ature of 275.9 K. While these results are tentative, they certainly suggest that the sign of ρ as a mechanistic criterion is suspect. At temperatures below 276 K, 4-chlorotoluene is expected to be more reactive than toluene to bromine-atom abstraction. This corresponds to a change in the sign of ρ. All of our attempts to determine the relative reactivity at temperatures below 0 °C failed because of inhomogeneity of the reaction mixture.

The warning given by Kwart about giving mechanistic significance to the value of a primary isotope effect obtained at a single temperature and the value of applying his "full" criterion based upon the temperature dependence of the kinetic isotope effect has recently been reviewed.[7] The results presented here suggest a similar warning about giving significance to the sign and magnitude of the value of ρ obtained at a single temperature is also pertinent.

Experimental Section

Toluene-α,α,α-d_3 was obtained as at least 99% isotopically pure from Merck Sharp and Dohme Isotopes. Toluene-d_8 was obtained as 99+% isotopically pure from Aldrich Chemical Co. Both were used as supplied.

A flask containing a benzene solution of toluene, 4-chlorotoluene, and chlorobenzene, each ca. 1 M, was placed in a constant-temperature bath for 20 min and nitrogen was bubbled through the solution to degas it. A benzene solution of 0.67 M bromine was then added by using a pressure-equalizing addition funnel, and the solution was irradiated with a 275-W Sylvania sunlamp, placed externally, until all bromine was consumed as shown by the KI test. The total toluene to bromine molar ratio was 10:3. The rate of addition of bromine was adjusted so that the reacting solution remained nearly colorless. Evolved hydrogen bromide was continuously entrained by bubbling nitrogen through the solution, through a water-cooled condenser and into a sodium hydroxide trap. This procedure has been shown to minimize or eliminate the reaction of the aralkyl radical with HBr.[5] Gas chromatographic analysis was carried out as previously described.[8]

Registry No. Deuterium, 7782-39-0; hydrogen, 1333-74-0; toluene, 108-88-3; 4-chlorotoluene, 106-43-4.

Efficient Synthesis of 2-Methyl-4-Hydroxy-2*H*-1,2-Benzothiazine 1,1-Dioxides

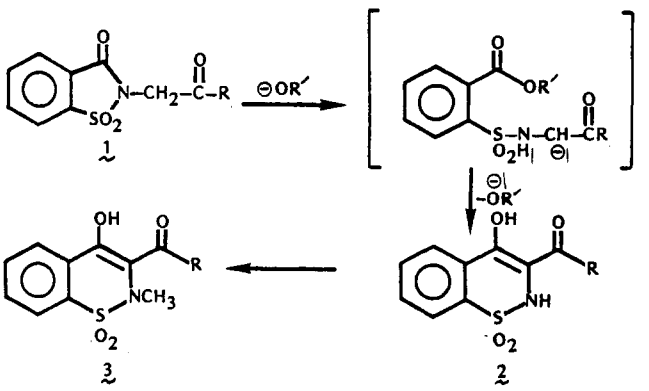
Paul D. Weeks,* Fredric J. Vinick, Ralph Breitenbach, and Stanley Jung

Pfizer Inc., Central Research, Groton, Connecticut 06340

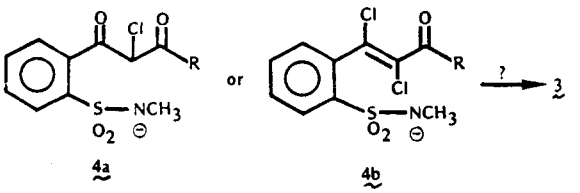
Received April 6, 1983

2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**3**) represent an important new class of antiinflammatory agents, which includes the drug piroxicam (**3**, R = 2-aminopyridyl).[1] Most previously reported syntheses of these valuable compounds proceed via the alkoxide-catalyzed rearrangement of a saccharin derivative (**1**) to afford a 4-hydroxy-1,2-benzothiazine (**2**),[2] which is then N-alkylated to afford the desired 2-methyl derivative, as shown in Scheme I.

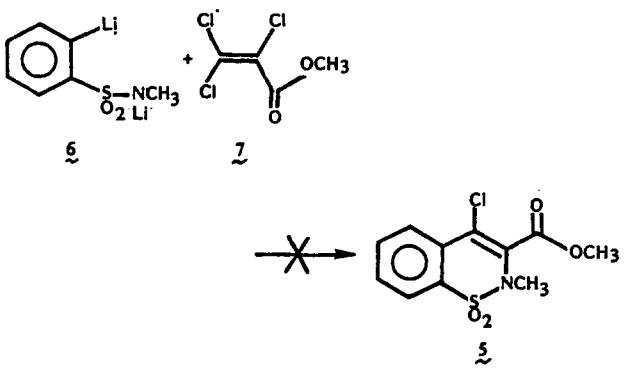
Scheme I



We wished to design a more efficient synthesis of compounds of type **3** and postulated that the closure of a derivative such as **4a** or **4b** might lead directly to the desired 2-methyl derivative.



Our initial attempts toward this end were directed toward the synthesis of **5**, potentially accessible through the reaction of the dianion **6**[3] with the readily available trichloroacrylate derivative **7**. It was presumed that the desired reaction would proceed via intermediate **4b** (R = OCH_3).



Unfortunately, only complex, intractable mixtures were obtained under a variety of experimental conditions. Returning to intermediate **4a** as an attractive precursor to benzothiazines **3**, we then investigated a Darzen's-like condensation of *N*-methylsaccharin (**8**) with chloroacetate **9**.[4] We report here the successful synthesis of **3** utilizing this pathway.

Results and Discussion

When readily available *N*-methylsaccharin (**8**) was combined with chloroacetate **9**[4] in the presence of 1 equiv of NaH in THF, vigorous gas evolution was noted. Surprisingly, upon quenching with dilute acid, only the starting materials **8** and **9** were recovered. However, when 2 equiv of metal hydride (NaH or KH) were employed and

(1) For a recent review on Benzothiazine Pharmacology, see: Lombardino, J. G.; Wiseman, E. H. *Trends Pharmacol. Sci.* **1981**, *2*, 132. Piroxicam literature has been reviewed by: Wiseman, E. H.; Lombardino, J. G., In "Chronicles of Drug Discovery"; Bindra, J. S., Lednicer, D., Eds.; Wiley: New York, 1981.

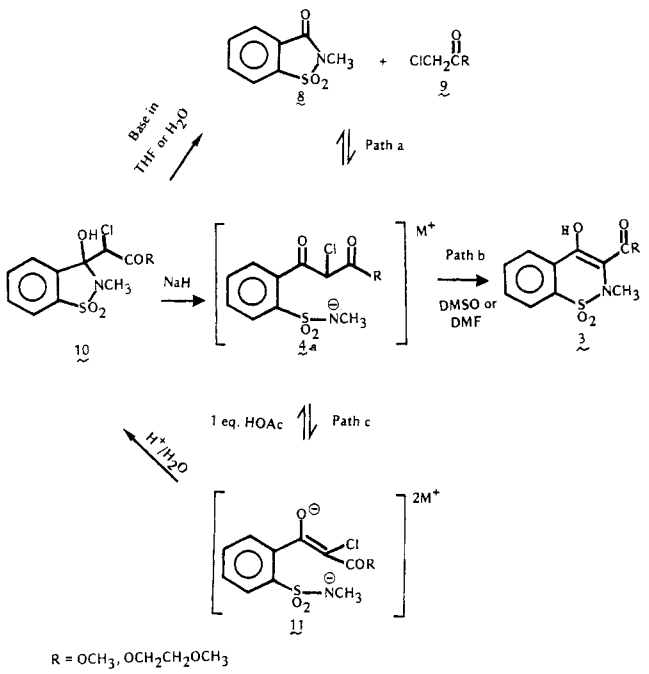
(2) For recent reviews on the chemistry of these systems, see: Catsoulacos, P.; Camoatsis, C. *J. Heterocycl. Chem.* **1979**, *16*, 1503. Lombardino, J. G.; Kuhla, D. E. *Adv. Heterocycl. Chem.* **1981**, *28*, 73. For a recent discussion on the alkoxide rearrangement 1 → 2 see: Schapira, C. B.; Perillo, I. A.; Lamdan, S. *J. Heterocycl. Chem.* **1980**, *17*, 1281.

(3) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900.

(4) The transformations discussed herein were carried out with both the methyl and methoxyethyl esters of **9**; identical results (see Experimental Section for details) were observed in all cases.

0022-3263/83/1948-3601$01.50/0

Scheme II



the reaction was quenched, a new product was isolated in good yield. NMR data suggested that this material was a 1:1 adduct of **8** and **9**. Although several possible structures for this new compound were considered, all spectral and analytical data (see Experiment Section) supported chlorohydrin derivative **10**.

Exposure of **10** to 1 equiv of NaH in THF afforded a fair yield of *N*-methylsaccharin (**8**) and the α-chloro ester **9**, as did treatment of **10** with NaOH in H_2O. However, reaction of **10** with 1 equiv of NaH in either DMF or Me_2SO gave good yields of the desired benzothiazine ester **3**. With the knowledge that a polar aprotic solvent, i.e., Me_2SO or DMF, was apparently necessary for the displacement of halide in the conversion of **10** into **3** via **4a**, we then studied the reaction of **8** and **9** in these solvents.

When equal amounts of **8** and **9** were added to 1 equiv of NaH in Me_2SO at 40 °C, vigorous gas evolution resulted. After acidification, a mixture of **8**, **10**, and **3** was obtained. When 2 equiv of NaH was added slowly to a 40 °C solution of **8** and **9** in Me_2SO or DMF, a good yield (76%) of the desired ester **3** was isolated.

A possible interpretation of the above results is presented in Scheme II. Initial reaction of the anion of **9** with *N*-methylsaccharin (**8**) generates a monoanion such as **4**; in THF this reaction is reversible, and quenching affords only starting material (path a). Irreversible halide displacement (path b) is facilitated by the polar aprotic solvents Me_2SO and DMF. Moreover, 2 equiv of base is necessary for the complete conversion into **3**, due to the high acidity of **3**. With 2 equiv of hydride in THF, a dianion such as **11** is apparently produced (path c) in which the chloride atom is no longer subject to displacement. Rapid quenching of **11** then leads to chlorohydrin **10**.

Consistent with this hypothesis, generation of a monoanion by treatment of authentic **10** with hydride in THF affords only **8** and **9**, while in Me_2SO or DMF such conditions yield only **3**. Additional control experiments also support these hypotheses. When the dianion **11** is generated as previously described (path c) and then 1 equiv of acetic acid is slowly added to the THF solution, **8** and **9** are the sole products isolated upon standard workup. In contrast, when the same sequence is carried out but the THF is removed and replaced by Me_2SO *before* the addition of 1 equiv of a proton source (HOAc), only **3** is produced.

Conclusion

The condensation of α-halo acetate **9** with *N*-methylsaccharin can follow a variety of reaction pathways; the reaction is highly dependent on the type of solvent and amount of base employed. the use of 2 equiv of metal hydride in DMF or Me_2SO effects a high-yield, one-step conversion of *N*-methylsaccharin (**8**) and chloroacetate **9** (both readily available) to the valuable 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**3**).

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded by using a Perkin-Elmer Model 21 727B spectrometer. NMR spectra were obtained with a Varian XL-100 or LM360L spectrometer with Me_4Si as an internal standard. Mass spectra were taken with an AEI MS-30 mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. The analytical thin-layer chromatography (TLC) was performed on Brinkman precoated silica gel plates. Unless otherwise noted, plates were eluted with a 9:1 benzene/acetic acid solvent system, with UV visualization, where **8** has an R_f of 0.65, **3** (both R = OCH_3 and $OCH_2CH_2OCH_3$) has an R_f of 0.60 ($FeCl_3$ positive), and **10** has an R_f of 0.30. *N*-Methylsaccharin was obtained from Eastman Kodak. Methyl chloroacetate (**9**, R = OCH_3) was available from Aldrich Chemical Co. Methoxyethyl chloroacetate [bp 79 °C (15 mm)] was obtained by reaction of chloroacetyl chloride (Aldrich Chemical Co.) and 2-methoxyethanol under standard conditions. Gas chromatographic (GC) analysis of **9** (R = $OCH_2CH_2OCH_3$) was done by using a Varian 90P instrument (130 °C, 5% XE-60, 5 ft × 1/4 in. column, 60 cm^3/min flow rate); retention time of **9** (R = $OCH_2CH_2OCH_3$) = 5.6 min. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to usage.

Reaction of *N*-Methylsaccharin (8) with Methoxyethyl Chloroacetate (9, R = $OCH_2CH_2OCH_3$) in the Presence of 1 Equiv of NaH. To a solution THF (15 mL), **8** (1.97 g, 0.01 mol), and **9** (R = $OCH_2CH_2OCH_3$; 1.52 g, 0.01 mol) was added 99% NaH (Alpha; 0.24 g, 0.01 mol), and the reaction mixture was heated to 40 °C for 2 h. Gas evolution was noted upon the NaH addition. Aliquots were removed every 10 min, quenched by 5% HCl, and extracted with CH_2Cl_2, and the extracts were subjected to GC and TLC assay as described above. There was no decrease in the amount of **8** and **9** observed under these conditions. Final quenching of the remaining reaction mixture (about half of the initial volume) with 50 mL of cold 5% HCl and filtration yielded 0.80 g (40%) of *N*-methylsaccharin **8**. None of the chlorohydrin **10** or the ester **3** was seen under these conditions by TLC assay.

Reaction of *N*-Methylsaccharin (8) with Methoxyethyl Chloroacetate (9, R = $OCH_2CH_2OCH_3$) in the Presence of 2 Equiv of NaH. Isolation of the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$). In a flame-dried flask under an N_2 atmosphere was placed 11.6 g of sodium hydride (50% dispersion in mineral oil, 0.24 mol). The mineral oil was then removed by pentane washing and decantation, and dry tetrahydrofuran (50 mL) was added followed by *N*-methylsaccharin (20.0 g, 0.10 mol) in 30 mL of tetrahydrofuran. This mixture was heated to 40 °C, and a solution of methoxyethyl chloroacetate (15.4 g, 0.10 mol) in THF was added dropwise over 1 h. An exothermic reaction with gas evolution occurred, and a temperature of 40–50 °C was maintained for 2 h following this addition. TLC analysis of a HCl quenched aliquot at this time showed good conversion to a new product, **10**, with only a trace of **8** remaining. The reaction was then quenched slowly by pouring the mixture into a cooled, well-stirred solution of 500 mL of 5% HCl. The aqueous solution, with a gummy solid visible, was extracted with four portions of dichloromethane (100 mL each). The organic layers were combined, dried ($MgSO_4$), and concentrated to yield 37.6 g of a viscous yellow orange oil. This crude oil was dissolved in hot dichloromethane, and hexane was added until turbidity was observed. Cooling and filtration produced 20.65 g of **10** (R = $OCH_2CH_2OCH_3$), mp 125.5–126.5 °C. The filtrate was concentrated to yield another

two crops of **10** (methoxyethyl 1,2-dihydro-3-hydroxy-2-methyl-1,2-benzisothiazole-3-chloroacetate 1,1-dioxide) weighing 2.1 g. The combined yield of crystalline **10** was 65%. This material was recrystallized to a constant melting point from dichloromethane/hexane to yield pure **10**: mp 133–133.5 °C; IR (KBr) 3250, 1754 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.6–8.2 (5 H, m), 5.1 (1 H, s), 4.0 (2 H, m) 3.3 (2 H, m), 3.1 (3 H, s), 2.7 (3 H, s); ^{13}C NMR (Me_2SO-d_6) δ 23.0 (q), 58.1 (q), 60.6 (d), 65.0 (t), 69.2 (t),88.0 (s), 120.4 (d), 126.1 (d), 131.1 (d), 133.3 (d), 134.3 (s), 136.7 (s), 165.8 (s). Anal. Calcd for $C_{13}H_{16}O_6SNCl$: C, 44.64; H, 4.61; N, 4.00; S, 9.17; Cl, 10.14. Found: C, 44.29; H, 4.65; N, 3.98; S, 9.00; Cl, 10.48.

Isolation of the Chlorohydrin 10 (R = OCH_3). In an analogous fashion to the example above, *N*-methylsaccharin (15.7 g, 0.08 mol) and methyl chloroacetate (8.67 g, 0.08 mol) were reacted with NaH (0.20 mol) in THF to yield, after the workup, 21.0 g of an amber oil. NMR and TLC analysis of this oil indicated it to be the desired chlorohydrin **10** (86%) along with traces of *N*-methylsaccharin and the benzothiazine ester **3** (R = OCH_3; see below). Attempts to purify this oil by column chromatography on silica gel led to decomposition. However, when a portion of the crude oil was set aside for several days, a white solid separated from the remaining oil. This material was filtered, washed with isopropyl alcohol, and dried to yield pure **10** (R = OCH_3): mp 122–125 °C; mass spectrum, *m/e* 305, parent; IR (KBr) 3279, 1739 cm^{-1}; ^1H NMR δ 8.1–7.6 (5 H, m), 5.05 (1 H, s), 3.45 (3 H, s), 2.7 (3 H, s). Anal. Calcd for $C_{11}H_{12}O_5NSCl$: C, 43.31; H, 3.96; N, 4.58; S, 10.49; Cl, 11.60. Found: C, 43.10; H, 3.97; N, 4.56; S, 10.49; Cl, 11.62.

Reaction of the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$) with NaH in THF. To the chlorohydrin **10** (R = OCH_2CH_2O-CH_3; 1.72 g, 0.049 mol) in 10 mL of THF was added 99% NaH (Alpha; 0.12 g, 0.50 mol), and the reaction mixture was stirred at room temperature for 30 min. TLC showed good conversion to *N*-methylsaccharin (**8**). The reaction was then quenched by addition of the mixture to 50 mL of cold 5% HCl, and this was extracted with CH_2Cl_2. GC analysis of this extract showed that 0.41 g of **9** (R = $OCH_2CH_2OCH_3$) was present (54%). The CH_2Cl_2 extract was concentrated and the residue extracted into 5 mL of DMF. This solution was in turn added to cold 5% HCl. Upon filtration, 0.60 g of *N*-methylsaccharin (61%) was isolated.

Reaction of the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$) with NaOH in H_2O. To the chlorohydrin **10** (R = OCH_2CH_2-OCH_3; 0.65 g, 0.00186 mol) in 10 mL of H_2O was added 1.85 mL of 1 N NaOH solution. After the mixture was stirred for 3 h, TLC showed complete conversion of **10** to *N*-methylsaccharin (**8**). Filtration of the solids after cooling yielded 0.27 g (74%) of *N*-methylsaccharin.

Formation of Methyl 2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3, R = OCH_3) from the Chlorohydrin 10 (R = OCH_3). To pentane-washed NaH (50% dispersion; 0.63 g, 0.0013 mol) in 8.0 mL of Me_2SO under an N_2 atmosphere was added a solution of **10** (R = OCH_3; 0.40 g, 0.0013 mol) in 8.0 mL of Me_2SO (dropwise addition over 10 min). The internal temperature rose to 34 °C. The reaction mixture was stirred at this temperature for 1.5 h. TLC showed no starting **10** and a good conversion to the ester **3** (R = OCH_3). Isolation by quenching by addition of the mixture to 80 mL of 5% HCl followed by heating and filtration yielded 0.28 g (80%) of the ester **3**, mp 162–163 °C (lit.[5] mp 162–165 °C). This material was identical in its chromatographic and spectral properties with a sample of **3** (R = OCH_3) made via the procedure of Lombardino.[5]

Formation of Methoxyethyl 2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3, R = $OCH_2CH_2OCH_3$) from the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$). Following the procedure above, the ester **3** (R = $OCH_2CH_2OCH_3$) was isolated: 82% yield; mp 101–105 °C; IR (KBr) 3475, 1680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.0 (4 H, m), 4.5 (2 H, m), 3.7 (2 H, m), 3.34 (3 H, s), 2.90 (3 H, s). Anal. Calcd for $C_{13}H_{15}O_6NS$: C, 49.83; H, 4.83; N, 4.47; S, 10.23. Found: C, 49.97; H, 4.71; N, 4.48; S, 10.24.

Replacement of Me_2SO by DMF resulted in a 67% isolated yield of **3** (R = $OCH_2CH_2OCH_3$) by using the above conditions.

(5) Lombardino, J. G.; Wiseman, E. H.; McLamore, W. M. *J. Med. Chem.* **1971**, *14*, 1171.

Formation of Methyl 2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3, R = OCH_3) from *N*-Methylsaccharin (8) and Methyl Chloroacetate (9, R = OCH_3). To a solution of *N*-methylsaccharin (**8**; 3.0 g, 0.15 mol) and methyl 2-chloroacetate (**9**, R = OCH_3; 9.8 g, 0.09 mol) in 15 mL of Me_2SO (or DMF) at 40 °C was added over 2 h 0.81 g (0.33 mol) of sodium hydride 99% (Alpha). Stirring was continued for an additional 2 h while maintaining a temperature of 40–50 °C. The reaction was then quenched by addition of the mixture described above, and 3.07 g (76%) of the benzothiazine ester **3** (R = OCH_3) was isolated. Comparable results were obtained in the methoxyethyl series.

Control Experiments. Controlled Quenching with 1 Equiv of Acetic Acid. In a flame-dried flask under N_2 was placed 1.18 g (0.02 mol) of sodium hydride (50% dispersion in mineral oil). The mineral oil was removed by pentane washing and decantation. Dry THF (15 mL) was added, followed by *N*-methylsaccharin (1.97 g, 0.01 mol), and this mixture heated to 35 °C. To the resultant reaction mixture was added dropwise a solution of methoxyethyl chloroacetate (**9**, R = $OCH_2CH_2OCH_3$; 1.52 g, 0.01 mol) in 10 mL of THF. An exothermic reaction resulted, accompanied by gas evolution and foaming. After the addition of **9** was completed (30 min), the reaction mixture was stirred at 40–45 °C for an additional 2 h. At this point, quenching of an aliquot of the reaction mixture by addition into dilute cold HCl and analysis by TLC and GC showed the absence of appreciable amounts of **9** and **8** and a good conversion to the chlorohydrin **10**. Next a solution of 0.6 g of HOAc (0.01 mol) in 5 mL of THF was slowly added to the reaction mixture, and the mixture was stirred another 30 min. Quenching of another aliquot by addition into dilute HCl followed by GC and TLC analysis showed appreciable quantities of the starting materials **8** and **9**. The workup of the remainder of the reaction with 100 mL of cold 5 N HCl and filtration yielded 0.90 g (46%) of *N*-methylsaccharin (**8**).

The identical procedure described above was followed, but after the initial 2-h reaction time the THF was removed from the reaction in vacuo (15 mm) and replaced with 20 mL of Me_2SO. Then, 0.6 g of HOAc (0.01 mol) was added dropwise in 5 mL of Me_2SO and the reaction mixture stirred for an additional 30 min at 40 °C. The reaction was quenched by addition of the mixture to 100 mL of cold 5% HCl, and it was stirred at 5 °C for 1 h. Filtration yielded 1.60 g (51%) of the benzothiazine ester **3** (R = $OCH_2CH_2OCH_3$).

Acknowledgment. We acknowledge helpful discussions with Professor D. S. Kemp and Dr. J. G. Lombardino.

Registry No. **3** (R = OCH_3), 35511-15-0; **3** (R = $OCH_2CH_2OCH_3$), 80201-74-7; **8**, 15448-99-4; **9** (R = $OCH_2CH_2OCH_3$), 13361-36-9; **9** (R = OCH_3), 96-34-4; **10** (R = OCH_3), 85727-15-7; **10** (R = $OCH_2CH_2OCH_3$), 85727-14-6.

Synthesis of Di-*tert*-butyl Methylenemalonate, a Sterically Hindered 1,1-Dicarbonyl Alkene

Paloma Ballesteros, Bryan W. Roberts,* and Janice Wong

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received November 29, 1982

Methylenemalonate esters are potentially useful electrophilic alkenes in important synthetic reactions, i.e., the Michael and Diels–Alder reactions. Their utility, however, has been restricted by their rapid polymerization. During our work on tetracarbonyliron complexes of alkenes,[1] we required a methylenemalonate ester, the ester groups of which could be readily cleaved in subsequent transfor-

(1) (a) Roberts, B. W.; Wong, J. *J. Chem. Soc., Chem. Commun.* **1977**, 20. (b) Baar, M. R.; Roberts, B. W. *Ibid.* **1979**, 1129. (c) Roberts, B. W.; Ross, M.; Wong, J. *Ibid.* **1980**, 428.

0022-3263/83/1948-3603$01.50/0