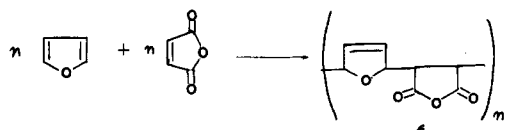


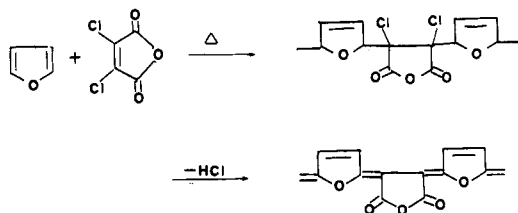
upon the release of high pressure the 1:1 adduct may undergo a retro-Diels-Alder reaction to yield the starting materials.

The configurational isomer *exo,exo* diadduct **5** was not detected, probably as a result of the great steric hindrance associated with the *syn* oxo configuration. The non-bonding lone pairs of electrons on both oxygens may constitute an undesirable steric interaction due to their close proximity in the *exo,exo* configuration. Therefore, the second furan molecule orients itself so that the oxygen atoms are *anti* to each other.

It is well-known that furan and maleic anhydride readily undergo the Diels-Alder reaction to form the cyclic adduct. However, the reaction also gives an alternating copolymer of structure **6** in the presence of a free-radical catalyst.<sup>7,8</sup>



When dichloromaleic anhydride in excess furan was heated under 1 atm of pressure in a sealed tube, polymerization was initiated and enhanced by the elimination of hydrogen chloride. The hydrogen chloride was readily eliminated due to the stabilization resulting from the  $\pi$ -electron conjugation associated with the growing polymer chain. The insolubility and infusibility of the black polymer obtained suggested that the polymer may either be high molecular weight or somewhat cross-linked.



### Experimental Section

**General Aspects.** Infrared spectra were recorded on a Perkin-Elmer 457 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a JEOL JNM-FX-90Q. Melting points were measured on an electrothermal apparatus and are uncorrected. High-pressure experiments were performed in Teflon capsules (3-mL capacity) in a stainless steel die and were compressed via a piston with a 200-ton hydraulic press.

**Materials.** Dichloromaleic anhydride and furan were purchased from Aldrich and purified by sublimation or distillation.

**Reactions between Dichloromaleic Anhydride and Furan.** Several reactions of dichloromaleic anhydride with furan were carried out under various conditions. A representative experiment follows. Dichloromaleic anhydride (5.0 g) dissolved in 30 mL of furan was placed in a sealed tube. After 2 weeks at room temperature, the solution turned a deep red color and a small amount of a black solid was isolated. The same solution (freshly prepared) was heated at 80–90 °C for 3 days. A black solid (3.5 g) was isolated and hydrogen chloride gas evolved from the solution as the tube was opened. The black material did not melt, even at 350 °C, and did not dissolve in organic solvents such as acetone, methylene chloride, benzene, and ethyl acetate. The chlorine content of the compound was found to be in the range of 0.1–2%. IR (KBr) 2950, 1740, 1600, 1250, 1000, 780  $\text{cm}^{-1}$ .

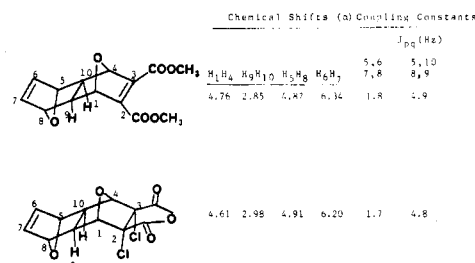
**Preparation of Endo,Exo Diadduct 4 of Dichloromaleic Anhydride with Furan.** Dichloromaleic anhydride (0.85 g)

dissolved in 3 mL of furan was pressurized to 5000 atm for 18 h at 50 °C. A red viscous solution was obtained and the liquid was removed under vacuum. The solid obtained was treated with ethyl acetate and a pale yellow solid (1.2 g) was obtained, mp 214–218 °C. The solid was recrystallized from acetone, mp 224 °C. Dichloromaleic anhydride (0.43 g) and furan (0.20 g) were dissolved in 3 mL of tetrahydrofuran and pressurized to 5000 atm at 50 °C for 20 h. The crude product (0.15 g) was isolated and purified by recrystallization (from acetone), mp 224 °C. The unreacted dichloromaleic anhydride (0.18 g) was recovered from the ethyl acetate solution and the monoadduct **2** or **3** could not be detected. White product **4**: mp 224 °C; IR (KBr) 3010, 2925, 1880, 1852, 1804, 1568  $\text{cm}^{-1}$ ; MS,  $m/e$  (relative intensity) 303 (73), 167 (100), 137 (30), 69 (80). Anal. Calcd for  $\text{C}_{12}\text{H}_8\text{O}_5\text{Cl}_2$ : C, 47.52; H, 2.64; Cl, 23.43. Found: C, 47.37; H, 2.70; Cl, 23.37; <sup>1</sup>H NMR ( $\text{Me}_2(\text{SO}-d_6)$ )  $\delta$  2.98 (2, m), 4.61 (2, s), 4.91 (2, m) 6.20 (2, t).<sup>9</sup>

**Acknowledgment.** This research was supported in part by a grant from Koppers Co., Inc.

**Registry No.** **4**, 86969-99-5; dichloromaleic anhydride, 1122-17-4; furan, 110-00-9.

(9) <sup>1</sup>H NMR spectra data for the *endo,exo* diadduct of dimethyl acetylenedicarboxylate with furan was reported<sup>10</sup> and these data were compared with those of **4**.



(10) McCulloch, M. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* 1973, 51, 4125.

### A New, Effective Catalytic System for Epoxidation of Olefins by Hydrogen Peroxide under Phase-Transfer Conditions

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Direct epoxidation of olefins by hydrogen peroxide is a long-standing goal in oxidation chemistry. This can be achieved only by means of suitable catalysts which are based mainly on group 5A,B and 6A,B metal oxides.<sup>1,2</sup> To date, however, valuable results in the case of simple, monosubstituted olefins have been obtained only by working under virtually anhydrous conditions.<sup>3,4</sup>

We now have found that the two-component association consisting of tungstate and phosphate (or arsenate) ions, under acidic conditions, represents a valuable catalytic

(1) (a) Payne, G. B.; Williams, P. H. *J. Org. Chem.* 1959, 24, 54. (b) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* 1978, 299. (c) Hori, T.; Sharpless, K. B. *J. Org. Chem.* 1978, 43, 1689.

(2) Jacobson, S. E.; Mares, F.; Zambri, P. M. *J. Am. Chem. Soc.* 1979, 101, 6946.

(3) Pralus, M.; Lecoq, J. C.; Schirmann, J. P. In "Fundamental Research in Homogeneous Catalysis"; Tsutsui, M., Ed.; Plenum: New York, 1979; Vol. 3, pp 327–343 and references therein.

(4) Dilute (30%) hydrogen peroxide has also been used for a highly selective epoxidation of terminal olefins (1-octene) in a triphase system, but a very low conversion has been attained.<sup>2</sup>

(7) Butler, G. B.; Badgett, J. T.; Sharahash, M. *J. Macromol. Sci., Chem.* 1970, A4, 51.

(8) Gaylord, N. G.; Maiti, S.; Patmiak, B. K.; Takahashi, A. *J. Macromol. Sci., Chem.* 1972, A6, 1459.

Table I. Epoxidation of Olefins with H<sub>2</sub>O<sub>2</sub> Catalyzed by the WO<sub>4</sub><sup>2-</sup>/PO<sub>4</sub><sup>3-</sup> Association<sup>a</sup>

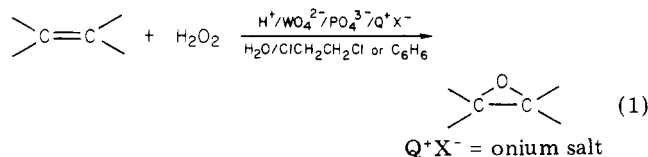
olefin (mmol)	Q <sup>+</sup> X <sup>-</sup> (mmol)	pH <sup>b</sup>	temp, °C	time, min	H <sub>2</sub> O <sub>2</sub> % conv	% yield (to epoxide) <sup>c</sup>
1-octene (200)	1 (2)	1.6	70	45	98	82
1-octene (200)	2 (2)	1.6	70	60	97	81
1-octene <sup>d</sup> (200)	1 (2)	1.6	70	45	96	79
1-octene (200)	3 (2)	1.6	70	60	95	71
1-dodecene (200)	1 (2)	1.6	70	60	97	87
allyl chloride <sup>e,f</sup> (550)	1 (2)	2	60 (bath)	150	96	80
styrene <sup>g-j</sup> (400)	2 (3)	3	40	180	93	77 <sup>k</sup>
α-methylstyrene <sup>g,l</sup> (750)	2 (3)	4.5	40	240	93	79 <sup>k</sup>
cyclohexene <sup>i,m</sup> (400)	2 (0.8)	3	70	25	98	88
cyclohexene <sup>m</sup> (400)	1 (0.8)	3	70	45	98	81

<sup>a</sup> Unless otherwise stated, the epoxidation was run in a 1,2-dichloroethane (15 mL)/8% aqueous H<sub>2</sub>O<sub>2</sub> (120 mmol) mixture with a molar ratio PO<sub>4</sub><sup>3-</sup>/WO<sub>4</sub><sup>2-</sup>/Q<sup>+</sup> of 5:2.5:1, the catalytic system resulting from Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O and 40% w/v H<sub>3</sub>PO<sub>4</sub>.

<sup>b</sup> Refers to the pH of choice of the aqueous solution, obtained by adjusting the original pH with 30% H<sub>2</sub>SO<sub>4</sub> or 10% NaOH.

<sup>c</sup> Unless otherwise stated, yields (based on H<sub>2</sub>O<sub>2</sub> charged) were determined by GLC by using an internal standard (β,β'-oxydipropionitrile column and, for 1,2-epoxydodecane, an OV-225 column). <sup>d</sup> Arsenate (as Na<sub>2</sub>HAsO<sub>4</sub>·7H<sub>2</sub>O) instead of phosphate ions were used. <sup>e</sup> Benzene (30 mL) as the solvent. <sup>f</sup> At the end of the reaction, the aqueous layer was salted out (NaCl) and extracted with Et<sub>2</sub>O, and the ethereal extract was added to the organic phase. <sup>g</sup> A mixture of 40% w/v H<sub>3</sub>PO<sub>4</sub> and NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O (in a 1:2 molar ratio) was used. <sup>h</sup> 15% H<sub>2</sub>O<sub>2</sub> was used; benzene (15 mL) was the solvent. <sup>i</sup> For a good phase separation centrifugation is usually required. <sup>j</sup> At the end of the reaction only little amounts (<2%) of polymerized olefin was found. <sup>k</sup> Determined by titration of the organic phase, after addition of anhydrous Na<sub>2</sub>SO<sub>4</sub> (7.5 g) and MgO (0.1 g): Sully, B. D. *Analyst (London)* 1960, 85, 895. <sup>l</sup> 15% H<sub>2</sub>O<sub>2</sub> was used, without solvent. <sup>m</sup> Same as in *g* but with a 1:1 molar ratio.

system for epoxidation of these olefins by very dilute (<10%) hydrogen peroxide according to the technique of phase-transfer catalysis (eq 1).



High selectivities to epoxide (80–90%) on both hydrogen peroxide and olefin at a substantially complete conversion of hydrogen peroxide are usually attained after relatively short reaction times and under mild conditions.

It should be pointed out that the unusual reactivity of hydrogen peroxide toward terminal alkenes and, in general, isolated alkenes obtainable by this method is reached only when both tungstate and phosphate (arsenate) ions are present. On the contrary, when used one by one, they show poor<sup>5,6</sup> or no catalytic activity, respectively.

This catalytic association<sup>7</sup> is formed in situ in the reaction mixture by simply introducing a suitable source of its two components. Water-soluble alkaline tungstates, on the one hand, and phosphoric (arsenic) acid or its alkaline salts or mixtures of both, on the other, preferably used in a 1:2 molar ratio, are particularly appropriate for the purpose.

The effectiveness of the method here reported appears to be a function of the pH of the aqueous phase. It increases as the pH decreases, and to the extent permitted by stability to hydrolysis of the epoxide formed, low pH values are those of choice. This is the case, for example, of epoxidation of long-chain olefins such as 1-octene, 1-dodecene and the like, for which a pH 1.6 is satisfactorily used. However, the method proves to be operative in a rather wide range of pH, provided that the olefin is sufficiently reactive. Therefore, it may be suited also to

prepare acid-sensitive epoxides, for example, aryloxiranes.<sup>8</sup>

It has to be emphasized that, in spite of the acidic conditions under which the reaction is conducted, hydrolytic cleavage of the oxirane ring in general is largely prevented. The epoxide stability is attributable to both the protecting effect of the double-phase and the relatively short contact times with the aqueous phase, which are made possible by the high efficiency of the catalyst and by the use of an excess of olefin. The latter is recommended in order to obtain the best yields of epoxide and to minimize side reactions which can cause destruction of the oxirane ring. Indeed, when the olefin was employed in a stoichiometric amount with respect to hydrogen peroxide, a substantial reduction (30–80%) in yield was observed. The extent of this excess depends on the reactivity of the substrate and the related epoxide, on the reaction conditions (pH and temperature), and, finally, on the amount of catalyst used. The excess olefin, however, is found substantially unchanged at the end of the reaction.

Solvents and phase-transfer agents (Q<sup>+</sup>X<sup>-</sup>) have not been fully explored. However, of those tried, chlorinated and aromatic hydrocarbons, on the one hand, and methyltri-octylammonium chloride (Aliquat 336, 1), dimethyl[di-octadecyl (75%) + dihexadecyl (25%)]ammonium chloride (Arquad 2HT,<sup>9</sup> 2), and hexadecyltributylphosphonium chloride (3), on the other, lead to successful oxidation. The reaction may also be run without solvent when the olefin is a liquid, with only slightly diminished yields.

Some significant results are reported in Table I.

It should be noted that also gaseous olefins such as propylene and butadiene could be epoxidized under pressure by the above method. In these cases, however, yields were considerably lower (30–40%) than those obtained with the other substrates tested. Butadiene gave the monoepoxide exclusively.

The reaction appears to be stereospecific, since only *trans*-2-hexene oxide was detected by either GLC or <sup>1</sup>H NMR analysis<sup>10</sup> when *trans*-2-hexene was subjected to epoxidation. Analogously, *cis*-2-hexene gave only *cis*-2-hexene oxide.

(5) In the absence of phosphate or arsenate ions, we could epoxidize terminal alkenes only in 25–35% selectivity at 30% conversion (on H<sub>2</sub>O<sub>2</sub>). Tungsten compounds are known to be poor catalysts for epoxidation of isolated olefins with aqueous H<sub>2</sub>O<sub>2</sub> in both monophasic (unless water is continuously removed)<sup>10,11</sup> and biphasic<sup>6</sup> systems.

(6) Napier, D. H.; Starks, C. M. U. S. Patent 3992 432, 1976.

(7) From some preliminary data, formation of a peroxidic derivative of a not yet known phospho(arseno)tungstic acid seems to be involved.

(8) Imuta, M.; Ziffer, H. *J. Org. Chem.* 1979, 44, 1351.

(9) Obtained from AKZO Chemie Italia SpA.

(10) Gagnaire, D.; Monzeglio, P. *C. R. Hebd. Seances Acad. Sci.* 1964, 259, 1128.

Further work is in progress to extent the scope of this method and to characterize the catalyst involved.

### Experimental Section

In a typical experiment, finely powdered  $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$  (1.65 g, 5 mmol), 40% w/v  $\text{H}_3\text{PO}_4$  (2.45 mL, 10 mmol), and 8% aqueous  $\text{H}_2\text{O}_2$  (51 g, 120 mmol) were introduced into a glass reactor. The pH of the aqueous solution was adjusted to 1.6 by 30%  $\text{H}_2\text{SO}_4$ , thereupon 1-octene (22.4 g, 200 mmol), 1,2-dichloroethane (15 mL), and Aliquat (0.82 g, ca. 2 mmol) were added. Under vigorous stirring the resultant biphasic mixture was heated to 70 °C for 45 min. The water and 1,2-chloroethane layers were then separated. The amount of unreacted  $\text{H}_2\text{O}_2$  was determined by iodometric titration of the aqueous phase. The organic layer was analyzed by GLC. In this way, 12.7 g (99 mmol) of 1,2-epoxyoctane was obtained (Table I, first entry).

The other olefins listed in Table I were epoxidized under similar conditions. In all cases combustion analyses, spectral data, and comparison with authentic samples confirmed the identity of the products.

**Registry No.** 3, 41272-12-2;  $\text{WO}_4^{2-}$ , 14311-52-5;  $\text{PO}_4^{3-}$ , 14265-44-2;  $\text{Na}_2\text{HAsO}_4$ , 7778-43-0; 1-octene, 111-66-0; 1-dodecene, 112-41-4; allyl chloride, 107-05-1; styrene, 100-42-5;  $\alpha$ -methylstyrene, 98-83-9; cyclohexene, 110-83-8.

### Improved Procedure for the Blaise Reaction: A Short, Practical Route to the Key Intermediates of the Saxitoxin Synthesis

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Since the discovery of the addition of zinc ester enolates to nitriles by Blaise in 1901,<sup>1</sup> this potentially useful  $\beta$ -keto ester synthesis has found little application in organic synthesis. The easy introduction of the functionalities and the straightforward nature of the conversion have been overshadowed by the problems of low yield, narrow scope, and competing side reactions.<sup>2-5</sup> We report a convenient modification of this reaction, which has proven surprisingly versatile and has provided a short, practical route to key intermediates in the total synthesis of the paralytic shellfish poisons, saxitoxin and gonyautoxins II and III.<sup>6</sup>

(1) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, 132, 478.

(2) (a) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, 132, 978. (b) Cason, J.; Rinehart, K. L. Jr.; Thornton, S. D., Jr. *J. Org. Chem.* **1953**, *18*, 1594. (c) Kagan, H. B.; Suen, Y.-H. *Bull. Soc. Chim. Fr.* **1966**, 1819. (d) Lhommet, G.; Eskenazi, C.; Maitte, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1974**, 279, 263. (e) Konrad, J.; Jezo, I. *Chem. Zvesti* **1980**, *34*, 125.

(3) Kagan and Suen reported an improvement for the Blaise reaction.<sup>2c</sup> Their procedure involved use of slow addition of a benzene solution of  $\alpha$ -bromo esters to a refluxing mixture of zinc and nitriles, providing excellent yields (70–83%) for  $\alpha,\alpha$ -di- and  $\alpha$ -monosubstituted  $\beta$ -keto esters, but yields for  $\alpha$ -unsubstituted  $\beta$ -keto esters exceeded 40% in only one case. Other workers have obtained only very low yields of  $\alpha$ -mono- and  $\alpha$ -unsubstituted  $\beta$ -keto esters by using this method.<sup>2d,e</sup>

(4) Twenty-seven representative examples reported in the papers quoted under ref 2 are summarized in the tables in the supplementary material.

(5) Since the completion of this work, Hiyama and Kobayashi (Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 1597) have reported the coupling of magnesium enolates of acetic acid esters. The reaction is limited to *tert*-butyl esters, and satisfactory reactions are reported for only a limited range of nitriles.

Table I

	1	2	3	4	
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield of 3, %	yield of 4, %
a	Me	H	(CH <sub>2</sub> ) <sub>4</sub> Cl	95	85
b	<i>t</i> -Bu	H	(CH <sub>2</sub> ) <sub>4</sub> Cl	87	83
c	Me	H	C(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> Cl	70	62
d	Me	H	C <sub>6</sub> H <sub>5</sub>	88	82
e	Me	Me	C <sub>6</sub> H <sub>5</sub>	84	79
f	Me	Me	(CH <sub>2</sub> ) <sub>4</sub> Cl	54 <sup>a</sup>	84

<sup>a</sup> The lower yield is due to facile hydrolysis of 3f to 4f.

Treatment of aliphatic or aromatic nitriles 2 with 3–5 molar excess of  $\alpha$ -bromo esters 1 in the presence of activated zinc dust in refluxing tetrahydrofuran yielded the corresponding enamino esters 3<sup>7</sup> or, after acid hydrolysis, the  $\beta$ -keto esters 4 as the only isolable products. Some representative examples are listed in Table I.<sup>8</sup> This procedure differs from the classical reaction conditions in the use of tetrahydrofuran as the solvent. In addition, two simple steps were found to be necessary to ensure the success of the reactions. First, the activated zinc was prepared by washing zinc dust sequentially with 3 N hydrochloric acid, distilled water, ethanol, and ether and drying under vacuum. Second, the  $\alpha$ -bromo ester is added over 30–60 min to minimize self-condensation. The required excess of bromoacetate decreased in the order methyl  $\sim$  ethyl  $>$  isopropyl  $>$  *tert*-butyl esters.

One consequence of these modifications was a substantial improvement in the yield of  $\alpha$ -monosubstituted  $\beta$ -keto esters, but most significant was the consistently successful reaction of bromoacetates to give  $\alpha$ -unsubstituted products, e.g., 4a–4d. These compounds were reported to be virtually unobtainable when using the classical reaction conditions.<sup>1-3,9</sup>

The possibility of in situ alkylation of the initial adduct offers an additional synthetic application for the Blaise reaction. In principle, the initial adduct 5 can cyclize in two different modes, leading to the N-alkylated product 6 or to the C-alkylated product 7 (Scheme I). As may be deduced from the principle of hard–soft acids and bases,<sup>10</sup> the course of the cyclization reaction depends primarily on the nature of the leaving group X. In the case of X = Br, the C-alkylated product 7 was found to be the major product. Among the conditions examined, heating the initial adduct in DMF for 30 min gave the cleanest results as a 15:85 mixture of 6 and 7 was isolated in about 80%

(6) For recent reviews on saxitoxins, see: (a) Schantz, E. *J. Pure Appl. Chem.* **1979**, *52*, 183. (b) LoCicero, V. R., Ed. "Proceedings of the 1st International Conferences on Toxic Dinoflagellate Blooms", Science and Technology Foundation: Wakefield, MA, 1975. (c) Shimizu, Y. In "Marine Natural Products"; Scheuer, P. J., Ed., Academic Press: New York, 1978; Vol. 1, pp 1–42. Also see: Koehn, F. E.; Hall, S.; Wichmann, C. F.; Schnoes, H. K.; Reichardt, P. B. *Tetrahedron Lett.* **1982**, *23*, 2247 and references cited therein.

(7) This type of enamino esters are known to exist predominantly as Z isomers. For example, see ref 13.

(8) Satisfactory spectroscopic data (<sup>1</sup>H NMR, IR, UV, MS) were obtained for all the new substances. For crystalline compounds, satisfactory elemental analyses were obtained.

(9) The known procedures, in particular, the one described by Kagan and Suen,<sup>2c</sup> are very reliable for the preparation of  $\alpha,\alpha$ -disubstituted  $\beta$ -keto esters in excellent yield.

(10) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. Pearson, R. G., Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899. Saville, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 928.