Table I. Substituted 1,4-Phenanthraquinones Prepared from 1,4-Benzoquinone and Substituted Styrenes

reactant	product	method	reactn scale, mmol of styrene	yield, mg (% theor)	mp, °C	lit. mp, °C (yield, %)[a]
$PhCH=CH_2$	1,4-PhQ	A	10	615 (31)	147-148	145 (14)
			1	60 (30)		
$2\text{-}(MeO)PhCH=CH_2$	8-MeO-1,4-PhQ	A	1	120 (50)	208-209	204 (30)
			5	495 (42)		
$3\text{-}(MeO)PhCH=CH_2$	7-(MeO)-1,4-PhQ	B	1	48 (20)	152-153	140 (19)
	5-(MeO)-1,4-PhQ[b]			15 (6)	106.5-108.5	
$4\text{-}(MeO)PhCH=CH_2$	6-(MeO)-1,4-PhQ	A	1	100 (42)	202-203	195 (31)
			5	310 (26)		
$2,3\text{-}(MeO)_2PhCH=CH_2$	7,8-$(MeO)_2$-1,4-PhQ[b]	C	1	170 (63)	196-198	
$3,4\text{-}(MeO)_2PhCH=CH_2$	6,7-$(MeO)_2$-1,4-PhQ	C	1	83 (31)	235-236	236 (21)
$2,5\text{-}(MeO)_2PhCH=CH_2$	5,8-$(MeO)_2$-1,4-PhQ[b]	C	1	100 (37)	173-175	

[a] Reference 1. [b] Satisfactory analytical data (±0.3% for C and H) were reported for all new compounds in the table. Low-resolution mass spectra and ^1H magnetic resonance spectra are contained in the supplementary material.

pected due to the alternative orientation for cycloaddition. The fine yield of 5,8-dimethoxy-1,4-phenanthraquinone, however, does make clear that steric interaction alone does not preclude successful dione formation because, in this instance, no alternative orientation is available.

Experimental Section

All melting points were determined by using a Fisher-Johns hot-stage apparatus and are uncorrected. Mass spectra were taken on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 data system. Magnetic resonance spectra were taken on a Varian XL-100 spectrometer, using $CDCl_3$ (0.5% Me_4Si) as solvent. Microanalyses were performed by Galbraith Laboratories. All styrenes not prepared below were obtained from Polysciences, Inc.

Preparation of Styrenes. The reactants 3-methoxystyrene,[9] 2,3-dimethoxystyrene,[10] and 2,5-dimethoxystyrene[11] were prepared by applying the general Wittig method of Tagaki et al.[12] to the respective benzaldehydes (obtained from Aldrich).

Method A. To 15–20 mL of toluene were added 5 mmol of substituted styrene, a five- or tenfold molar excess of *p*-benzoquinone, and 50 mg of the trichloroacetic acid. The mixture was placed in a 100 °C oil bath for a period of 1–7 days. The progress of each reaction was monitored by thin-layer chromatography, using silica gel GF places (Analtech) and benzene as the eluting solvent. When no styrene was visible, the reaction mixture was poured hot on to a short column of dry, neutral alumina and the product eluted by chloroform. After removal of solvent by rotary evaporation, the solid was sublimed and further purified by column chromatography on Silicar CC-7 (Mallinkrodt) with benzene or 1:1 benzene–hexane as solvent. The methoxy-substituted 1,4-phenanthraquinones were recrystallized from ethanol or benzene–ethanol.

Method B. This was the same as method A except that the product dione isolated was found to be predominantly the dihydro adduct of the Diels–Alder reaction. The material was placed in 8 mL of nitrobenzene and 2 mL of pyridine and heated to reflux for 5 h. Purification occurred as in method A.

Method C. To 10 mL of toluene were added 1 mmol of dimethoxy-substituted styrene and 10 mmol of *p*-benzoquinone. Ten milligrams of trichloroacetic acid was added as a catalyst. The mixture was placed in a 100 °C oil bath for 3–6 days, with the progress of the reaction being monitored as in method A. The dimethoxy-1,4-phenanthraquinones were purified as in method A.

(9) Frank. R. L.; Adams, C. E.; Allen, R. E.; Gander, R.; Smith, P. V. *J. Am. Chem. Soc.* **1946** *68*, 1365.
(10) Tsatsas, G.; Margomenou-Leonidopoulou, G. *Bull. Soc. Chim. Fr.* **1967** 2353.
(11) Hashimoto, M.; Uno, K.; Cassidy, H. G. *J. Polym. Sci., Polym. Chem. Ed.* **1968** *6*, 2729.
(12) Tagaki, W.; Inone, I.; Yano, Y.; Okanogi, T. *Tetrahedron Lett.* **1974** 2587.

Acknowledgment. This research was supported by Contract NO1-CO-75380 with the National Cancer Institute, NIH, Bethesda, MD 20205. The authors thank Mr. S. S. Huang for determination of the mass spectra.

Registry No. Styrene, 100-42-5; 2-methoxystyrene, 612-15-7; 3-methoxystyrene, 626-20-0; 4-methoxystyrene, 637-69-4; 2,3-dimethoxystyrene, 17055-36-6; 3,4-dimethoxystyrene, 6380-23-0; 2,5-dimethoxystyrene, 14568-68-4; 1,4-phenanthraquinone, 569-15-3; 8-methoxy-1,4-phenanthraquinone, 63216-08-0; 7-methoxy-1,4-phenanthraquinone, 63216-07-9; 5-methoxy-1,4-phenanthraquinone, 73453-72-2; 6-methoxy-1,4-phenanthraquinone, 63216-06-8; 7,8-dimethoxy-1,4-phenanthraquinone, 73453-73-3; 6,7-dimethoxy-1,4-phenanthraquinone, 63216-09-1; 5,8-dimethoxy-1,4-phenanthraquinone, 73453-74-4; 1,4-benzoquinone, 106-51-4.

Supplementary Material Available: Proton magnetic resonance spectra and mass spectra of new compounds (6 pages). Ordering information is given on any current masthead page.

Convenient Syntheses of Methyl Diformylacetate[1]

Masami Nakane, Harold Gollman, C. Richard Hutchinson,*[2] and Philip L. Knutson

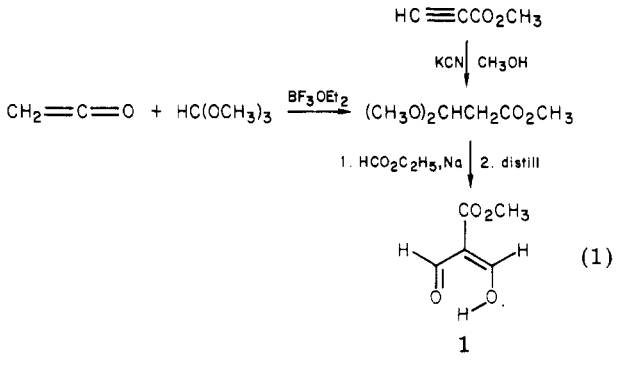
School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

Received January 8, 1980

The title compound (1) is a useful starting material for the total synthesis of cyclopentanomonoterpene aglucons[3] and α-substituted lactones[4] as well as other organic compounds.[5] Büchi and co-workers were the first to prepare this compound,[3a] employing a two-step reaction sequence to 1 from ketene and trimethyl orthoformate (eq 1). However, the overall yield of 1 was only 13% due to the poor yield obtained in the first step, which on a large scale also necessitates the tedious preparation of ketene.[6] The

(1) Supported in part by a research grant from the National Institutes of Health (CA 17127).
(2) Research Career Development Awardee of the National Cancer Institute (CA 00253), 1976–1981.
(3) (a) Büchi, G.; Carlson, J. A.; Powell, J. E., Jr.; Tietze, L.-F. *J. Am. Chem. Soc.* **1973**, *95*, 540. (b) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *Ibid.* **1973**, *95*, 532. (c) Tietze, L.-F. *Chem. Ber.* **1974**, *107*, 2499. (d) Kinast, G.; Tietze, L.-F. *Ibid.* **1976**, *109*, 3626. (e) Hutchinson, C. R.; Mattes, K. C.; Nakane, M.; Partridge, J. J.; Uskokovic, M. R. *Helv. Chim. Acta* **1978**, *61*, 1221.
(4) (a) Baldwin, S. W.; Gawley, R. E.; Doll, R. J.; Leung, K. H. *J. Org. Chem.* **1975**, *40*, 1865. (b) Baldwin, S. W.; Gawley, R. E. *Tetrahedron Lett.* **1975**, 3969. (c) Baldwin, S. W.; Crimmins, M. T.; Cheek, V. I. *Synthesis* **1978**, 210.
(5) Tietze, L.-F.; Brüggemann, K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 540.

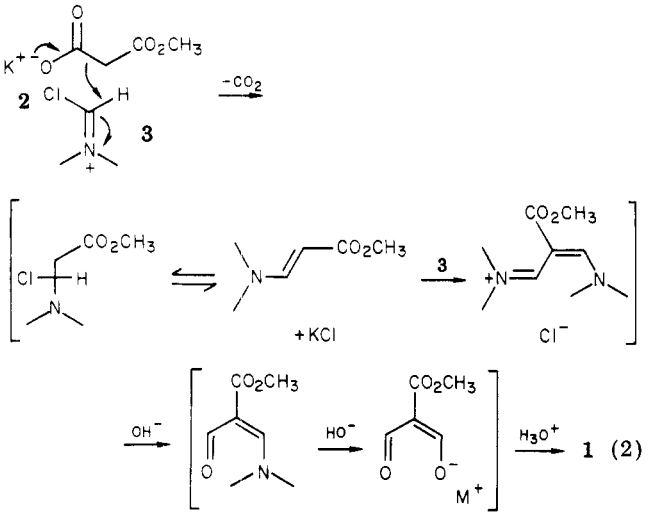
0022-3263/80/1945-2536$01.00/0



(1)

title compound also can be prepared[7] by a slight modification of eq 1 wherein the methyl 3,3-dimethoxypropanoate is made by Michael addition of methanol to methyl propiolate using KCN to catalyze the reaction.[8] This preparation of 1 is easier than that from ketene, but is quite expensive (>$520 per mole based on a 50% overall yield). We now describe two new methods for the synthesis of 1, as well as its simple analogues, that are convenient and inexpensive enough for large-scale preparations.

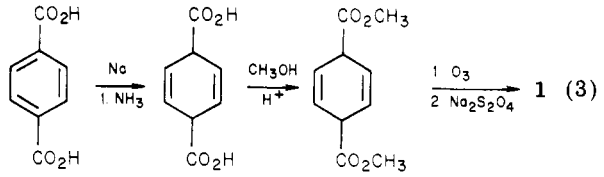
The first method (A) is a modification of the known synthetic method for the preparation of α-substituted-β-(dimethylamino)acrylaldehydes reported by Arnold.[9] Reaction of the potassium salt of monomethyl malonate (2) with the Vilsmeyer reagent (3), made from DMF and $POCl_3$, at 90 °C followed by treatment of the crude reaction mixture with first base and then acid and distillation of the Et_2O solubles gives 1 in 50–55% overall yield (eq 2). This preparation can be done easily on a 0.5-mol scale



(2)

in 2 days and is inexpensive. The mechanism of the condensation reaction between 2 and 3 is unknown;[9] the representation shown in eq 2 is one possibility.

The second method (B) is unique because it permits the acid- and base-sensitive 1 to be formed under neutral conditions and because it should enable the preparation of almost any ester analogue of 1. In this method ozonolysis and reductive workup of the dimethyl 2,5-cyclohexadiene-1,4-dicarboxylate[10] (5) gives 1 in 50% overall yield from terephthalic acid (eq 3). Reductive workup of the ozonide can be done with $Na_2S_2O_4$ or with $(Ph)_3P$. Zn



(3)

4 5

(H^+), KI, H_2/Pd(C), or organic sulfides (Me_2S or n-Bu_2S) are unsatisfactory for reductive workup because 1 either forms chelates, addition products, inseparable azeotropes, or is reduced rapidly (at 1 atm) with these methods and reagents or their oxidation products. This method is as inexpensive as method A, but it is not as convenient for large-scale work if one must start with terephthalic acid due to the cumbersome nature of the Birch reduction.

Experimental Section

General. Chemicals were reagent grade and were used as commercially available. Solvents were dried by distillation from suitable drying agents (BaO or $Mg(OMe)_2$). NMR spectra were determined on a Varian EM 360 or 390 spectrometer as $CDCl_3$ solutions; chemical shifts (δ) are given by reference to $CHCl_3$ (δ_H 7.26) as the internal standard. Melting points are uncorrected. Concentration in vacuo refers to rotary evaporation at <30 °C, using a H_2O aspirator vacuum.

Methyl Diformylacetate (1). Method A. Potassium monomethyl malonate (2) was made from dimethyl malonate by hydrolysis with KOH in absolute MeOH at 25 °C for 18 h, concentration of the reaction mixture containing white crystalline solid in vacuo, and dilution of the concentrated mixture with Et_2O (to force out rest of crystalline product) followed by filtration. The recovered white crystals (2) were dried under high vacuum before use in the following reaction; mp 204–207 °C.

The Vilsmeyer reagent (3) from DMF (1558 mL, 19.8 mol) and distilled $POCl_3$ (368.5 mL, 3.95 mol) was made by slowly mixing the reactants at 25 °C in a 3-L three-necked flask equipped with a mechanical stirrer and thermometer and protected from the atmosphere with a drying tube. After the resulting dark solution was cooled to 0 °C, potassium monomethyl malonate (205.5 g, 1.32 mol) was added slowly over a 30-min period, keeping the temperature of the mixture below 90 °C, and then the reaction mixture was stirred at 90 °C for 4 h. Gas evolved initially from the dark red-brown mixture on heating. The solvent and excess reagents were removed by evaporation at ca. 2 torr on a steam bath, and the resulting residue was poured onto ice (4 kg). A saturated aqueous solution of K_2CO_3 was added carefully (to minimize foaming) to the ice-cold mixture obtained from the reaction to bring the mixture's pH to 12. The resulting basic solution was stirred at 25 °C for 48 h and then extracted with EtOAc (2 × 2 L). The organic extracts were discarded. The aqueous phase was saturated with KCl (500 g), mixed with ice (1 kg), acidified to pH 1 with ice-cold 6 N HCl, and extracted thoroughly with Et_2O (4 × 2 L). The combined cold Et_2O extracts were washed with saturated aqueous KCl (4 L) and dried over Na_2SO_4 for 1 h or more. The Et_2O decanted from the drying agent plus an Et_2O wash of the latter were combined, concentrated in vacuo to ca. 500 mL, and redried over Na_2SO_4 as before. Removal of the Et_2O in vacuo followed by removal of the solvent in vacuo at 25 °C and distillation of the resulting residue at 2 torr using a N_2 bleed into a dry ice cooled receiver gave 1, bp 58–61 °C, as a colorless, crystalline distillate, which melted at ca. 10 °C, in 50% yield. Its ^1H NMR spectrum was identical with that of an authentic reference standard.[3a]

Method B. Dimethyl 2,5-cyclohexadiene-1,4-dicarboxylate (5) was made from terephthalic acid by Birch reduction[10] followed by esterification of the crude reduction product (4), using absolute MeOH and a catalytic amount of concentrated H_2SO_4 at reflux temperature for 1 h. The overall yield of 5 was 91% on a 0.054-M scale. Diacid 4 or diester 5 must be stored in evacuated O_2-free bottles at ≤4 °C to avoid spontaneous aromatization to terephthalic acid or its diester. The latter's occurrence can be detected easily by ^1H NMR spectroscopy of $CDCl_3$ solutions: 5 (δ_H 3.65 (s), 6.00 (s)) vs. dimethyl terephthalate (δ_H 4.00 (s), 8.12 (s)).

(6) Hurd, C. D. "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. 1, p 330. Andreades, S.; Carlson, H. D. *Ibid.*; 1973; Collect. Vol. 5, p 679.
(7) S. W. Baldwin, personal communication, 1979.
(8) Walia, J. S.; Walia, A. S. *J. Org. Chem.* **1976**, *41*, 3765.
(9) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051.
(10) Kauer, J. C.; Benson, R. E.; Parshall, G. W. *J. Org. Chem.* **1965**, *30*, 1431. Brown, G. W.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, *89*, 7116.

Diester **5** (3.9 g, 19.6 mmol) was dissolved in $CHCl_3$–MeOH (1:1, 250 mL) and an O_2/O_3 mixture was bubbled through the stirred solution at −78 °C until a faint blue coloration appeared. N_2 was then bubbled through the solution at −78 °C until the blue coloration disappeared, whereupon $Na_2S_2O_4$ (14 g, 54 mmol, 2.8 equiv) dissolved in H_2O (20 mL) was added to the cold solution to reduce the ozonide. (Ph_3P also can be used as the reductant.) The resulting mixture was warmed slowly to 22 °C and the solvents were removed in vacuo. An oily gum-like residue was obtained that was dissolved in ice-cold saturated aqueous K_2CO_3 (58 mL) and extracted with EtOAc (2 × 100 mL) to remove neutral compounds. The remaining aqueous phase was cooled to ice-bath temperatures and was acidified carefully with 6 N HCl to pH 1 such that the temperature of the solution remained at <10 °C. After saturation of the ice-cold acidic solution with solid KCl, it was extracted thoroughly with Et_2O (4 × 150 mL), and the combined ether extracts were worked up as described in method A to give **1** (2.6 g, 51%).

Acknowledgment. We thank Drs. Milan R. Uskokovic and John J. Partridge, Hoffman-La Roche, Inc., Nutley, N.J., for an authentic sample of **1** and Professor S. W. Baldwin, Duke University, for the information regarding the preparation of **1** from methyl propiolate.

Registry No. 1, 39947-70-1; 2, 38330-80-2; 3, 44205-36-9; 4, 1515-23-7; 5, 38201-52-4; terephthalic acid, 100-21-0.

Useful Route to Alkenyl *S*-Phenyl Thiocarbonates: Reagents for the Introduction of the Enyloxycarbonyl Moiety in Synthesis

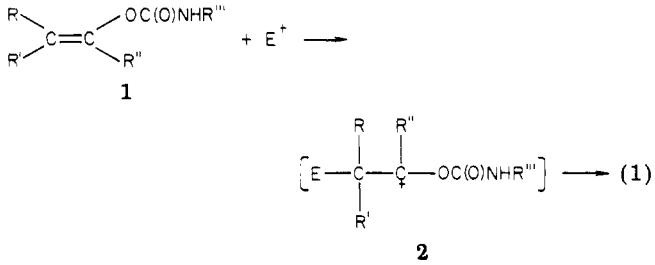
R. A. Olofson* and John Cuomo

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received October 29, 1979

In recent publications from this laboratory,[1-3] vinyl chloroformate (H_2C=CHOC(O)Cl, VOC-Cl) was introduced as a useful reagent for amino protection, especially in peptide synthesis.[1] The utility of VOC-Cl in masking hydroxyls[3] and in selective tertiary amine N-dealkylation also has been reported.[2,3]

In peptide chemistry, certain substituted (vinyloxy)carbonyl groups might be expected to be even more valuable than the VOC moiety itself. For example, substituents in **1** (eq 1) could be incorporated (a) to increase crystal-



1 **2** (1)

linity and so simplify isolation or (b) to inductively and/or sterically reduce the sensitivity of **1** (vs. VOC-NHR) toward alkaline hydrolysis, a significant limitation. By stabilizing the intermediate cation **2** (e.g., with an α-alkyl residue), the normal electrophilic cleavage–removal of the blocking group also could be facilitated.

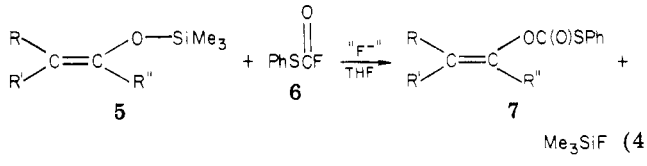
Efforts to test these possibilities have been thwarted in the past by the inaccessibility of substituted enol haloformates using the pyrolytic route to VOC-Cl[4] and by the lack of an alternative practical synthesis of such reagents.[5] Recently, however, Duggan and Roberts described the preparation of VOC-SPh (**4**) as in eq 2 and 3 and showed

$$\text{THF} + n\text{-BuLi} \rightarrow n\text{-BuH} + H_2C{=}CH_2 + \underset{\mathbf{3}}{H_2C{=}CHOLi} \quad (2)$$

$$\mathbf{3} + \text{PhSC(O)Cl} \rightarrow \underset{\mathbf{4}\ (\text{VOC-SPh})}{H_2C{=}CHOC(O)SPh} \xrightarrow[\text{pH 9.5}]{\text{AA}} \text{VOC-AA} + PhS^- \quad (3)$$

that this reagent readily transferred its VOC unit to the amino function of amino acids.[6] In this transacylation, loss of the enolate, vinyl oxide, did not compete with thiophenoxide elimination, a somewhat surprising and very useful discovery.

We now report a second, efficient synthesis of **4** which unlike the Duggan–Roberts process also can be generalized to the economical preparation of substituted vinyl *S*-phenyl thiocarbonates (**7**). In the new method, **7** is formed by the room temperature reaction of a trimethylsilyl enol ether precursor (**5**) in THF with phenyl thiofluoroformate (**6**) in the presence of a "naked fluoride" ion catalyst (eq 4). The process is analogous to a synthesis of enol car-



5 **6** **7** Me_3SiF (4)

bonates and carbamates previously developed in this laboratory and shown to be both regiospecific and stereospecific with respect to the enol surrogate, **5**.[7] Both $PhCH_2NMe_3{}^+F^-$ (BTAF) and KF/18-crown-6 have been utilized as the "naked fluoride"[8] source (the latter is better; see below), and the fluoroformate reagent (**6**) is readily available from the corresponding chloroformate by halide exchange with NaF in acetonitrile (92% yield).[9] All Me_3Si ethers (**5**) were easily prepared by standard procedures[10-14] except the parent, H_2C=CHOSiMe_3, which finally was made in 62% yield by a substantially modified version of the general House method.[10]

The results for several syntheses of thiocarbonates **7** by the new methodology are summarized in Table I. Reaction times were determined by periodic VPC assay, and

(1) R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, *Tetrahedron Lett.*, 1563 (1977).
(2) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Lett.*, 1567 (1977); R. A. Olofson and J. P. Pepe, *ibid.*, 1575 (1977).
(3) R. A. Olofson and R. C. Schnur, *Tetrahedron Lett.*, 1571 (1977).
(4) Reaction of ethylene glycol with phosgene to give the bis(chloroformate) followed by pyrolysis: F. E. Kung, U.S. Patent 2 377 085 (1945); L.-H. Lee, *J. Org. Chem.*, **30**, 3943 (1965).
(5) For an impractical route which does, however, yield some of these compounds, see: R. A. Olofson, B. A. Bauman, and D. J. Wancowicz, *J. Org. Chem.*, **43**, 752 (1978); R. A. Olofson, J. Cuomo, and B. A. Bauman, *ibid.*, **43**, 2073 (1978).
(6) A. J. Duggan and F. E. Roberts, *Tetrahedron Lett.*, 595 (1979).
(7) R. A. Olofson and J. Cuomo, *Tetrahedron Lett.*, 819 (1980). For background, see: I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975).
(8) W. P. Weber and G. W. Gokel, "Phase Transfer Catalysis in Organic Synthesis", Springer-Verlag, New York, 1977.
(9) K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 3170 (1965).
(10) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(11) S. A. Rhone-Poulenc, Britrish Patent 1 060 910 (1967).
(12) F. Runge and W. Abel, *Makromol. Chem.*, **120**, 148 (1968).
(13) A. R. Bassindale, A. G. Brook, P. Chen, and J. Lennon, *J. Organomet. Chem.*, **94**, C21 (1975).
(14) G. M. Rubottom, J. M. Gruber, and G. M. Mong, *J. Org. Chem.*, **41**, 1673 (1976).

0022-3263/80/1945-2538$01.00/0