 160 (M^+).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.76; H, 10.07.

3-(Methoxymethyloxy)nonaldehyde (14b) was obtained in 61% distilled yield: bp 73–74° (0.30 Torr); ir (film) 2710, 1723, 1640, 1370, 1205, 1150, 1100, 1031, 915 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, 3), 1.0–1.8 (m, 10), 2.6 (d of d, J = 7, 2 Hz, 2), 3.4 (s, 3), 4.1 (p, 1), 4.7 (s, 2), 9.8 (t, J = 2 Hz, 1).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.15; H, 10.80.

3-Cyclopentyl-3-(methoxymethyloxy)propionaldehyde (14c) was obtained in 59% distilled yield: bp 74–75 (0.35 Torr); ir (film) 2710, 1723, 1450, 1210, 1155, 1095, 1031, 915, 753 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.4 (m, 9), 2.6 (d of d, J = 7, 2 Hz, 2), 3.4 (s, 3), 4.0 (p, 1), 4.7 (s, 2), 9.8 (t, J = 2 Hz, 1).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.22; H, 9.83.

1-Alkyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = *n*-Propyl, *n*-Hexyl, Cyclopentyl). A suspension of benzyltriphenylphosphonium chloride (1.5 g) in 10 ml of dry THF was treated with an equivalent quantity of *n*-butyllithium at 0°. The reddish-brown solution was stirred for 45 min and 1.0 equiv of the aldehyde **14a** or **14c** in 1–2 ml of THF was added. The color of the phosphorane disappeared and the solution was stirred for 8 hr at room temperature. The reaction mixture was poured into 10–12 ml of water and acidified (pH 4) and the mixture was extracted with 4 × 25 ml of ether. The dried (K_2CO_3) extracts were concentrated and the residue was passed through 10–15 g of Florosil using hexane–benzene (1:1). The olefins were examined by GLC. The yields of **15** (R = *n*-propyl), **15** (R = cyclopentyl), and **15** (R = *n*-hexyl) were 78, 71, and 84%, respectively.

1-*n*-Propyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = *n*-propyl) was composed of 82% trans and 18% cis isomers. Collected from GLC (FFAP) was pure trans isomer: NMR ($CDCl_3$) δ 0.9 (m, 3), 1.5 (m, 4), 2.4 (t, J = 7 Hz, 2), 3.4 (s, 3), 3.6 (m, 1), 4.7 (s, 2), 6.1 (d of d, J = 6, 16 Hz, 1), 6.5 (d, J = 16 Hz, 1), 7.3 (m, 5).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.69; H, 9.22.

1-*n*-Hexyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = *n*-hexyl) was composed of 76% trans and 24% cis isomers. No separations were attempted. The NMR spectrum was quite similar to that of **15** (R = *n*-propyl) at chemical shifts downfield from 2 ppm.

1-Cyclopentyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = cyclopentyl) was isolated from Florosil (hexane–benzene) as a 63:37 mixture of trans:cis isomers. The NMR spectrum was indicative of the mixture and showed considerable similarities downfield from 2 ppm to **15** (R = *n*-propyl).

1-Alkyl-1-hydroxy-4-phenyl-3-butenes (16). The olefinic acetals **15** (0.5–0.6 g) were dissolved in a solution comprised of THF (0.23 ml), water (2 ml), and 6 *M* hydrochloric acid (5 ml) and heated at 50–55° for 6–8 hr. The reaction mixture was poured into an equal volume of saturated sodium chloride solution and the mixture was extracted with ether (3 × 10 ml). The dried ethereal extracts (K_2CO_3) were concentrated to give the homoallylic alcohols **16**. GLC analysis indicated that the ratio of the cis to trans isomers were unchanged.

1-(*n*-Hexyl)-1-hydroxy-4-phenyl-3-butene (16, R = *n*-hexyl) was recovered in 94% yield, cis:trans (25:75): ir (film) 3400, 3030, 3060, 3080, 1599, 1493, 1040, 963, 930, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.0 (m, 3), 1.2–1.8 (m, 10), 1.9 (s, 1, exchangeable with D_2O), 2.4 (d of d, m, 2), 3.7 (m, 1), 6.1 (d, J = 16, 0.76 Hz), 6.5 (d, J = 16, 0.76 Hz), 7.3 (m, 5); *m/e* 232 (M^+, weak).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.58; H, 10.27.

1-Cyclopentyl-1-hydroxy-4-phenyl-3-butene (16, R = cyclopentyl) was recovered in 95% yield, cis:trans (37:63): ir (film) 3400, 3020, 3060, 3080, 1595, 1490, 1445, 1030, 965, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.2 (m, 9), 2.1 (s, 1, exchangeable with D_2O), 2.4 (m, 2), 3.5 (m, 1), 5.6–6.7 (m, 2, cis and trans vinyl H), 7.3 (m, 5); *m/e* 216 (M^+, weak).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 82.99; H, 9.22.

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Registry No.—**1**, 2346-00-1; **2a**, 55089-92-4; **2b**, 55089-93-5; **2c**, 55089-94-6; **2** (R = H; R′ = CH=CHPh), 55089-95-7; **3a**, 55089-96-8; **3b**, 55089-97-9; **3c**, 55089-98-0; **3** (R = H; R′ = CH=CHPh), 55089-99-1; **4a**, 39850-43-6; **4b**, 39850-40-3; **4c**, 55090-00-1; **5**, 38754-96-0; **7**, 13466-40-5; **8**, 55090-01-2; **9**, 55090-02-3; **13c** (R = cyclopentyl), 55090-03-4; **13c** (R = *n*-hexyl), 55090-04-5; **13c** (R = *n*-propyl), 55090-05-6; **13c** (R = Ph), 55090-06-7; **14a**, 55090-07-8; **14b**, 55090-08-9; **14c**, 55090-09-0; *cis*-**15a**, 55090-10-3; *trans*-**15a**, 55090-11-4; *cis*-**15b**, 55090-12-5; *trans*-**15b**, 55090-13-6; *cis*-**15c**, 55090-14-7; *trans*-**15c**, 55090-15-8; *cis*-**16b**, 54985-33-0; *trans*-**16b**, 54985-37-4; *cis*-**16c**, 55090-16-9; *trans*-**16c**, 55090-17-0; benzaldehyde, 100-52-7; cyclohexanecarboxaldehyde, 2043-61-0; cinnamaldehyde, 104-55-2; β-ionone, 14901-07-6; 1-methyl-4-piperidone, 1445-73-4; acetaldehyde, 75-07-0; cyclopentanecarboxaldehyde, 872-53-7; chloromethyl methyl ether, 107-30-2; *n*-heptaldehyde, 111-71-7; butyraldehyde, 123-72-8.

References and Notes

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A Novel General Synthesis of 2-Substituted 1,2-Benzisothiazolin-3-ones. Cyclization of N-Substituted 2-Methoxycarbonylbenzenesulfenamides

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Reaction of methyl 2-mercaptobenzoate (2) or dimethyl 2,2′-dithiodibenzoate (3) with bromine, chlorine, or sulfuryl chloride gave 2-methoxycarbonylbenzenesulfenyl halides (4), which were not isolated. Halides 4 reacted with primary aliphatic, aromatic, and heterocyclic amines to yield N-substituted 2-methoxycarbonylbenzenesulfenamides 5. The latter underwent catalytic cyclization by strong bases, providing 2-substituted 1,2-benzisothiazolin-3-ones (6) in good to excellent overall yields. Evidence supports a general base catalyzed mechanism initiated by the abstraction of a proton from the sulfenamide nitrogen, and followed by intramolecular attack on the ester carbonyl group and expulsion of methoxide ion. This route is simple and presented as a new general method for the synthesis of 2-substituted 1,2-benzisothiazolin-3-ones.

The first preparation of 1,2-benzisothiazolin-3-one was reported[1] by McKibben and McClelland in 1923. A few years later the synthesis of 2-substituted 1,2-benzisothiazolin-3-ones (6) was achieved.[2] The chemistry of 6 was reviewed[3] in 1947. Since that time, it has been discovered that structure 6 possesses high antibacterial and antifungal activity,[4,5] which have also been reviewed recently.[6] A few years ago, the first commercial product (6, R = H) useful for the preservation of aqueous media containing organic matter was introduced.[7] It seems quite possible that other members of the benzisothiazolinone series will be introduced for similar commercial applications.

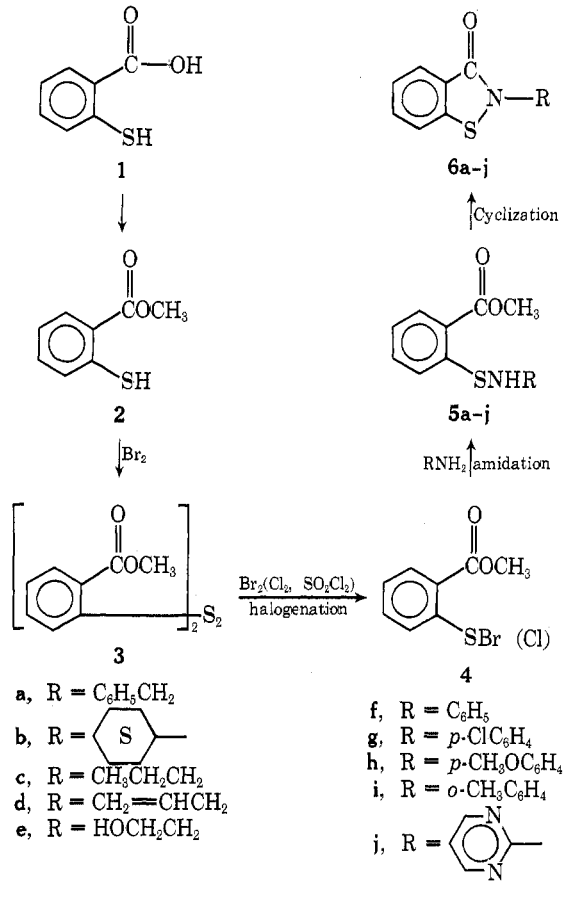
Benzisothiazolinones are prepared according to two well-established routes,[8] both of which use 2,2′-dithiodibenzoic acid as starting material. The acid is firstly[9] treated with thionyl chloride to give 2,2′-dithiodibenzoyl chloride, which is converted into the desired diamide, treated with bromine, and cyclized in boiling glacial acetic acid. Alternatively, halogenation of the acid chloride can precede amidation and cyclization. In this report, a third general synthesis utilizing methyl 2-mercaptobenzoate for starting material is presented.

Results and Discussion

Our continued interest in the chemistry of benzisothiazolinones led to a search for a different synthetic route, possibly circumventing the key intermediate 2,2′-dithiodibenzoyl chloride. For this purpose methyl 2-mercaptobenzoate (2), obtained directly by the Sandmeyer reaction on methyl anthranilate, was chosen as the starting material. It was thought that 2, or its oxidation product 3, could be easily converted into sulfenamides 5, which might subsequently undergo cyclization to 6 (Scheme I).

In this work, methyl 2-mercaptobenzoate (2) was prepared from commercially available 1 by passing dry hydrogen chloride through a solution of 1 in methanol.[10] Oxidation of 2 by the theoretical amount of bromine gave solid 3, which was also used extensively as starting material. In fact, oxidation of 2 to 3 by bromine was found to be a more convenient laboratory preparation as compared to the known preparation of 3 by esterification[11] of 2,2′-dithiodibenzoic acid or methanolysis[12] of its acid chloride. Furthermore, the isolation of 3 in high yield confirmed existing evidence[13] that nearly all of the thiol is converted into disulfide before the latter is cleaved into sulfenyl halide by halogenating agents. Attempts to prepare 6a from 2 by treating 4 with an equimolar amount of benzylamine in pyridine gave 7.

Scheme I



The fact that 7 (mp 131–132°) was not disulfide 3 (mp 131–133°) was shown conclusively by elemental analysis, mixture melting point, and the appearance of the methylene signal (singlet at 4.62 ppm) in the NMR spectrum. When an excess of benzylamine or triethylamine was used instead of pyridine, amidation of 4 to 5a proceeded