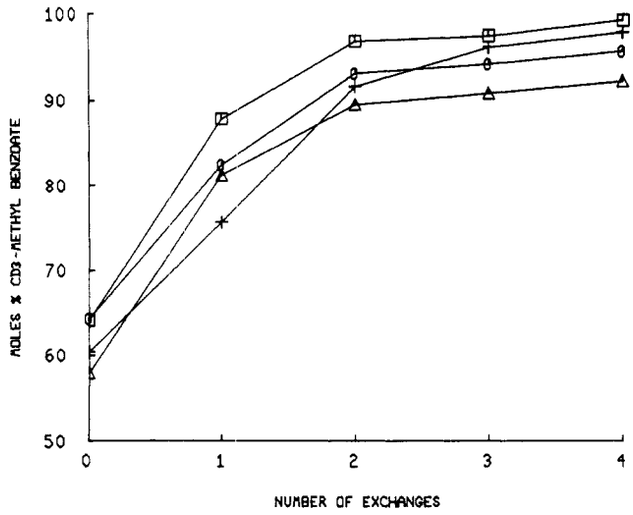

Figure 2. Multiple exchange experiments. Experimental points are connected. Key: +, system 1; △, system 2; ○, system 3; □, system 4.

function reflecting separate rates for exchange and solubility.

Multiple exchanges were effected by mixing fresh aqueous solutions in systems 1–4 in a microgenerator, separating the phases after 15 min, and either reacting the diazomethane with benzoic acid-*O*-*d* or mixing with additional aqueous phase. An exchange time of 15 min was chosen as a compromise between enrichment and yield of diazomethane. Highest enrichments were observed in systems 1 (97.7 mol % D_3) and 4 (99.1 mol % D_3) as shown in Figure 2. The lower isotopic enrichment observed with system 3 was probably due to the hygroscopic nature of the catalyst and the difficulty of preparing a D_2O solution with 99% deuterium.

Yields were somewhat variable, but using the precautions of keeping all solutions and flasks cold and basic, 25–35% of theoretical yield was obtained after five exchanges. For unexchanged diazomethane, 50–60% yield was obtained. Use of phase transfer catalysts did not significantly alter yields. We have used the methods described to exchange diazomethane generated on a larger scale (50–100 mmol) with similar enrichments and yields.

Experimental Section

Low resolution electron ionization mass spectra were recorded with a Finnigan 3200 quadrupole GC–MS. Samples were introduced via the gas chromatograph using a 10% Apolar 10c on 100/200 mesh gas Chromosorb Q (2 m × 2 mm) column at a temperature of 145 °C. Data were obtained by selected ion recording from *m/e* 134–144 ($M^{+\cdot}$). Precise isotopic enrichments were calculated by comparing labeled vs. unlabeled methyl benzoate using LABDET, a program in the NIH-EPA Chemical Information System.[9] Prior to all series of experiments, glassware was washed with D_2O and heated to 200 °C for 12 h. Anhydrous solvents were partitioned with D_2O prior to use.

Phase Transfer Catalysts. Cetyltrimethylammonium bromide (CTAB) was purchased from Aldrich. Hexadecyltributylphosphonium bromide[8] (HDTPB) was prepared by heating 1-bromohexadecane (10 g, 0.06 mol) and tri-*n*-butylphosphine (12.2 g, 0.06 mol) at 60–70% for 3 days. The resulting solid was filtered and recrystallized from hexane. The product was freeze dried giving the salt in 63% yield: mp 53–54 °C (lit.[8] mp 54 °C). A solution of 5% NaOD (Aldrich, 99 + atoms % D) and 5% quaternary ammonium or phosphonium salt in D_2O was used in all exchanges.

Benzoic Acid-*O*-*d*. Monodeuterated benzoic acid was prepared by exchanging benzoic acid five times with excess methanol-*O*-*d* (Merck, 99.7 atoms % D). Generally, for each series of experiments the final stock solution of benzoic acid-*O*-*d* in methanol-*O*-*d* (150 mg/10 mL) was equally divided between five screw capped tubes (Kimax) and the solvent was removed with dry nitrogen. The residue was redissolved in diethyl ether (1 mL).

Diazomethane-d_2. Partially deuterated diazomethane was prepared in a diazomethane microgenerator by the action of 40% NaOD on *N*-methyl-*N*-nitrosoguanidine (13 mg) as described by Fales and Jaouni.[7a] The product was trapped in ice-cooled diethyl ether (3 mL) over a 30-min period.

(a) Time Course Study. Following generation of diazomethane the apparatus was opened and 2 mL of the ice-cooled aqueous catalytic solution was transferred into the trap. After resealing the microgenerator the two phases were mixed by intermittent shaking over 30 min. At various time intervals (0, 5, 10, 15, 20, and 30 min) aliquots of the diazomethane–diethyl solution were transferred to ice-cooled benzoic acid-*O*-*d* solutions and capped. After a further 10 min at room temperature excess diethyl ether was removed with dry nitrogen and the residue was dried under vacuum.

(b) Multiexchange Study. Same procedure as for (a). Each exchange was allowed to proceed for 15 min with intermittent shaking. After this time the aqueous phase was withdrawn by pipet and replaced with fresh catalytic solution. Following the final exchange, the ethereal diazomethane solution was transferred to the reaction tube as outlined.

Registry No.—CD_2N-2, 14621-84-2; CH_2N_2, 334-88-3; NaOD, 14014-06-3; D_2O, 7789-20-0; HDTPB, 14937-45-2; 1-bromohexadecane, 112-82-3; tributylphosphine, 998-40-3; benzoic acid-*O*-*d*, 1005-01-2; benzoic acid, 65-85-0.

References and Notes

(1) Visiting Fellow, Laboratory of Chemistry, National Heart, Lung, and Blood Institute.
(2) A. F. Thomas, "Deuterium Labeling in Organic Chemistry", Appleton-Century-Crofts, 1971, New York, N.Y., 1968 pp 63–64, literature review.
(3) (a) J. R. Campbell, *Chem. Ind. (London)*, 540 (1972). (b) Deutero Diazald Kit from Aldrich Chemical Co.
(4) L. E. Geller, *Atomlight*, **19**, 11 (1961).
(5) S. P. McManus, J. T. Caroll, and C. L. Dodson, *J. Org. Chem.*, **33**, 4272 (1968).
(6) (a) J. O. Halford, L. D. Anderson, and G. H. Kissin, *J. Chem. Phys.*, **5**, 927 (1937); (b) G. W. Robinson and M. McCarty, Jr., *J. Am. Chem. Soc.*, **82**, 1859 (1960); (c) T. D. Goldfarb and G. C. Pimental, *ibid.*, 1865 (1960).
(7) (a) H. M. Fales, T. M. Jaouni, and J. F. Babashak, *Anal. Chem.*, **45**, 2302 (1973). (b) Generator available from Wheaton Scientific, Millvill, N.J. 08332.
(8) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
(9) S. R. Heller, G. W. A. Milne, and R. J. Feldman, *Science*, 195, 253 (1977).

Approaches to the Mitomycins: A Novel Pyrrole Photooxidation Product

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The photooxidation of pyrroles has been studied thoroughly in the past decade and a half.[2] The oxidation has been of some use in the introduction of the angular oxygen function in mitomycin-like molecules.[3] The accepted mechanism of the reaction has featured the photosynthesis of singlet oxygen which then attacked pyrrole. The transient endoperoxide **2**, which is initially formed, then fragments to yield a variety of products. One important proposed pathway involves cleavage of the O–O bond of **2** to yield 5-hydroxypyrrolines **3**, while a second postulated route requires bimolecular nucleophilic opening of the endoperoxide to yield **4a** or a unimolecular opening to yield peroxy isopyrrole **4b** which is trapped by nucleophiles.[4] In either event, products such as **5** and **6** are obtained. In addition it has been suggested that either endoperoxide **2** or hydroperoxide **4b** can rearrange to a dioxetane **7** which can then fragment to ring-cleaved products. In this note, we wish to describe a product of pyrrole photooxidation that has hitherto been unobserved and which might require reconsideration of currently accepted mechanisms.

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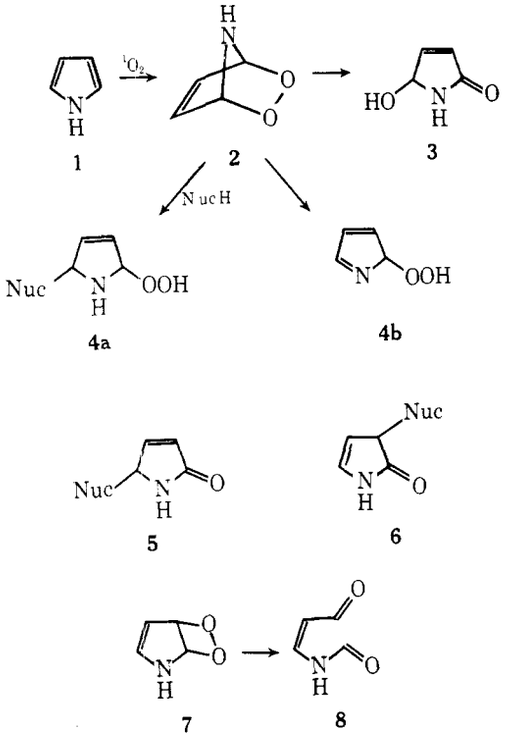
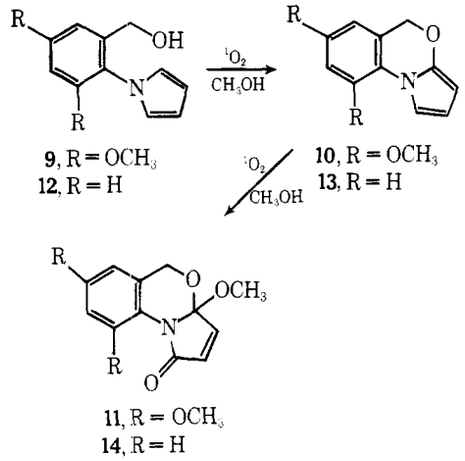
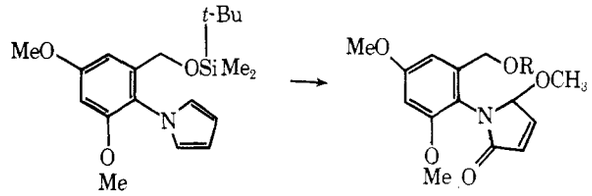


When pyrrole alcohol **9** is photooxygenated in methanol using Rose Bengal as a sensitizer, there can be isolated in 74% yield the oxygen insertion product **10.** Ether **10** is very reactive and can be further oxidized to lactam **11.** Insertion product



10 is unambiguously characterized by its NMR spectrum, which, inter alia, exhibits three pyrrole protons, its mass spectrum, *m/e* 231, and its IR spectrum with no carbonyl band. Lactam **11** with its C=O at 1704 cm^{-1} in the IR and its extra OCH_3 δ 3.30, and its benzylic AB quartet δ 4.62 and 5.08 (J = 15 Hz), in the NMR was easily identified as well. When the oxidation was attempted with pyrrole **12,** only lactam **14** could be isolated. Although there was some TLC evidence for **13** having a transitory existence, its isolation was not achieved. In order to be certain that ether **10** was indeed a photooxidation product, we performed three control experiments, namely treatment of **9** with dye and oxygen in the dark, irradiation of **9** with dye under anaerobic conditions, and irradiation of **9** with oxygen but in the absence of a sensitizer. All these experiments failed to yield insertion product.

In order to rule out some exceptional behavior of the particular aromatic system, we studied the oxidation of **15** where the alcohol is blocked with a dimethyl-*tert*-butylsilyl group. Photooxidation yielded the normal lactam **16** demonstrating that in the absence of a free alcohol function, the dimethoxyphenylpyrrole system is not unusual in its reaction with a singlet oxygen. Furthermore, hydrolysis of the silyl ether to afford free alcohol **17** revealed no unusual interaction; thus we discount any mechanism for the oxidation of **9** which requires a normal product such as **17** which would be subsequently transformed to **10.**



There are several plausible mechanisms that can rationalize the oxygen oxidative insertion of the alcoholic oxygen into the pyrrole. They all predict H_2O_2 as a reduction product to account for the two hydrogens released in the insertion reaction. Thus, the initial reactant solution was subjected to the $Ti(SO_4)_2$ assay[5] which afforded the yellow color indicative of H_2O_2, whereas control solutions gave negative results.

Our observations do not permit the postulation of a mechanism of pyrrole oxidation different from that in the literature, but they do suggest the presence of some novel participation by alcohols in the photooxidation process. Extrapolation of our observation could explain the isolation of small amounts of maleimides in many photooxidations of pyrroles. An intermolecular version of our reaction would yield alkoxy- or hydroxypyrroles which upon oxidation with a second equivalent of $^1O_2$ would be converted to maleimide.

Experimental Section

1-(2,4-Dimethoxy-6-hydroxymethylphenyl)pyrrole (9). A solution of 1-(2,4-dimethoxy-6-methoxycarbonylphenyl)pyrrole (6 g, 0.023 mol) in 50 mL of ether was added to lithium aluminum hydride (1 g, 0.26 mol) in 100 mL of anhydrous ether at such a rate that a gentle reflux was maintained. The solution was refluxed for 45 min longer under N_2. After workup, evaporation of the solvent afforded 5.11 g (95%) of off-white crystalline pyrrole alcohol **9:** mp 125–127 °C; NMR ($CDCl_3$) δ 1.93 (1 H, br s), 3.75 (3 H, s), 3.89 (3 H, s), 4.38 (2 H, s), 6.35 (2 H, t, J = 2.1 Hz), 6.54 (1 H, d, J = 2.6 Hz), 6.69 (2 H, t, J = 2.1 Hz), 6.75 (1 H, d, J = 2.6 Hz).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.85 H, 6.51; N, 5.96.

1-(2-Hydroxymethylphenyl)pyrrole (12). To a suspension of lithium aluminum hydride (0.5 g, 0.013 mol) in 40 mL of anhydrous ether was added 1-(2-carboxyphenyl)pyrrole (2.01 g, 0.01 mol) in 20 mL of ether slowly with stirring. The solution was refluxed under N_2 for 1 h. After workup evaporation of the solvent yielded almost pure alcohol **12** as an oil (1.71 g, 99%) which solidified and was recrystallized from hexane, to afford 1.49 g (85%) of pyrrole alcohol **12** as white needles: mp 42–43 °C; NMR ($CDCl_3$) δ 2.36 (1 H, br s), 4.54 (2 H, s), 6.36 (2 H, t, J = 2.2 Hz), 6.90 (2 H, t, J = 2.2 Hz), 7.3–7.6 (4 H, m).

7,9-Dimethoxy-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine (10). A solution of 1-(2-hydroxymethyl-4,6-dimethoxyphenyl)pyrrole (**9**) (233 mg, 1 mmol) and Rose Bengal (15 mg) in 150 mL of methanol was irradiated with four General Electric cool white fluorescent lamps (15 W per lamp) for 2 h while a slow stream of O_2 was swept through the solution. Removal of the solvent afforded a dark pink residue which was subjected to preparative TLC on silica gel using $CHCl_3$ to yield 170 mg (74%) of the oxygen-inserted product **10** (R_f 0.81) which was very unstable and turned red on exposure to light and air: NMR ($CDCl_3$) δ 3.75 (3 H, s), 3.85 (3 H, s), 4.95 (2 H, s), 5.45 (1 H, dd, J = 3.5, 2.0 Hz), 6.01 (1 H, t, J = 3.5 Hz), 6.30 (1 H, d, J = 2.5 Hz), 6.52 (1 H, d, J = 2.5 Hz), 7.25 (1 H, dd, J = 3.5, 2.0 Hz); mass spectrum *m/e* (rel intensity) 231 [M^+] (100), 216 [M − 15] (10), 202 [M − 29] (10), 188 [M − 43] (13.8).

3a,7,9-Trimethoxy-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1(3a*H*)-one (11). A solution of pyrrole alcohol **9** (233 mg, 1 mmol) and Rose Bengal (25 mg) in 150 mL of methanol was irradiated under the conditions described for the formation of oxazine **10.** Irradiation

of the reaction mixture was continued even after the disappearance of the starting material. Evaporation of the solvent after 5 h of irradiation of the reaction mixture afforded a dark pink residue which upon preparative TLC in $CHCl_3$ gave 24 mg (10%) of oxazine **10** from the fastest band and 129 mg (46%) of alkoxy lactam **11** from a slower moving band (R_f 0.17): NMR ($CDCl_3$) δ 3.30 (3 H, s), 3.83 (3 H, s), 3.94 (3 H, s), 4.62 and 5.08 (2 H, AB quartet, J_{AB} = 15 Hz), 6.31 (1 H, d, J = 6.0 Hz), 6.58 (1 H, d, J = 2.5 Hz), 6.72 (1 H, d, J = 2.5 Hz), 7.02 (1 H, d, J = 6.0 Hz): IR ($CHCl_3$) 1704 cm^{-1}; mass spectrum *m/e* (rel intensity) 277 (5), 262 (100).

3a-Methoxy-5H-pyrrolo[1,2-a][3,1]benzoxazin-1(3a*H*)-one (14). A solution of alcohol **12** (173 mg, 1 mmol) in 100 mL of methanol with added Rose Bengal (10 mg) was irradiated under the conditions described for the formation of **10**. After the consumption of the starting material which took 6 h, no oxazine **13** could be isolated by preparative TLC in $CHCl_3$, but an alkoxy lactam **14** was obtained from a slow moving band (R_f 0.12) as a yellow solid: (56 mg, 20%) NMR ($CDCl_3$) δ 3.34 (3 H, s), 4.92 and 5.37 (2 H, AB quartet, J_{AB} = 15 Hz), 6.44 (1 H, d, J = 6.0 Hz), 7.17 (1 H, d, J = 6.0 Hz), 7–7.3 (3 H, m), 8.12 (1 H, dd, J = 8.0, 2.5 Hz).

1-[α-(*tert*-Butyldimethylsiloxy)-4,6-dimethoxy-*o*-tolyl]pyrrole (15). To a solution of pyrrole alcohol **9** (466 mg, 2 mmol) in 2 mL of DMF were added dimethyl-*tert*-butylsilyl chloride (450 mg, 3 mmol) and imidazole (204 mg, 3 mmol) at 0 °C under nitrogen. The solution was stirred at this temperature for 10 min and at room temperature for 1 h. Workup involved diluting the reaction mixture with ether. The ethereal layer was washed with H_2O and dried over Na_2SO_4 and the solvent was removed in vacuo. Silica gel chromatography of the crude reaction mixture on three 20 × 20 cm preparative TLC plates ($CHCl_3$) yielded 556 mg (80%) of silyl ether **15** as a colorless gum. An analytical sample was prepared by sublimation of **15** at 100 °C (0.03 Torr): NMR ($CDCl_3$) δ 0.05 (6 H, s), 0.90 (9 H, s), 3.72 (3 H, s), 3.85 (3 H, s), 4.42 (2 H, s), 6.31 (2 H, t, J = 2.1 Hz), 6.48 (1 H, d, J = 2.5 Hz), 6.62 (2 H, t, J = 2.1 Hz), 6.83 (1 H, d, J = 2.5 Hz).

Anal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.70; H, 8.35; N, 4.02. Found: C, 65.80; H, 8.33; N, 4.08.

1-[α-(*tert*-Butyldimethylsiloxy)-4,6-dimethoxy-*o*-tolyl]-5-methoxy-3-pyrrolin-2-one (16). A 250-mL Pyrex graduated cylinder inside of which was placed a filter (soft glass) was charged with alcohol **15** (150 mg, 0.43 mmol), Rose Bengal (15 mg), and 150 mL of methanol. The solution, with a slow stream of oxygen passed through, was irradiated with a Sylvania tungsten Halogen quartz lamp No. Q/Cl (80 V) which was in a water-cooled immersion apparatus. The reaction was carried out at 0 °C in an ice bath and was monitored by TLC (3% MeOH/$CHCl_3$). After 40 min the reaction was complete. The solvent was removed on a rotary evaporator below 45 °C, and the dark residue was roughly separated by column chromatography on silica gel (8 in. × 1 in.) eluting successively with $CHCl_3$ and 3% MeOH/$CHCl_3$. The combined fractions were purified by preparative thin-layer chromatography to give one major product (R_f 0.46 in 3% MeOH/$CHCl_3$) (68 mg, 45%): IR ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.6 (6 H, s), 0.93 (9 H, s), 3.28 (3 H, s), 3.76 (3 H, s), 3.83 (3 H, s), 4.78 (2 H, s), 5.65 (1 H, m), 6.25 (1 H, dd, J = 6.0, 1.0 Hz), 6.43 (1 H, d, J = 2.5 Hz), 6.88 (1 H, d, J = 2.5 Hz), 7.03 (1 H, dd, J = 6.0, 1.5 Hz).

Desilylation of 16. A solution of silyl lactam **16** (40 mg, 0.11 mmol) in 5.5 mL of an acetic acid–H_2O–THF mixture (3:1:1.5) was stirred overnight at 50 °C. The reaction mixture was diluted with EtOAc and washed with 5% $NaHCO_3$, water, and brine and then dried with Na_2SO_4. Removal of solvent afforded 30 mg of crude alcohol **17**: NMR ($CDCl_3$) δ 3.32 (3 H, s), 3.80 (3 H, s), 3.88 (3 H, s), 4.52 (2 H, s), 5.72 (1 H, m), 6.38 (1 H, dd, J = 6.0, 1.0 Hz), 6.52 (1 H, d, J = 2.5 Hz), 6.72 (1 H, d, J = 2.5 Hz), 7.2 (1 H, dd, J = 6.0, 1.0 Hz); IR ($CHCl_3$) 1710 cm^{-1}.

Registry No.—**9**, 66769-50-4; **10**, 66769-51-5; **11**, 66769-52-6; **12**, 61034-86-4; **14**, 66769-53-7; **15**, 66769-54-8; **16**, 66787-42-6; **17**, 66769-55-9; 1-(2,4-dimethoxy-6-methoxycarbonylphenyl)pyrrole, 66769-56-0; 1-(2-carboxyphenyl)pyrrole, 10333-68-3; dimethyl-*tert*-butylsilyl chloride, 18162-48-6.

References and Notes

(1) Taken from the Ph.D. thesis of F.Z.B., Fordham University, 1977.
(2) D. A. Lightner, G. S. Bisacchi, and R. D. Norris, *J. Am. Chem. Soc.*, **98**, 803 (1976). Experimentation designed to yield mechanistic evidence in pyrrole oxidation and a thorough review of the literature.
(3) (a) T. Kametani, T. Ohsawa, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 1637 (1976); (b) R. W. Franck, K. Miyano, and J. F. Blount, *ibid.*, in press.
(4) (a) A. Ranjon, *Bull Soc. Chim. Fr.*, 2068 (1971); (b) ref 3a.
(5) J. W. Mellor, Ed., "A Comprehensive Treatise on Inorganic and Theoretical Chemistry", Vol. 1, Longmans, Green and Co., London, 1922, p 951.

(6) Analyses were performed by Spang Laboratories, Ann Arbor, Mich. NMR spectra were determined with Varian A-60A and Perkin-Elmer R12B spectrometers with chemical shifts expressed in δ units. For funds used to purchase the Perkin-Elmer R12B, we acknowledge Biomedical Sciences Support Grant RR 07150 from DHEW. Further we acknowledge the National Cancer Institute for Grant CA 11421.

Preparation of Carboxylic Acids from Protected Aldehydes

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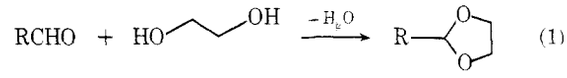
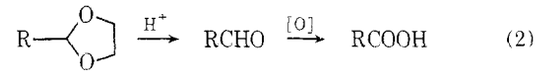
The acetal is the most common protecting group for aldehydes and 1,3-dioxolanes are the most commonly encountered type of acetal, usually prepared by reaction of the aldehyde with ethylene glycol with azeotropic removal of water (eq 1).[1] Regeneration of the carbonyl is normally carried out with aqueous acid.[2]



(1)

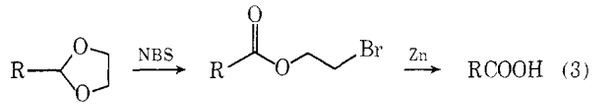
We have been concerned with the general problem of converting dioxolanes into carboxylic acids without employing acid to first remove the protecting group (eq 2). The nonacidic



(2)

alternative to eq 2 would allow the introduction of acid groups into a molecule containing various acid-sensitive functionalities.[3]

Our solution to this problem is outlined in eq 3. Prugh and McCarthy in 1966[4] showed that cyclic acetals are converted



(3)

into bromo esters when treated with *N*-bromosuccinimide (NBS).[5,6] Indeed, a variety of dioxolanes give good yields of the corresponding 2-bromoethyl esters when refluxed with NBS in CCl_4 (see Table I). For example, 2-phenyl-1,3-dioxolane gives a 98% yield of 2-bromoethyl benzoate (88% after distillation).

The transformation of eq 3 is completed by a zinc-induced 1,2 elimination which yields the acid upon workup (see Table I). Despite the precedent for this second step,[7,8] a variety of reaction conditions failed to give any acid from 2-bromoethyl benzoate. Zinc in refluxing THF gave no reaction. Even zinc which had been activated with copper sulfate was ineffective and ultraactive zinc from the potassium metal[9a] or sodium naphthalenide[9b] reduction of zinc chloride also failed to promote elimination. Zinc in refluxing methanol or ethanol gives 42–46% benzoic acid plus 47–52% of transesterification product. Ester interchange can be avoided by using zinc in refluxing aqueous THF to give a 44% yield of benzoic acid and a 41% recovery of starting material. Addition of catalytic sodium iodide improves the yield of benzoic acid from this reaction to 86% with only 13% of starting material recovered.

Because of the general catalytic effect of zinc halides,[10,11] we tried a mixture of zinc and zinc chloride. Indeed, this combination of reagents in refluxing THF for 24 h converts

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