was washed three times with 25-mL portions of water, twice with 25-mL portions of 5% aqueous K_2CO_3, and finally with saturated salt solution. The organic layer was dried over $MgSO_4$ and concentrated.

1-Acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene was isolated by fractional crystallization from ether at low temperatures, and after recrystallization from ether 0.75 g of white crystals was obtained: mp 84–85 °C; ^1H NMR ($CDCl_3$) δ 1.17 (s, 6 H, $C(CH_3)_2$), 1.43 (s, 6 H, $C(CH_3)_2$), 1.81 (s, 2 H, protons on C-4), 2.70 (s, 2 H, protons on C-6), 2.27 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.49; H, 7.93; N, 5.80. Found: C, 59.81; H, 8.33; N, 5.35.

The remaining liquid was distilled under reduced pressures and 1.33 g of clear yellow liquid of 1-acetoxy-6-nitro-3,3,5,5-tetramethylcyclohexene was obtained: bp 90–95 °C (0.4 torr); ^1H NMR ($CDCl_3$) δ 1.03 (s, 3 H, CH_3), 1.19 (s, 6 H, $C(CH_3)_2$), 1.26 (s, 3 H, CH_3), 1.74 (s, 2 H, protons on C-4), 2.13 (s, 6 H, $COCH_3$), 4.78 (s, 1 H, $CHNO_2$), 5.67 (s, 1 H, olefinic proton).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.49; H, 7.93; N, 5.80. Found: C, 59.17; H, 7.65; N, 5.83.

Registry No. **1a**, 589-92-4; **1b**, 5441-51-0; **1c**, 5432-85-9; **1d**, 98-53-3; **1e**, 591-24-2; **1f**, 936-99-2; **1g**, 873-94-9; **1h**, 14376-79-5; **1i**, 5064-52-8; **2a**, 22422-17-9; **2b**, 77507-06-3; **2c**, 77507-07-4; **2d**, 7360-39-6; **2e**, 15786-53-5; **2f**, 77507-08-5; **2g**, 4883-56-1; **2h**, 56763-68-9; **2i**, 20826-66-8; **3e**, 22336-10-3; **3f**, 66464-47-9; **3g**, 5011-67-6; **4a**, 74609-67-9; **4b**, 74609-69-1; **4c**, 74609-71-5; **4d**, 74609-73-7; **4g**, 74609-81-7; **5a**, 74609-68-0; **5b**, 74609-70-4; **5c**, 74609-72-6; **5d**, 74609-74-8; **5e**, 74609-64-6; **5f**, 74609-66-8; **5g**, 74609-82-8; **6e**, 74609-75-9; **6f**, 74609-77-1; **6g**, 74609-79-3; **7e**, 74609-76-0; **7f**, 74609-78-2; **7g**, 74609-80-6; *trans*-2-nitro-2-methyl-4-*tert*-butylcyclohexanone, 77507-09-6; 2-nitro-4-*tert*-butylcyclohexanone K, 77507-10-9; 2-nitro-3,3,5,5-tetramethylcyclohexanone, 74609-83-9; 1-acetoxy-2-nitro-3,3,5,5-tetramethylcyclohexene, 77507-11-0; 1-acetoxy-6-nitro-3,3,5,5-tetramethylcyclohexene, 77507-12-1.

Catechol and Substituted Catechol-Derived Ortho Esters, Models for Protected Active Esters in Peptide Synthesis

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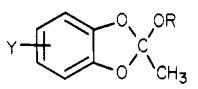
Monoalkyl orthoacetates derived from catechol, 4-nitrocatechol, and tetrabromocatechol have been prepared, and mild conditions (NaI–BF_3OEt_2) have been found that convert them to the corresponding catechol monoacetates in high yield. Possible applications of ortho esters as protected active esters for peptide synthesis are discussed.

In this paper we describe model studies of catechol-derived ortho esters 1 which demonstrate the potential application of these species as "safety-catch" protected active esters.



1

In 1968 Jones and Young[1] advanced the concept of safety-catch activation of carboxylic acids through their use of *o*-benzyloxyphenyl esters as blocked amide-forming reagents. Subsequently, Corvell and Jones have used these species for the synthesis of sequential polypeptides.[2] Because the *o*-benzyloxyphenyl esters are relatively inert to aminolysis under the usual conditions of peptide synthesis, they can be used as C-terminal blocking groups that are carried unchanged through several synthetic steps. Hydrogenolytic debenzylation generates a catechol monoester which can undergo rapid aminolysis resulting from anchimeric assistance by the phenolic hydroxyl group.

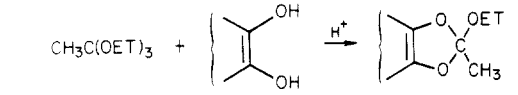
This ingenious amide-forming process has several intrinsic disadvantages, of which the most serious is the relatively low aminolytic reactivity of *o*-hydroxyphenyl esters, which confines their use to efficient couplings that can be run at relatively high concentrations or with unhindered amino acids. Introduction of electron-withdrawing groups to increase the rate of aminolysis of the *o*-hydroxyphenyl ester is also expected to increase the lability of the *o*-benzyloxyphenyl ester which is its precursor. A second problem is thus seen to be the benzyloxy function which is an imperfect safety catch that only masks hydroxyl catalysis and not the intrinsic ester reactivity.[3]

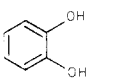
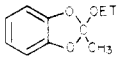
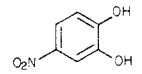
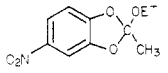
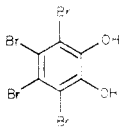
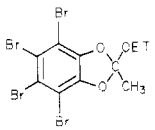
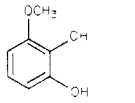
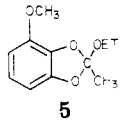
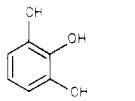
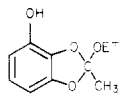
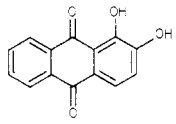
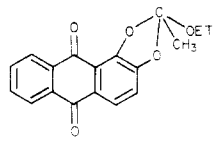
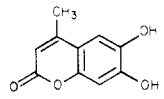
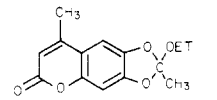
The ready formation of *o*-phenylene orthoacetate from a transketalization reaction between catechol and triethyl orthoacetate[4] and the availability of carbobenzyloxyglycine triethyl ortho ester[5] suggested the possibility of using an ortho ester as a safety catch for a catechol or substituted catechol monoester. Ortho esters as safety catches offer the potential advantage that they completely mask any ester reactivity. In addition, they are inert to a variety of neutral and/or basic conditions but are labile to acid. As in the case of urethane groups this acid lability can vary greatly depending on structure. Although the use of ortho esters in peptide synthesis would restrict the use of acid-labile amine protection, these species should be compatible with a variety of base-labile protective groups or those removed by hydrogenation. Three issues must be resolved before attempts can be made to apply ortho esters to the synthesis of large polypeptides. (1) Model systems must be prepared that demonstrate conditions that quantitatively convert catechol-derived ortho esters to the corresponding catechol monoesters. This demonstration may be relevant to many situations requiring a protected, activated carboxyl. (2) A general method must be found to

(1) Jones, J. H.; Young, G. T. *J. Chem. Soc. C* **1968**, 436.
(2) Corvell, R. D.; Jones, J. H. *J. Chem. Soc. C* **1971**, 1082.
(3) A phenacyl group can be used in place of the benzyl and can be removed under the milder conditions of zinc dust and acetic acid. This removal must be done, however, on an amine protected peptide. Trudelle Y. *Chem. Commun.* **1971**, 639.
(4) Gross, H.; Rusche, J. *Ber. Dtsch. Chem. Ges.* **1966**, *99*, 2625.
(5) Zemlicka, J.; Chladek, S. *Collect. Czech. Chem. Commun.* **1966**, *31*, 3755.

0022-3263/81/1946-3087$01.25/0

Table I



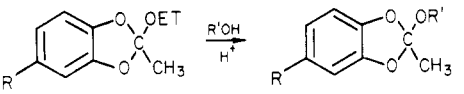
dihydroxyphenyl deriv	product[a]	yield, %
	 **2**	96
	 **3**	86
	 **4**	70
	 **5**	97
	 **6**	34
	 **7**	74
	 **8**	65

[a] As representatives, **2** and **3** were analyzed. Compounds **4–8** are characterized from the products of their acidic hydrolysis and their NMR spectra.

convert the carboxyl group of an optically active amino acid to an ortho ester. (3) It must be shown that racemization does not occur in the formation or decomposition of the ortho ester.

The first of these issues is the major subject of this paper. To resolve it we investigated the preparation of catechol and substituted catechol-derived ortho esters. We found the transketalization reaction between catechol and triethyl orthoacetate reported by Gross and Rusche in 1966[4] to be a general reaction that works satisfactorily for a variety of 1,2-dihydroxyphenyl systems. Thus, the reaction between triethyl orthoacetate and 4-nitrocatechol, tetrabromocatechol, 3-methoxycatechol, 1,2-dihydroxyanthraquinone, 1,2,3-trihydroxybenzene, and 4-methyl-6,7-dihydroxycumarin gave in each case the corresponding ortho ester as shown in Table I. When the triethyl orthoacetate and catechol derivative are heated together, alkylation of the phenolic hydroxyl groups may compete with ortho ester formation. This known reaction[6] can often be minimized by the addition of a solvent such as toluene or xylene which forms an azeotrope with ethanol, and it is striking and important for this study that alkylation is avoidable even with the acidic nitrocatechol.

From 2-ethoxy-2-methylbenzo-1,3-dioxolane (**2**) and its nitro derivative **3** we have been able to effect an exchange of the ethoxy group by alkoxy functions bearing a variety of electronegative substituents, forming ortho esters **9–11** (eq 1). Thus by a two-step acid-catalyzed reaction sequence with careful control of alcohol and catechol stoichiometry it is possible to prepare a wide variety of alkoxybenzodioxolanes of interest for the present study.



(1)

9, R = H; R′ = CH_2CCl_3
10, R = H; R′ = $CH_2CO_2CH_3$
11, R = NO_2; R′ = CH_2CCl_3

Having the appropriate model ortho esters in hand, we turned our attention to their hydrolysis. Hydrolysis of simple ortho esters has been shown to occur by an A1 mechanism involving general-acid catalysis[7] (eq 2 and 3).

$$RC(OR')_3 + HX \underset{}{\overset{k_1\ \text{(rate determining)}}{\rightleftharpoons}} RC^+(OR')_2 + HOR' + X^- \quad (2)$$

$$RC^+(OR')_2 + H_2O \xrightarrow{\text{fast}} RCO_2R' + R'OH + H^+ \quad (3)$$

For the cases of interest for this study two dialkoxy carbocations can be formed by rate-determining protonation; from the benzodioxolenium cation **12** (Scheme I) the desired catechol half-ester can be formed; from the unsymmetrical oxocarbocation **13**, catechol and an ethyl ester are the expected products.

Since the two general-acid-catalyzed steps that form these species are expected to have somewhat different Brønsted α values, the possibility existed that varying the acid catalyst could result in a change in the product ratio. As seen in Table II, a considerable variation of product ratio was in fact observed for the hydrolysis of 2-ethoxy-

Scheme I

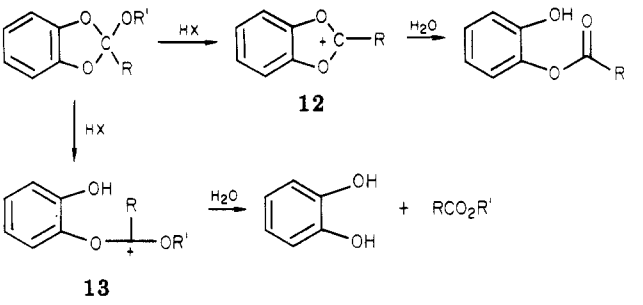
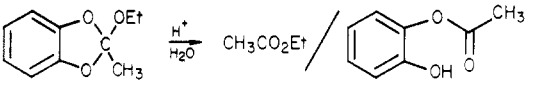


Table II



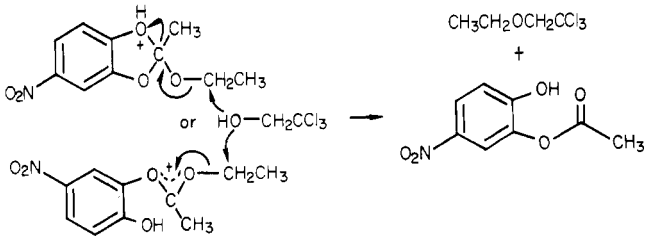
acidic condition	EtOAc/catechol monoacetate[a]
p-toluenesulfonic, picric, or dilute sulfuric acid	1/1
formic, phosphoric, or trichloroacetic acid	4/1
sulfuric or *p*-toluenesulfonic acid + LiBr	1/4

[a] The ratio of esters was determined by ^1H NMR spectroscopy.

(6) Smith, B. *Acta Chem. Scand.* **1956**, *10*, 1006.

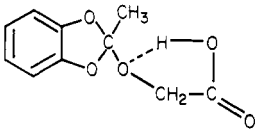
(7) DeWolfe, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970; pp 134–146.

Scheme II



2-methylbenzo-1,3-dioxolane in a mixture of acetone-d_6–D_2O in the presence of a variety of acids, and comparison of the first and third entries of Table II reveals a significant salt effect that favors formation of the catechol half-ester. Unfortunately, no condition could be found that generated this species as the sole product.

In an attempt to control product formation by intramolecular general-acid catalysis we prepared **14** by sapo-

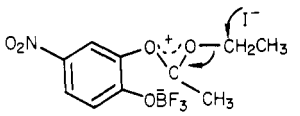


14

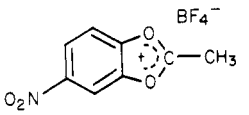
nification of the corresponding methyl ester **10**. Upon being allowed to stand at room temperature, **14** hydrolyzes to yield exclusively catechol monoacetate. Intramolecular catalysis thus constitutes one solution to the problem of selective hydrolysis.

Since the partitioning to form **12** and **13** is expected to be sensitive to electron-withdrawing benzo substituents, any conclusions concerning partitioning must be reexamined for each new substrate. The 4-nitrocatechol esters were of particular interest as analogues of *p*-nitrophenyl esters, although the effect of a 4-nitro group on aminolytic reactivity of a catechol monoester is difficult to predict since an electron-withdrawing group is expected to make the phenolate of the ester a better leaving group and to render the neighboring phenolate anion a weaker base which is less effective at anchiomeric assistance. In fact, at 25 °C in acetonitrile, 4-nitrocatechol monoacetate reacts 4 times more rapidly with benzylamine than with *p*-nitrophenyl acetate, and the nitro ester therefore shows a sufficient reactivity to warrant further study.[8]

Species **11** was observed to hydrolyze in acetone–water containing a trace of sulfuric acid to give 80% 4-nitrocatechol monoacetate. This yield could not be improved and falls short of the requirements of peptide synthesis. The preparation of **11**, which proceeded in relatively low yield from the ethoxy analogue by transketalization with trichloroethanol, provided an important clue toward an improved method of hydrolysis. The side reaction during transketalization appears to be S_N2 attack by trichloroethanol at the ethyl group of the unsymmetrical carbocation (Scheme II). This reaction suggested to us the possibility of using nucleophilic attack under acidic conditions to generate 4-nitrocatechol monoacetate directly from **3**, thereby avoiding any need to modify the ortho ester function by transketalization. Since it is well-known[9] that ortho esters react with boron trifluoride etherate to give dialkoxyoxonium ions, reaction of **3** with boron trifluoride etherate should generate either **15** or **16**. Only **15** is capable of reacting with a nucleophile like iodide ion, and therefore reaction of **3** with these reagents in combination should give exclusively 4-nitrocatechol monoacetate.



15



16

When **3** was treated with a fivefold excess of sodium iodide and 1.33 equiv of boron trifluoride etherate in dichloromethane acetone at 0 °C for 5 min, a 100% yield (98% isolated) of 4-nitrocatechol monoacetate was isolated. Ortho ester **4** yielded only 2,3,4,5-tetrabromocatechol monoacetate under these conditions. Both **3** and **4** were found to be inert to sodium iodide in boiling acetone in the absence of acid and water as well as to a variety of basic conditions. Although in theory a variety of acids could be used for the decomposition, boron trifluoride was found to be most convenient, and it should be noted that this and similar Lewis acids have been successfully used in peptide synthesis.[10]

In this study we have shown that protected active esters can be readily prepared from triethyl ortho esters and dihydroxyphenyl derivatives and that these ortho esters can be quantitatively decomposed to give the active ester under mild conditions. Applications of these results to peptide synthesis will be reported subsequently.

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt apparatus and are uncorrected. The ^1H NMR spectra were obtained on either a Varian T-60, a Perkin Elmer R-22, or a Hitachi Perkin-Elmer R24B spectrometer with tetramethylsilane as an internal standard; the coupling constants are given in hertz. Microanalyses were performed by Midwest Microlab, Ltd.

Preparation of the Benzo-1,3-dioxolanes. Method A. Without Solvent. A mixture of the dihydroxy compound (1 equiv), triethyl orthoacetate (3 equiv), and 1 drop of a saturated solution of HCl in ethanol is heated in a microdistillation apparatus at 100–110 °C for 2–3 h. During this time ethanol is slowly collected in the receiver. At the end of the reaction a heat gun is applied to the apparatus to drive any remaining ethanol over. The reaction is quenched by adding a 1 N sodium hydroxide solution (1 mL) with rapid stirring. Ethyl ether (60 mL) is then added to the quenched solution, and the ether layer is washed twice with 1 N sodium hydroxide (30 mL) and then once with water (30 mL). The ether layer is then dried over anhydrous potassium carbonate and evaporated to yield the crude ortho ester which is distilled or recrystallized.

Method B. With Solvent. A mixture of the dihydroxy compound (1 equiv), triethyl orthoacetate (3 equiv), toluene or xylene (5 mL/mmol of dihydroxy compound), and 1 drop of a saturated solution of HCl in ethanol is heated in a distillation apparatus. The solvent is distilled over until only a small amount is left, and then an additional portion of solvent is added. This process is repeated twice more before the reaction is quenched with 1 N sodium hydroxide. The workup is then as described in method A.

2-Ethoxy-2-methyl(5-nitrobenzo)-1,3-dioxolane (3). Procedure A was used with 4-nitrocatechol (2.0 g, 13 mmol) and triethyl orthoacetate (8 g, 50 mmol) which gave 2.5 g (86%) of

(8) Strikingly, 4,5-dinitrocatechol monoacetate reacts with benzylamine in acetonitrile at 25 °C only slightly more rapidly than 4-nitrocatechol monoacetate.

(9) (a) Perst, H. "Oxonium Ions in Organic Chemistry"; Verlag Chemie/Academic Press: New York, 1971; p 39. (b) Dimroth, K.; Heinrich, P.; Schromm, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 873.

(10) (a) Yajima, H.; Kawasaki, K.; Kinomura, Y.; Oshima, T.; Kimoto, S.; Okamoto, M. *Chem. Pharm. Bull.* **1968**, *16*, 1342. (b) Hiskey, R. G.; Beacham, L. M.; Matl, V. G.; Smith, T. N.; Williams, E. B.; Thomas, A. M.; Wolters, E. T. *J. Org. Chem.* **1971**, *39*, 488. (c) Guttman, S. In "Peptides Proceeding of the Sixth European Peptide Symposium, Athens, 1963"; L. Zervas, Ed.; Pergamon Press: Oxford, 1966; p 107.

a yellow liquid [bp 93–96 °C (0.15 mm)] that crystallized on standing: ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 1.9 (s, 3 H), 3.6 (q, 2 H), 6.9 (half of an AB q, J = 4, 1 H), 7.7 (d, J = 1, 1 H), 7.9 (dd, J = 4, 1, 1H).

Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.55; H, 4.92; N, 6.22. Found: C, 53.05; H, 4.75; N, 6.33.

2-Ethoxy-2-methyl(tetrabromobenzo)-1,3-dioxolane (4). Procedure B was used with tetrabromocatechol (5 g, 12 mmol), triethyl orthoacetate (6.6 mL, 36 mM mmol), and toluene (50 mL) which gave 5.8 g (93%) of crude ortho ester. Recrystallization from ethyl acetate–petroleum ether afforded 4 g (70%) of white needles: mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3 H), 1.9 (s, 3 H), 3.6 (q, 2 H).

2-Ethoxy-2-methyl(4-methoxybenzo)-1,3-dioxolane (5). Procedure A was used with 3-methoxycatechol (3 g, 20 mmol) and triethyl orthoacetate (16 mL, 86 mmol) which gave 4.1 g (97%) of a liquid: bp 67–70 °C (0.015 mm); ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3 H), 1.8 (s, 3 H), 4.0 (q, 2 H), 6.6–7.1 (m, 3 H).

2-Ethoxy-2-methyl(4-hydroxybenzo)-1,3-dioxolane (6). Procedure A was used with 1,2,3-trihydroxybenzene (4 g, 32 mmol) and triethyl orthoacetate (14 mL, 95 mmol) which gave 3.6 g (57%) of crude ortho ester. Recrystallization from ethyl acetate–petroleum ether afforded 2.1 g (34%) of light brown crystals: mp 153–155 °C; ^{1}H NMR (acetone-d_6) δ 1.1 (t, 3 H), 1.2 (s, 3 H), 3.6 (q, 2 H), 6.1–6.7 (m, 3 H).

1,2-(Ethyl orthoacetyl)anthraquinone (7). Procedure B was used with alizarin (4 g, 17 mmol), triethyl orthoacetate (9.2 mL, 50 mmol), and toluene (50 mL) which gave 4.5 g (85%) of crude ortho ester. Recrystallization from ethyl acetate–petroleum ether afforded 3.9 g (74%) of yellow crystals: mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 2.0 (s, 3 H), 3.8 (q, 2 H), 7.3–8.6 (m, 6 H).

6,7-(Ethyl orthoacetyl)-4-methylcoumarin (8). Procedure A was used with 4-methylesculatin (1 g, 21 mmol) and triethyl orthoacetate (2.2 mL, 63 mmol) which gave 4.1 g (75%) of crude ortho ester. Recrystallization from ethyl acetate–petroleum ether afforded 3.6 g (65%) of white crystals: mp 140–141 °C; ^{1}H NMR (CD_3CN) δ 1.2 (t, 3 H), 1.9 (s, 3 H), 2.5 (s, 3 H), 3.8 (q, 2 H), 6.4 (finely split s, 1 H), 7.1 (s, 1 H), 7.4 (s, 1 H).

Study of the Acid Hydrolysis of 2-Ethoxy-2-methylbenzo-1,3-dioxolane (2). This species (~40 mg) was dissolved in a deuterium oxide–hexadeuterioacetone mixture (4:1, 0.5 mL) and added to an NMR tube. In the experiment, in which a salt such as lithium bromide was used, as much as possible of the salt was dissolved in the solvent mixture before the addition of the orthoacetate. A catalytic amount of the desired acid was then added at the NMR spectrometer and the spectra were taken. Since the reaction products, ethyl acetate and acetyl catechol, had significantly different NMR spectra, the ratio of the products formed could be determined by comparing the areas of their respective NMR signals. The acetate methyl of ethyl acetate appears at 2.0 ppm and the acetate methyl of the acetyl catechol at 2.3 ppm.

2-Methyl-2-(2,2,2-trichloroethoxy)benzo-1,3-dioxolane (9). A solution of **2** (4 g, 20 mmol), 2,2,2-trichloroethanol (5.2 mL, 60 mmol), toluene (15 mL), and 1 drop of concentrated sulfuric acid was heated in a microdistillation apparatus for 5 h at 120 °C. Toluene was replaced in the pot as it distilled over. After 2 h, into the reaction mixture was added an additional portion of 2,2,2-trichloroethanol (2 mL). The reaction mixture was then quenched and worked up as described in the preceding ortho ester preparations. The residual liquid was distilled to yield 1.7 g (59%) of the ortho ester: bp 85–92 °C (0.01 mm); ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 4.1 (s, 2 H), 6.8 (s, 4 H). The hydrolysis of **9** was performed as described for **2**.

2-[(Methoxycarbonyl)methoxy]-2-methylbenzo-1,3-dioxolane (10). A solution of **2** (4.8 g, 26 mmol), methyl glycolate (7.6 g, 84 mmol), and 1 drop of concentrated sulfuric acid was heated in a microdistillation apparatus at 150 °C for 1 h during which 1.2 g (100%) of ethanol was collected. The reaction mixture was then worked up as in the previous ortho ester preparations. The residual solid was recrystallized from ethyl acetate–petroleum ether to give 4 g (69%) of tan crystals: mp 65–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 3.8 (s, 3 H), 4.2 (s, 2 H), 6.9 (s, 4 H).

For analysis the substance was recrystallized three times from ethyl acetate–petroleum ether and dried in a dessicator over potassium hydroxide at room temperature for 5 h; mp 67–71 °C.

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.97; H, 5.52.

2-(Carboxymethoxy)-2-methylbenzo-1,3-dioxolane (14). To **10** (200 mg, 0.9 mmol) were added standardized 1 N sodium hydroxide (2.5 mL) and enough acetonitrile to make the solution homogeneous. After 5 h at room temperature, the solution was extracted once with ether. The water layer was acidified carefully to pH 7 with standardized 1 N hydrochloric acid. The neutral solution was then extracted three times with ether, and the combined ether layers were washed twice with water and after addition of acetonitrile (20 mL) was concentrated to give 130 mg (65%) of an oily crystalline solid. Purification was difficult due to the ease at which this ortho ester hydrolyzed at room temperature to give acetyl catechol and glycolic acid: ^{1}H NMR (CD_3CN) δ 1.9 (s, 3 H), 4.3 (s, 2 H), 6.9 (s, 4 H).

***O*-Acetyl-4-nitrocatechol.** Green's[11] method for the monoacetylation of catechol was adopted. To a stirred solution of 4-nitrocatechol (1.0 g, 6.5 mmol) and pyridine (1.0 g, 13 mmol) in ethyl acetate (15 mL) at 10 °C was added dropwise thionyl chloride (0.8 g). A precipitate formed after 6 h at 25 °C. The solution was filtered to yield pyridine hydrochloride (1.3 g). The filtrate was concentrated to yield 1.3 g (100%) of *O*-thionyl-4-nitrocatechol. A solution of this and pyridine (2 drops) in acetic acid (15 mL) was refluxed for 6 h. After cooling, the solution was emptied onto ice–water (200 mL). Filtration yielded 0.7 g (55%) of a white solid. Recrystallization from ethyl acetate–cyclohexane afforded 0.6 g (50%) tannish crystals: mp 138–144 °C; ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 7.2 (half of an AB q, J = 5, 1 H), 8.0 (s, 1 H), 8.1 (dd, J = 5, 1, 1 H).

Anal. Calcd for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.10. Found: C, 48.49; H, 3.52; N, 7.05.

***O*-Acetyl-4,5-dinitrocatechol.** To a solution of 4,5-dinitrocatechol[12] (0.57 g, 2.8 mmol) in pyridine (15 mL) was added acetic anhydride (0.29 g, 3 mmol). After the mixture had been allowed to stand overnight, methylene chloride was added, and the solution was washed once with water, three times with 3 N hydrochloric acid, and once with water, dried over magnesium sulfate, and evaporated to yield 0.6 g of a powder. Recrystallization from ethyl acetate–cyclohexane afforded 0.54 g (80%) of needles: mp 174–178 °C; ^{1}H NMR (CD_3CN) δ 2.4 (s, 3 H), 7.5 (s, 1 H), 8.0 (s, 1 H).

Anal. Calcd for $C_8H_6N_2O_7$: C, 39.68; H, 2.50; N, 11.57. Found: C, 39.68; H, 2.47; N, 11.66.

Aminolysis Rates for *p*-Nitrophenyl Acetate, *O*-Acetyl-4-nitrocatechol, and *O*-Acetyl-4,5-dinitrocatechol with Benzylamine. The acetate (1 equiv) was weighed directly in an NMR tube, and trideuterioacetonitrile (0.5 mL) was added. At the NMR spectrometer, freshly distilled benzylamine (2 equiv) was added to the NMR tube with a microsyringe. After a brief shaking of the tube, the NMR spectrum was immediately taken and retaken at time intervals suitable for following the aminolysis. The concentrations of acetate and amide were determined by comparing the intensity of the decreasing acetate methyl peak of the nitro esters at 2.4 ppm with the increasing acetate methyl peak of benzylacetamide at 2.0 ppm in the NMR spectrum.

2-Methyl-2-(2,2,2-trichloroethoxy)(4-nitrobenzo)-1,3-dioxolane (11). A mixture of **3** (1 g, 4.4 mmol) and 2,2,2-trichloroethanol (2.3 g, 26 mmol) was heated in a microdistillation apparatus until the solution was homogeneous, and then 1 drop of concentrated sulfuric acid was added. The reaction mixture was heated for 1.5 h at 120 °C, and then an additional portion of 2,2,2-trichloroethanol (2 g) was added. After another 1.5 h the reaction was quenched and worked up as previously described. The residual solid was recrystallized from ethyl acetate–cyclohexane to yield the product: 0.4 g (27%); mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3 H), 4.1 (s, 2 H), 6.8–8.0 (m, 3 H).

Reaction of 3 with BF_3–Etherate and NaI. To a solution of **3** (1.0 g, 4.4 mmol) in methylene chloride (5 mL) at 0 °C were added an anhydrous solution of NaI in acetone (3 equiv) and freshly distilled boron trifluoride etherate (1.33 equiv) under nitrogen. After 5 min at 0 °C, water (20 mL) and methylene chloride (20 mL) were added. The layers were separated, and after back-extraction of the water layer, the combined methylene chloride layers were dried over magnesium sulfate and evaporated

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to yield 0.84 g (97%) of O-acetyl 4-nitrocatechol; identical with the material prepared as described previously.

Reaction of 4 with BF_3 Etherate and NaI. To a solution of 4 (0.3 g, 0.6 mmol) in methylene chloride (2 mL) were added an anhydrous solution of NaI in acetone (3 equiv) and freshly distilled boron trifluoride etherate (1.33 equiv) under nitrogen. After 1 h at room temperature, the reaction was worked up as described for 2 and yielded 0.26 g (93%) of O-acetyl-tetrabromocatechol.

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Registry No. 2, 7555-18-2; 3, 77400-20-5; 4, 77400-21-6; 5, 77400-22-7; 6, 61627-35-8; 7, 77400-23-8; 8, 77400-24-9; 9, 77400-25-0; 10, 77400-26-1; 11, 77400-27-2; 14, 77400-28-3; triethyl arthoacetate, 78-39-7; catechol, 120-80-9; 4-nitrocatechol, 3316-09-4; tetrabromocatechol, 488-47-1; 3-methoxycatechol, 934-00-9; 1,2,3-trihydroxybenzene, 87-66-1; alizarin, 72-48-0; 4-methylesculatin, 529-84-0; ethyl acetate, 141-78-6; acetylcatechol, 2848-25-1; 2,2,2-trichloroethanol, 115-20-8; methyl glycolate, 623-50-7; acetyl-4-nitrocatechol, 77400-64-7; acetyl-4,5-dinitrocatechol, 77400-29-4; 4,5-dinitrocatechol, 77400-30-7; acetyltetrabromocatechol, 77400-31-8.

One-Step Spiroannelation. Synthesis of Spiro γ- and δ-Lactones

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Carbocyclic acid anhydrides can be converted to spiro γ- and δ-lactones by addition of di-Grignard reagents in tetrahydrofuran solution. Five- and six-membered rings have been formed in one-step reactions. Possible mechanistic pathways for this reaction are discussed. The conversion of spirolactones to 1-(ω-hydroxyalkyl)-cycloalkanols was accomplished by reduction with LAH to illustrate the versatility of these substances giving (after or upon treatment with tosyl chloride) the corresponding spiroethers.

Introduction

Considerable progress has been made in the development of various procedures for the elaboration of synthetic routes to γ- and δ-lactones.

A general method was the halogen–metal exchanges in esters of haloaryl acids.[1-9] Moreover, a variety of synthons containing carbanions at the convenient position has been developed[10-15] and their addition to aldehydes and ketones provided the skeletal arrangement which ultimately has been converted into γ- and δ-lactones.

Another method using the reaction of the lithium salt of 2,4,4-trimethyl-2-oxazoline with epoxides at low temperature after hydrolysis of the resulting hydroxypropyloxazolines produced the expected δ-butyrolactones.[16,17]

Recently, a direct synthesis was reported involving the addition of lithium β-lithiopropionate to aldehydes or ketones, followed by lactonization of the γ-hydroxy acid,[11] but according to the authors, the yield was low, especially in cases involving ketones as the carbonyl component. Within the past decade much research has been directed toward the formation of spirolactones, using general methods of lactonization.[5,18-23] Many of those methods were limited to the synthesis of spirolactones which often appeared in the literature (1-oxaspiro[4.4]nonan-2-one and 1-oxaspiro[4.5]decan-2-one); cyclohexanone and cyclopentanone were inevitably selected as substrates.[5,6,9-12,19-21,23-25,37]

In a previous article,[25] we described a new one-step synthesis of 1-(ω-hydroxyalkyl)cycloalkanols involving the reaction of bis(bromomagnesio)alkanes with lactones. Oxidation of these diols by Jones reagent provided a high yield of the corresponding spirolactones. This method was simple, versatile, and general for preparation of spirolactones.

The use of organodimagnesium compounds has now been extended to the reactions of cyclic anhydrides. As our preliminary note[26] showed, this facile one-step synthesis led to a variety of spirolactones. The great advantage of this method is that the intermediate carboxylate is stable under the reaction conditions and thus does not give byproducts.

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