Formation of Pyrroles from Dihydro-1,3-oxazines[1]

Thomas A. Narwid and A. I. Meyers*[2]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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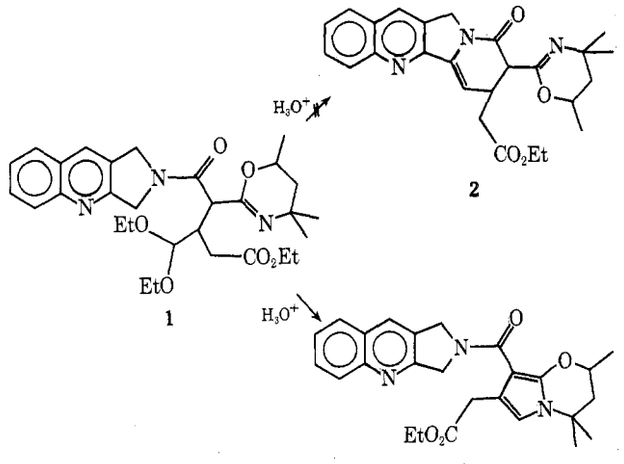
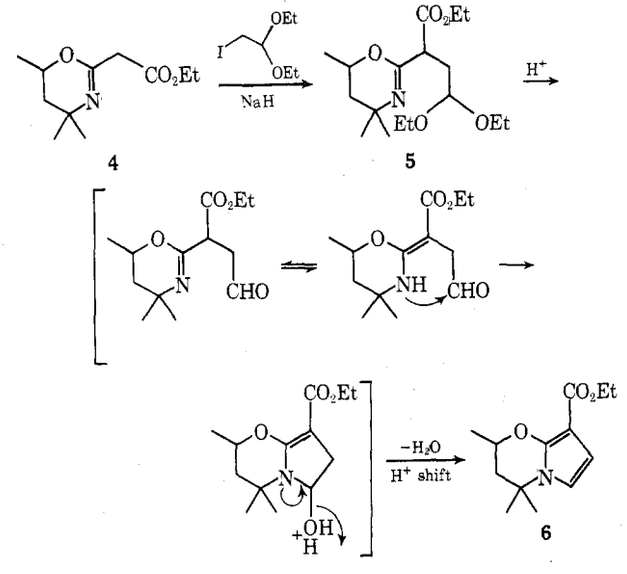
The reaction of carboethoxymethyloxazines with electrophilic aldehydes or olefins leads to a facile approach to polysubstituted pyrroles. The method allows, by appropriate choice of condition, either *N*-alkylpyrroles or fused pyrrolooxazines.

During the course of our total synthesis of camptothecin[3] we observed an unusually facile reaction involving the advanced intermediate 1 when an attempt was made to effect cyclization to the dihydropyridone **2.** Upon acid-catalyzed hydrolysis of **1,** none of the desired fused tetracyclic system could be obtained, although the fused pyrrole **3** was formed in 80% yield. After various attempts to circumvent this

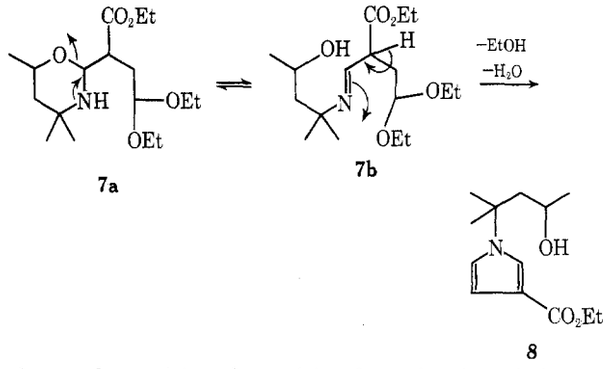


"undesirable" reaction, it soon became clear that **3** was the result of a much more favorable process than that leading to **2.** A study was undertaken to assess the generality of this pyrrole formation utilizing simpler systems and indeed proved that our anticipations were justified.

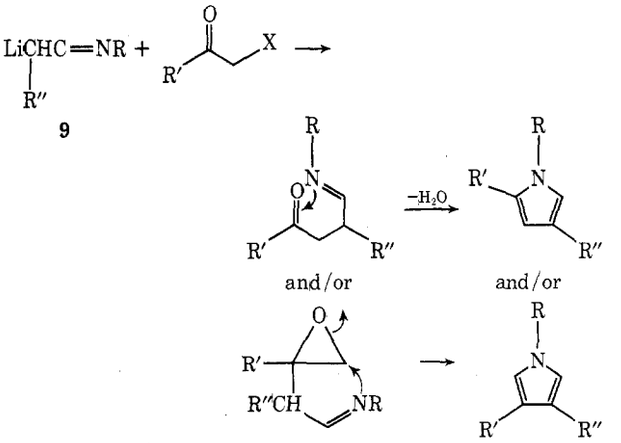
The oxazine ester **4** was employed as a suitable starting material, since it was readily available.[4] Alkylation of oxazine ester **4** with iodoacetaldehyde diethyl acetal in dimethyl sulfoxide using sodium hydride as base afforded the acetal ester **5** in 78% yield. Treatment of the latter with a



catalytic amount of trifluoroacetic acid in refluxing toluene, which had not been dried, for 2 hr led to the pyrrolooxazine **6** in 98% yield. None of the intermediates (proposed in brackets) could be isolated or detected in the crude reaction product. It was further found that reduction of the C=N link in **5** with aqueous sodium borohydride (−30°, pH 4–6)[4] gave **7a** in 92% yield as a crystalline product. Treatment of **7a** with a catalytic amount of trifluoroacetic acid in refluxing toluene led to an 83% yield of the *N*-alkyl-3-carboethoxypyrrole **8.** Mechanistically, the pyr-



role may be envisioned as arising from the ring–chain tautomerism[4] as shown in intermediates **7a,b** which ultimately undergoes ring closure after releasing the formyl group. This facile pyrrole synthesis is related to that recently reported by Wittig[5] which involves the reaction of lithio imines **9** with α-halo ketones. This reaction, however, may

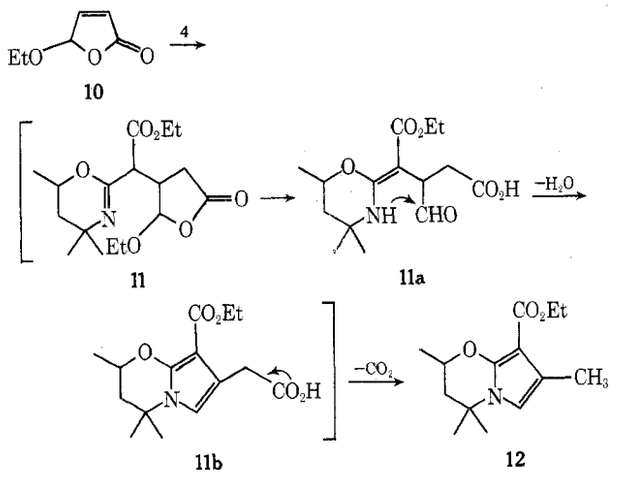


give rise to certain mixtures of isomers because of its dual pathway (*via* halide displacement or epoxide formation).

Another interesting reaction which led to pyrrole formation occurred when the ester oxazine **4** was treated with the unsaturated lactone **10** in acetonitrile or ethanol as solvent at 130–150° (sealed tube). No trace of the expected lactone **11** was observed. Instead, the pyrrole **12** was formed in 91% yield.

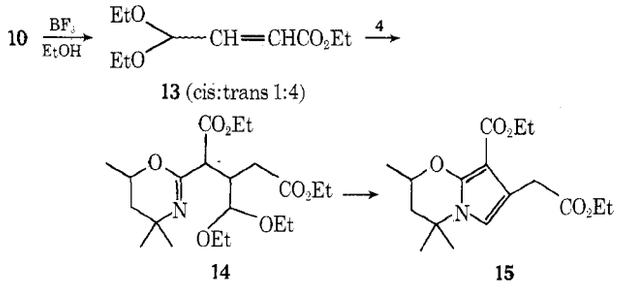
Although lactone **11** could not be detected in the reaction mixture, it most likely is a transient intermediate in the

formation of **12**. Following its formation, traces of water in the reaction mixture (the acetonitrile was not dried) would be expected to hydrolyze the lactone **11** to the aldehyde acid **11a**. With the free aldehyde now present, condensation to the pyrrole **11b** would occur followed by decarboxylation to give the pyrrole **12**. A similar mode of decarboxyla-



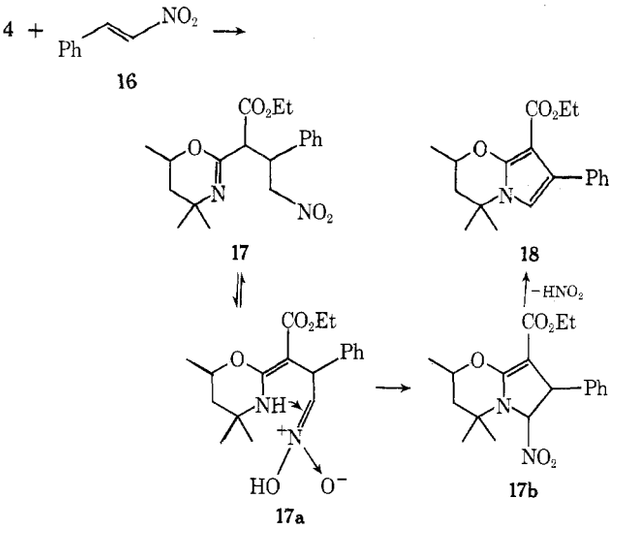
tion was noted for the free acid of **3** producing the corresponding methyl derivative.[3]

When lactone **10** was transformed into the unsaturated ester[3] **13** and treated with oxazine ester **4** (145°, EtOH, OEt^-), the adduct **14** was obtained in 62% yield. Heating



the latter at reflux in toluene containing a trace of trifluoroacetic acid produced the fused pyrrole **15** in 78% yield. Thus, while the free carboxylic group in **11b** is unstable and undergoes decarboxylation to **12**, the carboethoxy group in **14** remains intact en route to the pyrrole diester **15**. This was verified by hydrolysis of **14** in aqueous ethanol containing dilute hydrochloric acid. Under these conditions, a mixture (1:1) of **12** and **15** was indeed obtained.

The most novel and least expected pyrrole formation was observed when 1 equiv each of the oxazine ester **4** and β-nitrostyrene (**16**) were refluxed in *tert*-butyl alcohol for 20 hr. The crude viscous residue, after chromatography on basic alumina, afforded two products. The major component (63% yield) was the expected Michael addition product **17** while the minor component (28% yield) was fully characterized as the pyrrole **18**.



From a comparison of the infrared spectrum of the crude reaction product with that of the pyrrole **18**, it appears as though **18** was formed as a result of the reaction conditions, and not during the chromatographic separations.

If this is the case, the direct pyrrole formation may be considered to pass through intermediates **17a** and **17b** in an intramolecular Nef-type reaction. No attempt was made to optimize the pyrrole formation *via* the β-nitrostyrene route.

An effort was made to remove the *N*-alkyl group in the monocyclic pyrroles **8**, which would then lead to the unencumbered nucleus. Hydrolytic, photochemical, thermal and retro Michael additions (on the corresponding ketone) all failed to dealkylate **8**.[6]

In summary, a route to monocyclic pyrroles and their fused homologs appears viable from oxazine esters and their derivatives (amide-containing oxazines)[3] which place various substituents at the 1 and/or 2, 3, and 4 positions of the pyrrole nucleus.

Experimental Section[7]

Oxazine Ester Diethyl Acetal 5. To the oxazine **4** (5.0 g, 0.0235 mol) under an atmosphere of nitrogen in 25 ml of dry dimethyl sulfoxide (distilled from calcium hydride) was added sodium hydride (0.57 g, 1.0 g of 57% oil dispersion, 0.0235 mol). After hydrogen evolution had ceased, iodoacetaldehyde diethyl acetal (5.73 g, 0.0235 mol) was added dropwise at room temperature over a period of 10 min. The reaction mixture was then stirred for 16 hr, poured into 100 ml of ice water, and extracted with chloroform. The combined extracts were washed with water several times, dried over anhydrous potassium carbonate, and evaporated *in vacuo* to a yellow oil. Distillation (92–98°, 0.06 mm) afforded 6.0 g (78% yield) of **5** as a colorless oil. The analytical sample was chromatographed on silica gel (tlc, eluted with ether) followed by distillation (90–95°, 0.05 mm): ir (film) 1640, 1675, 1140–1120 cm^{-1}; nmr ($CDCl_3$) δ 4.58 (t, 1 H), 4.19 (t, 2 H, J = 7 Hz), 3.2–3.9 (complex multiplet, 5 H), 2.3–1.4 (m, 3 H), 1.4–1.1 (m, complex, 18 H); *m/e* 329 (molecular ion).

Anal. Calcd for $C_{17}H_{31}NO_5$: C, 61.98; H, 9.48; N, 4.25. Found: C, 61.82; H, 9.61; N, 4.32.

Pyrrolooxazine 6. To the oxazine acetal **5** (0.83 g, 2.52 mmol) in 10 ml of toluene was added trifluoroacetic acid (0.1 ml) and the reaction mixture was fitted with a Dean-Stark trap and refluxed under a nitrogen atmosphere for 2 hr. After cooling, the reaction mixture was washed with 10 ml of saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate and the toluene was removed under vacuum. The pale orange oil crystallized, 0.59 g (98% yield). The analytical sample was recrystallized twice from petroleum ether–ether: mp 82–83°; ir (neat) 1675, 1550 cm^{-1}; nmr ($CDCl_3$) δ 6.44 (d, 1 H, J = 4 Hz), 6.25 (d, 1 H, J = 4 Hz), 4.25 (q superimposed on a multiplet, 2 H, J = 7 Hz, m, 1 H), 1.90 (d, 2 H, J = 6 Hz), 1.47 (d, 3 H, J = 7 Hz), 1.50 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz); *m/e* 237 (molecular ion).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07. Found: C, 65.67; H, 7.90.

Tetrahydro-1,3-oxazine Acetal 7a. To the oxazine acetal **5** (1.64 g, 0.0050 mol) in 8 ml of tetrahydrofuran and 8 ml of ethanol (95%) cooled to −35 to −45° at pH 5 (made acidic at −35° with 9.7% hydrochloric acid solution) was added sodium borohydride solution dropwise (0.19 g, 0.005 mol dissolved in 1.5 ml of water and stabilized with 1 drop of 40% sodium hydroxide solution). During the slow addition of the borohydride solution (~20 min), the pH of the reaction mixture was maintained at 5 by dropwise addition of 9.7% hydrochloric acid solution as needed. After all the borohydride had been added, stirring was continued at −35 to −45° for 1 hr and then the reaction mixture was poured into a two-phase system of water (50 ml) (3 drops of 40% sodium hydroxide solution added) and dichloromethane (50 ml). After several extrac-

tions with dichloromethane, the combined extracts were dried over sodium sulfate, filtered and evaporated *in vacuo* to a pale yellow oil, 1.51 g.

The ir spectrum of the product showed only a very small amount of dihydrooxazine remaining. The product crystallized from pentane in the freezer: mp 54–55°; ir (neat) 3230, 1735 cm^{-1}; nmr ($CDCl_3$) δ 4.28 (4 H, complex multiplet), 3.60 (5 H, complex multiplet), 2.52 (1 H, J = 6.5 Hz), 2.0 (2 H, t, J = 6 Hz), 1.12 (m, 21 H); *m/e* 331 (molecular ion).

Anal. Calcd for $C_{17}H_{33}NO_5$: C, 61.60; H, 10.04; N, 4.23. Found: C, 61.51; H, 10.02; N, 4.29.

N,3-Disubstituted Pyrrole 8. The tetrahydrooxazine **7a** (0.55 g, 2.30 mmol) in 10 ml of toluene, along with a catalytic amount of trifluoroacetic acid, were refluxed for 2 hr under an atmosphere of nitrogen. The cooled solution was washed with 10 ml of saturated sodium bicarbonate solution, dried over anhydrous potassium carbonate, and concentrated *in vacuo* to an oil, 0.413 g. The total product was chromatographed on silica gel (tlc, 20 × 40 cm plate, eluted with acetone) and distilled (135–145°, 0.02 mm) to give 0.33 g (83% yield) of oily product: ir (film) 3350, 1705, 1695, and 1540 cm^{-1}; nmr ($CDCl_3$) δ 7.50 (m, 1 H), 6.82 (m, 1 H), 4.28 (q, 2 H, J = 7 Hz), 3.66 (m, 1 H), 1.92 (s, 1 H), 1.91 (s, 1 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 1.33 (t, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 6 Hz); *m/e* 239 (molecular ion).

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.41; H, 9.06; N, 5.96.

Pyrrolooxazine 12. The oxazine ester **4** (0.32 g, 1.5 mmol) and the lactone **10** (0.192, 1.5 mmol)[3] in 1 ml of dry ethanol were heated in a sealed Pyrex tube for 24 hr at 130–140°. The tube was cooled in a Dry Ice–acetone bath and opened, and the solvent was removed under vacuum. The deep scarlet residue partially crystallized. Trituration with ether–petroleum ether gave 0.097 g of light yellow crystalline solid, mp 107–108°. Evaporation of the filtrate gave a red oil which was chromatographed on silica gel (8.5 × 1 cm column) and eluted with ether. The first fractions afforded an additional 0.09 g of pyrrole (total yield 50%). The product was purified by sublimation (100–110°, 0.02 mm): mp 111–112.5°; ir (KBr) 1675, 1535 cm^{-1}; nmr ($CDCl_3$) δ 6.06 (q, 1 H, J = 1.5 Hz), 4.27 (q, superimposed on a multiplet, 2 H, J = 7 Hz, m, 1 H), 2.2 (d, 3 H, J = 1.5 Hz), 1.95 (s, 1 H), 1.83 (s, 1 H), 1.50 (d, 3 H, J = 6 Hz), 1.50 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz); *m/e* 251 (molecular ion).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.13; H, 8.40; N, 5.64.

When the oxazine ester **4** (0.93 g, 4.39 mmol) and the lactone **10** (0.56 g, 4.38 mmol) were heated at 140–150° for 4 hr in a sealed Pyrex tube in acetonitrile solvent and worked up as above, 1.0 g (91% yield) of **12** was obtained, mp 108–110°. The ir and nmr spectra were superimposable with those of the product obtained above.

Oxazine Diester 14. To the oxazine ester **4** (0.400 g, 1.88 mmol) and the unsaturated ester **13** (0.442 g, 2.18 mmol)[3] in 1.5 ml of dry ethanol (distilled from calcium hydride) in a Pyrex tube was added a catalytic amount of sodium ethoxide (prepared by dissolving ~15 mg of sodium metal in 0.3 ml of dry ethanol and then using 3 drops of this solution). The tube was sealed and heated at 145° for 42 hr. Concentration of the reaction mixture gave a viscous oil. The product **14** distilled at 120–145° (0.06 mm) (0.485 g, 62% yield): ir (film) 1740, 1670 cm^{-1}; *m/e* 415 (molecular ion).

Anal. Calcd for $C_{21}H_{37}NO_7$: C, 60.70; H, 8.98; N, 3.37. Found: C, 60.84; H, 9.01; N, 3.52.

Pyrrolooxazine 15. To the acetal **14** (0.357 g, 0.861 mmol) in 10 ml of toluene was added trifluoroacetic acid (3 drops), the flask was fitted with a Dean-Stark trap, and the contents were refluxed under a nitrogen atmosphere for 2 hr. The cooled solution was washed with 10 ml of saturated sodium bicarbonate solution and dried over sodium sulfate. The solvent was evaporated *in vacuo* to give 0.304 g of crude product which crystallized in a freezer overnight, 0.215 g (78% yield). The product crystallized from petroleum ether (bp 30–60°) (ether was used to dissolve product and then boiled off). Recrystallization from the same solvent system afforded the analytical sample: mp 94–95.5°; ir (film) 1740, 1675, 1550 cm^{-1}; nmr ($CDCl_3$) δ 6.24 (t, 1 H, J = 1.5 Hz), 4.21 (q, 2 H, J = 7 Hz), 4.28 (q, 2 H, J = 7 Hz), ~4.3 (m, 1 H), 3.68 (d, 2 H, J = 1.5 Hz), 1.92 (s, 1 H), 1.82 (s, 1 H), 1.48 (d, 3 H, J = 6 Hz), 1.48 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz), 1.27 (t, 3 H, J = 7 Hz); *m/e* 323 (molecular ion).

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.97; H, 7.98; N, 4.48.

Michael Addition of 4 to β-Nitrostyrene. Formation of 17 and 18. The oxazine ester **4** (2.88 g, 0.0135 mol) and β-nitrostyrene (**16**, 2.01 g, 0.0135 mol) were refluxed for 20 hr in dry *tert*-butyl alcohol. The solvent was evaporated *in vacuo* to give a light amber colored oil. The total product was chromatographed on alumina (Fisher, 80–200 mesh, 20 × 4 cm column). Elution was begun with benzene (650 ml), followed by increasing proportions of dichloromethane in benzene (5, 15, 25, 30, and 50%). These fractions afforded 1.3 g (28% yield) of pyrrole **18**: mp 136–137°; ir (mineral oil) 1700, 1545 cm^{-1}; nmr ($CDCl_3$) δ 7.41 (m, 5 H), 6.27 (s, 1 H), 4.13 (q, 2 H, J = 7 Hz), 4.43 (m, 1 H), 1.90 (d, 2 H), 1.5 (d, 2 H, J = 6 Hz), 1.5 (s, 6 H), 1.12 (t, 3 H, J = 7 Hz); *m/e* 313 (molecular ion).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.89; H, 7.74; N, 5.08.

Continued elution with dichloromethane and finally 95% ethanol afforded 3.0 g (63% yield) of viscous oil. The spectral data are consistent with **17**: ir (film) 1740, 1600, 1555 cm^{-1}; nmr ($CDCl_3$) δ 7.3 (m, 5 H), 5.15–4.80 (m, 2 H), 4.64–3.40 (m, 4 H), 1.80–0.7 (m, 14 H); *m/e* 362 (molecular ion).

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.68; H, 7.23; N, 7.77.

Iodoacetaldehyde Diethyl Acetal. To bromoacetaldehyde diethyl acetal (Aldrich, 19.7 g, 0.10 mol) in 250 ml of acetone was added sodium iodide (75.0 g, 0.2 mol) and the reaction mixture was refluxed for 6 days. The precipitated salts were removed by filtration and the solvent was evaporated *in vacuo*. The resulting mass was triturated with ether and the precipitate was filtered. Evaporation of the ether *in vacuo* gave a red oil. Distillation (32–34°, 0.075 mm) afforded 17.5 g (71% yield) of light yellow oil. The product was decolorized by filtration through finely ground sodium bisulfite: nmr (CCl_4) δ 4.60 (t, 1 H, J = 5.5 Hz), 3.56 (two quartets, 4 H, J = 7 Hz), 3.20 (d, 2 H, J = 5.5 Hz), 1.20 (t, 6 H, J = 7 Hz).

Anal. Calcd for $C_6H_{13}O_2I$: C, 29.5; H, 5.32; I, 52.1. Found: C, 29.43; H, 5.33; I, 52.09.

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Registry No.—**4**, 36867-19-3; **5**, 34579-33-4; **6**, 34579-31-2; **7a**, 34579-27-6; **8**, 34579-26-5; **10**, 2833-30-9; **12**, 51806-19-0; *cis*-**13**, 10602-40-1; *trans*-**13**, 2960-65-8; **14**, 34579-32-3; **15**, 34579-30-1; **16**, 102-96-5; **17**, 34579-29-8; **18**, 34579-28-7; iodoacetaldehyde diethyl acetal, 51806-20-3; bromoacetaldehyde diethyl acetal, 2032-35-1.

References and Notes

(1) Part 24 of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see G. R. Malone and A. I. Meyers, *J. Org. Chem.*, **39**, 623 (1974). A preliminary report of this study has appeared: A. I. Meyers, T. A. Narwid, and E. W. Collington, *J. Heterocycl. Chem.*, **8**, 875 (1971).
(2) Address all correspondence to this author at Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.
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(6) We thank Dr. Harvey Taylor for performing these experiments.
(7) All melting points are uncorrected. Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind.