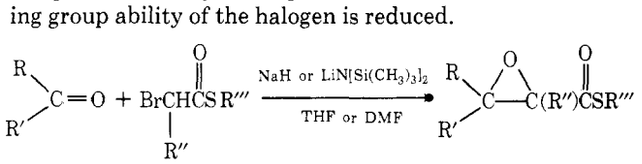
## The Darzens Synthesis of Glycidic Thiol Esters[1]

*Summary:* Using select conditions including polar, aprotic solvents, and nonnucleophilic bases, glycidic thiol esters have been prepared in high yield with the Darzens method when α-bromo thiol esters are used in place of α-chloro thiol esters.

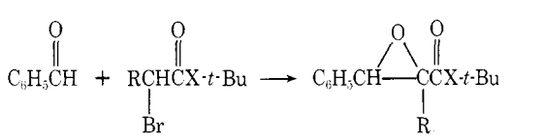
*Sir:* Despite the involvement of the thiol ester functional group in many metabolic transformations it has received much less attention in the literature than many other functional groups with little or no biological importance. There has been relatively little interest in the preparation of polyfunctional compounds containing the thiol ester group.[2] In connection with our interest in glycidic thiol esters,[3] we have developed the first Darzens synthesis of these compounds.[4] Interestingly the Darzens synthesis of glycidic thiol esters requires a nonnucleophilic base {NaH or LiN[$Si(CH_3)_3]_2$} and a polar, aprotic solvent (DMF or THF).[5] It is also important to use α-bromo thiol esters rather than α-chloro thiol esters. Chloro derivatives have been used in preference to bromo derivatives or iodo derivatives in the Darzens synthesis of epoxides substituted with all other types of electron-withdrawing groups reported to date.[6] Presumably the greater effectiveness of α-bromo thiol esters in the Darzens synthesis of glycidic thiol esters is due to an intramolecular nucleophilic acyl substitution reaction involving attack of the intermediate halohydrin oxyanion at the thiol ester group. This process may be expected to compete effectively with epoxide formation when the leaving group ability of the halogen is reduced.




To benzaldehyde (0.010 mol) and *tert*-butyl 2-bromothiolacetate[8] (**1a**, 0.010 mol) in dry THF (10 ml) at 0° under a nitrogen atmosphere was added $LiN[Si(CH_3)_3]_2$ (0.010 mol) in THF (12 mml) at a rate of 1 ml/min. The reaction was stirred at 0° for an additional 30 min and at room temperature for 30 min. Work-up followed by column chromatography on silica gel (Baker 60–200 mesh) eluting with petroleum ether followed by benzene–petroleum ether (1:1) gave a 9:1 mixture of trans and cis thiolglycidates (**2a**) in 59% yield. The pure trans isomer was obtained after preparative thin layer chromatography on silica gel (Merck GF254) developing five times with benzene–*n*-hexane (3:7). Recrystallization (*n*-hexane) gave *S-tert*-butyl (*E*)-3-phenyloxiranecarbothioate (**2a**) as colorless plates: mp 43–44°; nmr[9] ($CCl_4$, TMS) δ 7.20 (s, 5 H), 3.90 (d, 1 H, $J$ = 1.5 Hz), 3.33 (d, 1 H, $J$ = 1.5 Hz), 1.45 (s, 9 H); ir (KBr) 1660, 1690 $cm^{-1}$ (sh). *Anal.* Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.91; H, 6.99; S, 13.34.

The cis isomer, *S-tert*-butyl (*Z*)-3-phenyloxiranecarbothioate (**2a**), was the major product (70% *Z*, 30% *E*) when benzaldehyde and *tert*-butyl 2-bromothiolacetate (**1a**) were allowed to react with NaH in DMF solvent. The cis isomer was obtained as a colorless oil after short-path distillation [bath temperature 130–135° (1.0 mm)] of the mixture followed by thin layer chromatography on silica gel: nmr[9] ($CCl_4$, TMS) δ 7.25 (s, 5 H), 4.13 (d, 1 H, $J$ = 4.5 Hz), 3.72 (d, 1 H, $J$ = 4.5 Hz), 1.20 (s, 9 H); ir (thin film) 1665, 1695 $cm^{-1}$. Also of interest is the reaction of benzaldehyde with *tert*-butyl 2-bromothiolpropionate[10] (**1b**). A 57% sodium hydride dispersion in mineral oil (0.013 mol) was washed with *n*-hexane, and dry DMF (20 ml) was added at 0° under a nitrogen atmosphere. Benzaldehyde (0.010 mol) and *tert*-butyl 2-bromothiolpropionate (**1b**, 0.010 mol) in dry DMF (10 ml) were added dropwise over a period of 10–15 min. The reaction was stirred for an additional 30 min at 0° and then at room temperature for 30 min. Column chromatography on silica gel gave a 58% yield of a 9:1 mixture of trans and cis thiolglycidates (**2b**). The product was subjected to short-path distillation [125–130° bath temperature (0.15 mm)] to give pure *S-tert*-butyl (*E*)-2-methyl-3-phenyloxiranecarbothioate as a colorless oil: $n^{26}D$ 1.5287; nmr ($CCl_4$, TMS) δ 7.25 (s, 5 H), 4.05 (s, 1 H), 1.46 (s, 9 H), 1.20 (s, 3 H); ir (thin film) 1670 $cm^{-1}$. *Anal.* Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81. Found: C, 67.29; H, 7.15; S, 12.68.

The stereochemistry of this product was unequivocally established by independent synthesis using an exotic Schotten–Baumann procedure. Sodium (*E*)-2-methyl-3-phenyloxiranecarboxylate[11] (0.010 mol) was suspended in dry THF (25 ml) under a nitrogen atmosphere and the mixture was cooled to 0°. Pyridine (3–5 drops) was added followed by the dropwise addition over a period of 1 hr of freshly distilled oxalyl chloride (0.016 mol) in dry THF (5 ml) and the reaction mixture was stirred for an addditional 30 min at 0°. The THF was removed (below 15°) and DMF (40 ml) was added at 0° followed by immediate, separate, and simultaneous addition over a period of 20 min of *tert*-butyl mercaptan (0.010 mol) in DMF (5 ml) and Dabco (0.010 mol) in DMF (5 ml). The reaction was stirred at 0° for 4 hr and then at room temperature for an additional 2 hr before work-up. Column chromatography gave *S-tert*-butyl (*E*)-2-methyl-3-phenyloxiranecarbothioate (**2b**, 37%, $n^{26}D$ 1.5282). This compound had the same nmr and ir spectrum as the thiolglycidate prepared using the Darzens method.



| No. | 1 | | | | 2 | | |
|---|---|---|---|---|---|---|---|
| | X | R | Base | Solvent | % cis | % trans | % yield |
| a | S | H | $LiN[Si(CH_3)_3]_2$, NaH | THF | 10 | 90 | 59 |
| | | | NaH | DMF | 70 | 30 | 67 |
| b | S | $CH_3$ | NaH | DMF | 10 | 90 | 58[12] |
| c | O | $CH_3$ | NaH | DMF | 55 | 45 | 61 |

Bachelor and Bansal[13] have found that the per cent of cis isomer increases as the size of the ester alkyl group is increased in the reaction of benzaldehyde with alkyl 2-chloroacetates using KO-*t*-Bu in *t*-BuOH. This has also been our experience with the α-halopropionate oxygen esters. The cis isomer predominated in the reaction of benzaldehyde with *tert*-butyl 2-chloropropionate or *tert*-butyl 2-bromopropionate (**1c**) using either the KO-*t*-Bu–*t*-BuOH conditions (~75% cis) described by Bachelor and Bansal[13] or our NaH–DMF conditions (~55% cis). In contrast, in the

reaction of benzaldehyde with *tert*-butyl 2-bromothiolpropionate (**1b**) using the NaH–DMF conditions, the trans isomer predominated, although the cis thiolglycidate was favored in the reaction of *tert*-butyl 2-bromothiolacetate (**1a**) with benzaldehyde under the same conditions. Although the explanation for this result is not immediately apparent, the high percentage of the trans isomer obtained in the less polar THF solvent in the reaction of benzaldehyde with *tert*-butyl 2-bromothiolacetate (**1a**) could be explained on the basis of steric considerations assuming that the last, intramolecular substitution step in the reaction is rate limiting.[7] We are continuing our studies with glycidic thiol esters in an attempt to determine the origin of these unusual stereochemical results.

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## References and Notes

(1) Presented in part at the 6th Central Regional Meeting of the American Chemical Society, Detroit, Mich., April 21–24, 1974.
(2) For reviews of thiol ester chemistry, see T. C. Bruice in "The Chemistry of Organic Sulfur Compounds," Vol. 1, Pergamon Press, Oxford, 1961, p 421; M. J. Janssen in "The Chemistry of Functional Groups—The Chemistry of Carboxylic Acids and Esters," Interscience, London, 1969, p 724.
(3) J. Wemple, *J. Amer. Chem. Soc.*, **92**, 6694 (1970).
(4) An unsuccessful attempt has been reported: L. Field and C. G. Carlile, *J. Org. Chem.*, **26**, 3170 (1961).
(5) Protic solvents (alcohols) and nucleophilic (NaOEt) bases have been generally used in the Darzens reaction in the synthesis of epoxides substituted with a wide variety of electron-withdrawing groups. For example, aqueous methanolic NaOH has been used recently in the Darzens condensation of 1-chloro-3-diazopropanone with benzaldehyde: N. F. Woolsey and M. H. Khalil, *J. Org. Chem.*, **38**, 4216 (1973).
(6) M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 417 (1949). However, α-bromo esters have recently been shown to be preferred to α-chloro esters in the synthesis of glycidic esters from low molecular weight aldehydes such as acetaldehyde.[7]
(7) R. F. Borch, *Tetrahedron Lett.*, 3761 (1972).
(8) *tert*-Butyl 2-bromothiolacetate was obtained from bromoacetyl bromide, *tert*-butyl mercaptan, and pyridine as a colorless oil: $n^{26}$D 1.5077; nmr ($CCl_4$, TMS) δ 3.88 (s, 2 H), 1.48 (s, 9 H); ir (thin film) 1690 $cm^{-1}$.
(9) The epoxide proton coupling constants are in agreement with the trans (1.5 Hz) and cis (4.5 Hz) stereochemical assignments: R. L. Williamson, C. A. Lanford, and C. R. Nicholson, *J. Amer. Chem. Soc.*, **80**, 6389 (1958).
(10) $n^{26}$D 1.4965; nmr ($CCl_4$, TMS) δ 4.31 (q, 1 H, $J$ = 7.0 Hz), 1.77 (d, 3 H, $J$ = 7.0 Hz), 1.48 (s, 9 H); ir (thin film) 1690 $cm^{-1}$.
(11) Ethyl (*E*)-2-methyl-3-phenyloxiranecarboxylate was prepared according to the method of V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.*, **31**, 2509 (1966). It was hydrolyzed with NaOH in ethanol to give the corresponding sodium salt.
(12) The trans isomer also predominated (90% trans, 10% cis) in the reaction of benzaldehyde and *tert*-butyl 2-bromothiolbutyrate with NaH in DMF. It is interesting to note that in both cases the small amount of cis isomer was easily removed by short-path distillation at ~130°.
(13) See F. W. Bachelor and R. K. Bansal, *J. Org. Chem.*, **34**, 3600 (1969), and references cited therein.

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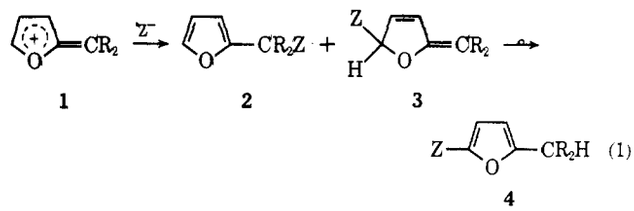
## Furfuryl Cationic Capture Processes. 5-Substituted $\Delta^{3,4}$-2,5-Dihydro-2-methylenefurans and Their Rearrangement to Furfuryl Derivatives

*Summary:* Decomposition of ethyl (2-furyl)diazoacetate (**9**) occurs carbenically to **17** and cationically by 1,1 and 1,5 solvent incorporation to derivatives of **2** and **3**; ring closures of **17** by hydroxylic solvents as catalyzed by silver(I) yield furans **3** which isomerize anionotropically to **2**.

*Sir:* Furfuryl cations (**1**) usually undergo nucleophilic conversion to furfuryl analogs (**2**, eq 1).[1a] Such cations (**1**)

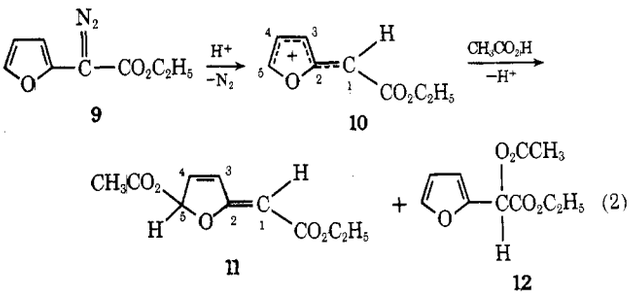


**1** **2** **3** **4** (1)

might also be expected to react at their 5 positions to give $\Delta^{3,4}$-2-alkylidene-2,5-dihydrofurans (**3**, eq 1) which tautomerize to 5-substituted 2-alkylfurans (**4**, eq 1).[1b-d,2] As yet, however, products analogous to **3** have been detected only in reaction of 2-furyldiphenylcarbinol (**5**) with methanolic hydrochloric acid to give $\Delta^{3,4}$-2-diphenylmethylidene-5-methoxy-2,5-dihydrofuran (**6**) and methyl 2-furyldiphenylcarbinyl ether (**7**).[3] Methanolic hydrochloric acid then effects prototropic rearrangement of **7** to 2-diphenylmethyl-5-methoxyfuran (**8**).[3]

We now report a series of cationic reactions of ethyl (2-furyl)diazoacetate (**9**) in which nucleophiles are incorporated at the 5-furano position (as **3** in eq 1); these products may then undergo anionotropic isomerization to ethyl α-substituted α-(2-furyl)acetates (**2**, eq 1) rather than tautomerization to ethyl (5-substituted 2-furyl)acetates (**4**, eq 1). Of further significance are that cationic conversion of **9** by nucleophiles may be directed to **2** or **3** by appropriate catalysts and that carbenic decomposition of **9** (eq 3) and subsequent reaction with hydroxylic solvents (eq 4) serves as a new method for synthesis of derivatives such as **3**.

Diazo ester **9**, prepared from ethyl (2-furyl)glyoxylate *p*-tosylhydrazone and tetramethylguanidine, reacts with acetic acid (eq 2) at 25° to give (*Z*)-$\Delta^{3,4}$-5-acetoxy-2-carbo-



**9** **10** **11** **12** (2)

ethoxymethylidene-2,5-dihydrofuran (**11**, 55%) and ethyl α-acetoxy-α-(2-furyl)acetate (**12**, 45%).[4] Esters **11** and **12** are apparently produced by reactions of acetic acid with α-carboethoxyfurfuryl carbenium ion **10** at its 5-furano and its furfuryl positions, respectively. It is not clear whether reaction to give **11** and **12** occurs by protonation of **9** or/and its subsequent carbene (**16**). The stereochemistry of **11** is assigned on the basis that it is not isomerized when heated and the supposition that the steric bulk about furano oxygen is less than that at C-3 H.

Isomerization of **11** occurs in acetic acid at 85° to give **12**; prototropic rearrangement of **11** to ethyl α-(5-acetoxy-2-furyl)acetate (**13**) does not take place. Reaction of **9** with acetic acid thus reveals that 1,5-cationic addition to give **11** is the major kinetic process, whereas **12**, formally the product of 1,1-cationic addition of acetic acid to **9**, may result from thermodynamic or kinetic circumstances. The present observations raise the possibility that solvolysis of furfuryl derivatives to furfuryl analogs (eq 1) may be more complex than has been apparent.

A study has also been made of reactions of **9** with alcohols. Thus **9** decomposes in methanol with nitrogen evolution to (*Z*)-$\Delta^{3,4}$-2-carboethoxymethylidene-5-methoxy-2,5-dihydrofuran[4] (**14**, 29%, eq 3) and ethyl α-methoxy-α-(2-furyl)acetate[4] (**15**, 17%, eq 3) along with ethyl 5-formyl-*cis*-