Oxidative Preparation of Aromatic Orthocarboxylates from Aldehydes

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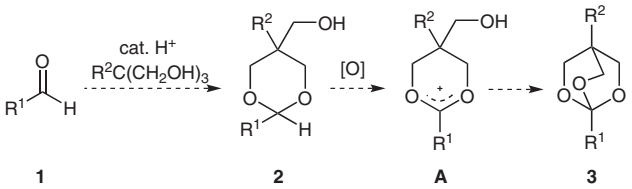
Abstract: Aromatic orthocarboxylates are oxidatively synthesized in good yields from hydroxyacetals derived from the corresponding aromatic aldehydes. In situ generation of hydroxyacetal and successive oxidation by DDQ provides a one-pot preparation of aromatic orthocarboxylates from aldehydes.

Key words: orthoester, oxidation, acetal, aldehyde, one-pot reaction

Due to their stability towards nucleophiles and strong bases and ease of conversion into carboxylic acid derivatives by acidic solvolysis, orthoesters have been paid much attention as masked carboxylic acids and esters.[1] Orthoesters are also important as a building block in organic synthesis in their own right.[2] It had been difficult to prepare orthoesters directly by reaction of carboxylic acids or esters with alcohols under acid catalysis, the conditions commonly used in the equivalent acetal formation from aldehydes or ketones.[1] Since E. J. Corey and N. Raju developed a practical synthetic method, involving Lewis acid mediated rearrangement of oxetane esters,[3] orthoesters have been widely used in organic synthesis, especially in natural product synthesis.[4] Improvements to this oxetane ester method have been reported[5] and other precursors such as nitriles,[6] imidoesters,[7] and orthoesters (for orthoester exchange)[8] have been used. Under these reaction conditions, however, functional-group acceptability is limited. Herein we report an oxidative preparation of bicyclic aromatic orthocarboxylates from aldehydes.

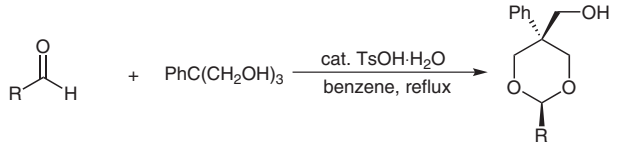
The conversion of an aldehyde into a bicyclic orthocarboxylate **3** was designed as depicted in Scheme 1,[9] in which the key intermediate, dialkoxy carbocation **A**, is generated by an oxidation of hydroxyl acetal **2**, which would be easily prepared from aldehyde **1** and a triol under acid-catalyzed azeotropic conditions.

Hydroxy acetals **2** were prepared from the corresponding aldehydes and triol **4**[10] in good yield as a mixture of diastereoisomers in 10:1 to 7:1 ratio (Table 1). The major isomers were isolated pure by silica gel column chromatography (hexane–EtOAc = 4:1) followed by recrystallization (hexane–EtOAc).[11]



Scheme 1

Table 1 Preparation of Hydroxy Acetal **2**[a]



Entry	R	Product	Yield (%)[b,c]
1	**1a** naphthalen-2-yl	**2a**	72
2	**1b** 4-$Me_2NC_6H_4$	**2b**	81
3	**1c** 4-$MeOC_6H_4$	**2c**	79
4	**1d** 4-MeC_6H_4	**2d**	73
5	**1e** Ph	**2e**	80
6	**1f** 4-BrC_6H_4	**2f**	69
7	**1g** 4-$MeO_2CC_6H_4$	**2g**	71
8	**1h** 2-phenylethen-1-yl	**2h**	77
9	**1i** 2-phenylethyl	**2i**	75

[a] Reaction conditions: aldehyde **1** (10 mmol), triol (12.5 mmol), $TsOH·H_2O$ (0.2 mmol), benzene (40 mL), reflux.
[b] Isolated yield of a major diastereomer separated by column chromatography and recrystallization (hexane–EtOAc).
[c] The relative stereochemistry of the major product was determined by NOESY analysis.

The oxidation of isolated hydroxyl acetals **2** was examined and various oxidants, such as *N*-bromosuccinimide (NBS),[12] cerium ammonium nitrate (CAN)[13] and $Pd(OAc)_2/O_2$[14] were tested. Finally, dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was found to be suitable for this purpose.[15] The investigation of solvents and reaction temperatures in the reactions of hydroxy acetal **2a** with DDQ is summarized in Table 2.

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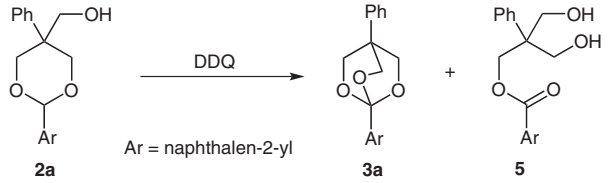
Particularly in halogenated solvents, the desired orthoester **3a** was obtained along with oxidative hydrolysis product **5**. Increasing the reaction temperature resulted in the orthoester **3a** being obtained in higher yield (entries 3–7). Finally, oxidation in refluxing 1,2-dichloroethane in the presence of 4 Å molecular sieves gave orthoester **3a** in 94% yield (entry 7).

Table 2 Optimization of Oxidative Preparation of Orthoester **3a**[a]



Entry	Solvent	Temp (bp)[b]	Time (h)	Yield of **3a** (%)	Yield of **5** (%)	Yield of **2a** (%)[c]
1	toluene	r.t.	20	0	30	58
2	MeCN	r.t.	14	0	0	88
3	CH_2Cl_2	r.t.	10	20	41	21
4	CH_2Cl_2	reflux (40 °C)	8	62	24	7
5	CCl_4	reflux (77 °C)	12	72	14	0
6[d]	CCl_4	reflux (77 °C)	4	87	12	0
7[d]	DCE	reflux (84 °C)	5	94	6	0

[a] Reaction conditions: hydroxyl acetal **2a** (0.2 mmol), DDQ (0.24 mmol), solvent (5 mL).
[b] Boiling point of the solvent.
[c] Numbers in parentheses show recovery of the starting material **2a**.
[d] 4 Å MS added (100 mg/0.2 mmol of **2a**).

Subsequently, the transformation of various hydroxyacetals of aromatic aldehydes was examined under the above optimized reaction conditions (Table 2). In the case of electron-rich aromatic acetals, the reactions proceeded smoothly, and the desired orthoesters were obtained in high yield (entries 2–4). Notably, hydroxyl acetal **2b**, having a *p*-dimethylaminophenyl group, was consumed rapidly at room temperature to give orthoester **3b** in 93% yield (entry 2). On the other hand, electron-deficient acetals **2e** and **2f** required longer reaction times and gave lower yields of orthoesters **3**. Even in such cases, high yields were achieved by using excess of DDQ (entries 5 and 6). Hydroxyacetal **2g**, having a *p*-MeO_2C group, however, was not easily oxidized even by excess of DDQ and resulted in only a 14% yield of orthoester **3g** (entry 7). The process was not restricted to aryl aldehydes; hydroxy acetal **2h**, derived from an alkenyl aldehyde, was found to be efficiently converted into the corresponding α,β-unsaturated orthoester **3h** (entry 8).

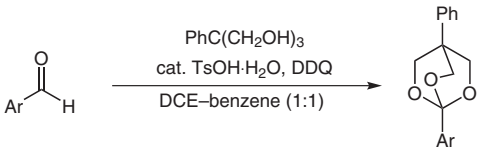
We then attempted one-pot preparation of orthoesters from aldehydes without isolation of the intermediate hydroxyl acetals (Table 4). When naphthalenecarbaldehyde **1a** was treated with triol **4** and catalytic amount of toluenesulfonic acid hydrate ($TsOH·H_2O$) in the presence of

Table 3 Preparation of Orthoester from Hydroxy Acetal[a]

Entry	Hydroxy acetal **2** Ar		DDQ[b]	Time (h)	Orthoester **3**	Yield (%)
1	naphthalen-2-yl	**2a**	1.2	5	**3a**	94
2[c]	4-$Me_2NC_6H_4$	**2b**	1.2	0.5	**3b**	93
3	4-$MeOC_6H_4$	**2c**	1.2	7	**3c**	92
4	4-MeC_6H_4	**2d**	2.0	20	**3d**	78
5	Ph	**2e**	10.0	7	**3e**	79
6	4-BrC_6H_4	**2f**	10.0	11	**3f**	89
7	4-$MeO_2CC_6H_4$	**2g**	10.0	10	**3g**	14
8	2-phenylethen-1-yl	**2h**	1.2	0.2	**3h**	93

[a] Reaction conditions: hydroxyl acetal **2** (0.2 mmol), DDQ (0.24–2.0 mmol), 4 Å MS (100 mg), DCE (5 mL).
[b] Numbers show the molar amounts of DDQ.
[c] Reaction was performed at r.t.

Table 4 One-Pot Preparation of Aromatic Orthocarboxylate from Aldehyde[a]



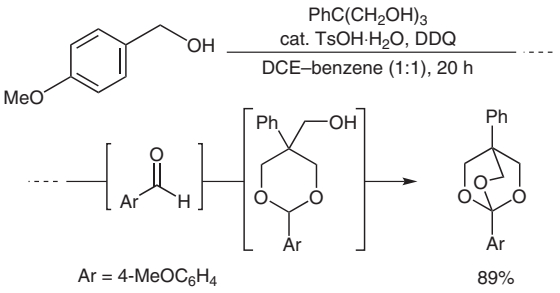
Entry	Ar		Time (h)	Orthoester **3**	Yield (%)
1	naphthalen-2-yl	**1a**	20	**3a**	92
2[b]	4-$Me_2NC_6H_4$	**1b**	10[c]	**3b**	92
3	4-$MeOC_6H_4$	**1c**	24	**3c**	90
4	4-MeC_6H_4	**1d**	24	**3d**	87
5[b]	2-phenylethen-1-yl	**1h**	20	**3h**[c]	92
6	2-furyl	**1j**	24	**3j**	88
7	2-thienyl	**1k**	24	**3k**	91

[a] Reaction conditions: aldehyde 1 (0.5 mmol), triol (0.55 mmol), DDQ (0.55 mmol), $TsOH·H_2O$ (0.055mmol) with Soxhlet filled with 4 Å MS.
[b] DDQ was added after the confirmation of complete consumption of aldehyde.
[c] The reaction time after the addition of DDQ.

1.2 molar amounts of DDQ and heated at reflux temperature in a dichloromethane–benzene (1:1) mixed solvent,

orthoester **3a** was obtained in 92% yield (entry 1). However, *p*-dimethylaminobenzaldehyde (**1b**) and cinnamaldehyde (**1h**) were found to be easily oxidized by DDQ before the acetalization and gave complex mixtures. When DDQ was added after the complete acetalyzation of these aldehydes, the desired orthoesters **3b** and **3h** were obtained in good yields (entries 2 and 5). This methodology is applicable for the preparation of heteroaromatic orthocarboxylates (entries 6 and 7).

Additionally, orthoesters were expected to be prepared from the corresponding alcohols if the alcohols were oxidized to aldehyde by DDQ. As DDQ is used to deprotect *p*-methoxybenzyl (PMB) ethers,[16] we attempted the conversion of *p*-methoxybenzyl alcohol to the orthoester (Scheme 2). When *p*-methoxybenzyl alcohol was treated with triol **4**, DDQ, and a catalytic amount of $TsOH·H_2O$ in a mixed solvent of 1,2-dichloroethane and benzene (1:1), the corresponding orthoester **2c** was obtained in 89% yield.



Scheme 2

In conclusion, a convenient method to prepare aromatic orthocarboxylates has been developed starting from aldehydes as their precursors.

General Procedure for the One-Pot Preparation of Orthocarboxylic Ester 3

To a 30 mL three-neck round-bottom flask equipped with a Soxhlet condenser containing 4 Å MS, a solution of aldehyde (0.5 mmol), triol (0.55 mmol), and $PTSA·H_2O$ (0.055 mmol) in a mixture of DCE (5 mL) and benzene (5 mL) was added. After heating for the period described in the text, the reaction mixture was filtered though Celite. The volatile materials were removed under reduced pressure and the crude material purified by column chromatography on Florisil (hexane–EtOAc = 2:1).

1-(Naphthalen-2-yl)-4-phenyl-2,6,7-trioxabicyclo [2.2.2]octane (3a)

^1H NMR (400 MHz, $CDCl_3$): δ = 4.55 (6 H, s), 7.20–7.22 (2 H, m), 7.33–7.34 (1 H, m), 7.37–7.41 (2 H, m), 7.46–7.50 (2 H, m), 7.76–7.78 (1 H, m), 7.82–7.89 (3 H, m), 8.19 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.0, 72.2, 108.2, 123.2, 125.1, 125.2, 126.0, 126.4, 127.5, 127.9, 128.0, 128.6, 129.1, 132.7, 133.6, 134.4, 135.8. IR (ZnSe): 3054, 1326, 1268, 1132, 1022, 970, 900, 858, 694 cm^{-1}. Anal. Calcd (%) for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.11; H, 5.82.

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