An Efficient and Solvent-Free Synthesis of Mixed Ortho Esters

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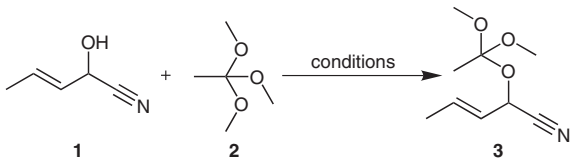
Abstract: Primary, secondary and electron-deficient tertiary alcohols react rapidly with ketene dimethyl acetal to form mixed ortho esters, without catalysts and under solvent-free conditions. 1,2-Diols yield bis(mixed ortho esters), rather than cyclic ortho esters.

Key words: ortho esters, ketene dimethyl acetal, alcohols, cyanohydrins, 1,2-diols

Ortho esters are versatile synthetic intermediates. They form a range of functionalised acetals on treatment with various nucleophiles, such as Grignard reagents,[1] Reformatsky reagents,[2] nitromethane,[3] phenylacetylene,[4] reducing agents such as DIBAL-H,[5,6] cyanide reagents[7–9] and $TMSN_3$.[10] Ortho esters have also been used for the synthesis of imidate esters[11] and are useful protecting groups for alcohols and carboxylic acids, because of their ability to withstand alkaline conditions whilst being readily removed by dilute aqueous acid.[12] Mixed ortho esters, e.g. **3** (Table 1), are defined by a central carbon atom directly bound to an alkyl group and three alkoxy groups, where two of the alkoxy groups are usually structurally simple and the third may be structurally complex. They are of particular interest as they constitute the intermediate formed in the Johnson–Claisen rearrangement.[13,14] The difficulties associated with synthesising mixed ortho esters have recently been discussed by Beifuss et al.[15] General access to mixed ortho esters is quite limited because the standard procedures involve the use of trimethyl orthoacetate with an acid catalyst, require long reaction times and further purification.[14,16,17] The last of these is problematic, owing to the instability of these compounds towards silica gel.[17]

As part of our studies on the chemistry of cyanohydrins derived from enals **1** (Table 1), we required a method for the synthesis of mixed ortho ester derivatives of these compounds. Using the general method of Albizati et al.[16] we initially examined the transesterification of (*E*)-2-hydroxy-3-pentenenitrile (**1**) with trimethyl orthoacetate (**2**; Table 1, entry 1). Unfortunately, this method was low yielding and required long reaction times. Consequently, we tested a modified procedure of Sawada et al.[14] (entry 2) and found it to have a shorter reaction time but only a modest yield of product **3** could be obtained.

Table 1 Optimised Reaction Yields

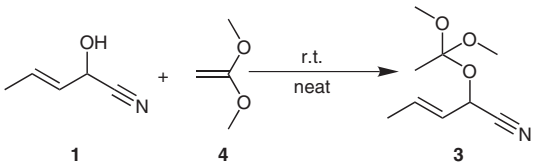


1 2 3

Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)[c]
1[a]	$MgCl_2$	r.t.	72	20
2[b]	$EtCO_2H$	70	17	43

[a] Reaction conditions: cyanohydrin **1** (5.2 mmol), trimethyl orthoacetate (**2**; 58 mmol), $MgCl_2$ (1.4 mmol) and CH_2Cl_2 (10 mL).
[b] Reaction conditions: cyanohydrin **1** (1.1 mmol), trimethyl orthoacetate (**2**; 8 mmol), $EtCO_2H$ (ca. 0.1 mmol), quenched with K_2CO_3.
[c] Isolated yields.

As a consequence of the difficulties encountered with the established methods,[14,16,17] we investigated the simple addition of ketene dimethyl acetal **4** to **1**, without solvent or acid catalyst (Equation 1). The addition reaction proceeded rapidly, with the evolution of heat, resulting in the formation of the mixed ortho ester **3** in high purity and in quantitative yield. Subsequent investigation of the literature unearthed a few isolated accounts of uncatalysed reactions of alcohols with ketene acetals. In 1936 McElvain et al.[18] reported that ketene diethyl acetal reacts rapidly with ethanol to form triethyl orthoacetate. The same author later reported that phenyl ketene dimethyl acetal reacts with methanol to form (2,2,2-trimethoxyethyl)benzene.[19] Other examples of addition reactions of alcohols and ketene acetals all use various catalysts and/or solvents, including HCl,[20] AcOH,[21] PhOH,[22,23] $PdCl_2$(COD)–toluene,[24] *t*-BuOH[25,26] and H_3PO_4.[27] We now report an efficient and uncatalysed synthesis of mixed ortho esters using ketene dimethyl acetal (Table 2).



1 4 3

Equation 1

SYNLETT 2008, No. 16, pp 2425–2428
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Table 2 Reaction of Various Alcohols with Ketene Dimethyl Acetal To Form Mixed Ortho Esters

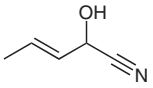
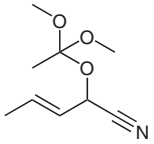
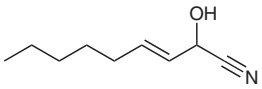
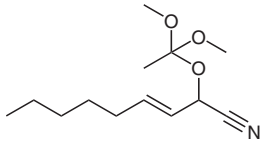
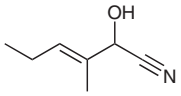
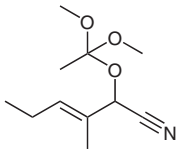
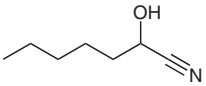
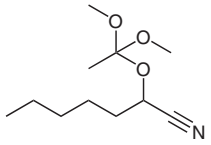
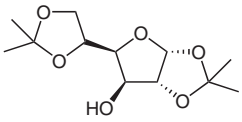
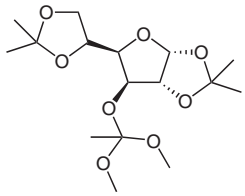
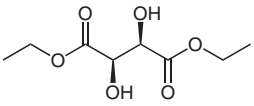
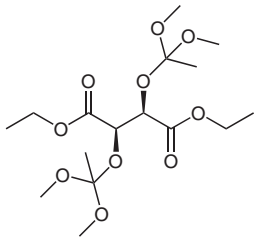
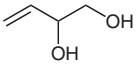
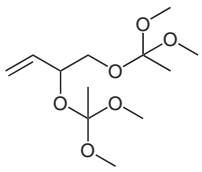
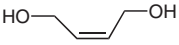
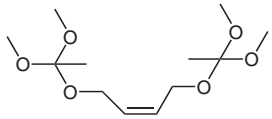
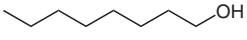
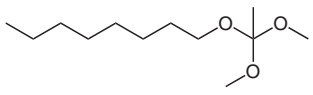
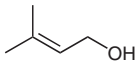
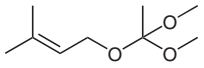
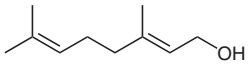
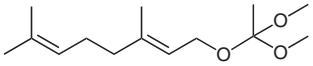
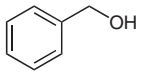
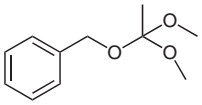
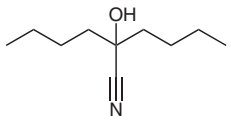
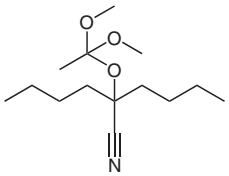
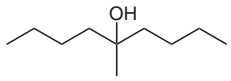
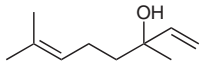
Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1**	0.5	 **3**	Quant.
2	 **5**	0.5	 **6**	Quant.
3	 **7**	0.5	 **8**	Quant.
4	 **9**	0.5	 **10**	Quant.
5	 **11**	0.5	 **12**	Quant.
6	 **13**	0.5	 **14**	Quant.
7	 **15**	12	 **16**	Quant.
8	 **17**	0.5	 **18**	Quant.
9	 **19**	0.5	 **20**	Quant.

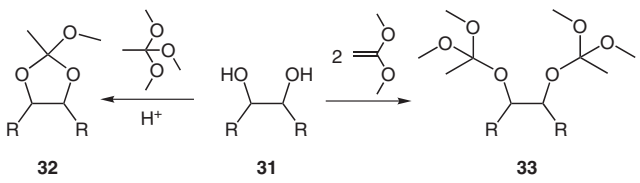
Table 2 Reaction of Various Alcohols with Ketene Dimethyl Acetal To Form Mixed Ortho Esters (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[a]
10	 **21**	0.5	 **22**	Quant.
11	 **23**	0.5	 **24**	Quant.
12	 **25**	0.5	 **26**	Quant.
13	 **27**	1	 **28**	Quant.
14	 **29**	12	No product formed	0
15	 **30**	4	No product formed	0

[a] Isolated yields.

Primary alcohols (entries 8–12) readily reacted with **4** to form the mixed ortho ester in high yield and purity at room temperature. Secondary alcohols (entries 1–6), including a hindered alcohol **11** (entry 5) also reacted rapidly with **4** to efficiently form their respective mixed ortho esters in quantitative yield. The longest reaction time for generating a mixed ortho ester was observed for 3-butene-1,2-diol (**15**, entry 7), presumably because **4** adds to the primary alcohol first, making access to the secondary alcohol more hindered. Interestingly, substrates possessing a tertiary alcohol only reacted if they also possessed an electron-withdrawing nitrile group (entry 13). In contrast tertiary alcohols possessing electron-donating groups (entries 14 and 15) did not react under these conditions. Mixed ortho ester **28** was very unstable and started to decompose while running the ^{13}C NMR spectrum in toluene-d_8.

Notable were the reactions of 1,2-diols (entries 6 and 7). Under acid catalysis, these systems invariably yield a cyclic ortho ester **32** (Scheme 1).[14,17,28,29] However, under the conditions described here, the products were the acyclic bis(ortho esters) **14** and **16**.[30,31] To the best of our knowledge this is the first report where acyclic bis(ortho esters) **33** form instead of a cyclic mixed ortho ester **32**.



32 **31** **33**

Scheme 1

In summary, we have described a mild, solvent-free, uncatalysed, quantitative procedure for the synthesis of mixed ortho esters from alcohols.[32] Furthermore, the ready availability of the ketene acetal coupled with the ability to generate the mixed ortho ester cleanly such that subsequent purification is unnecessary, attest to the viability of this procedure. We envisage that this procedure will serve as a useful alternative to the other methods available for synthesising mixed ortho esters.

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(30) Compound **14**: light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (s, 2 H), 4.09–4.23 (m, 4 H), 3.27 (s, 6 H), 3.23 (s, 6 H), 1.42 (s, 6 H), 1.26 (t, 6 H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 115.4, 60.9, 50.33, 50.31, 19.7, 14.1. HRMS (ESI, +ve): m/z $[M + Na]^+$ calcd for $C_{16}H_{30}O_{10}$: 405.1737; found: 405.1732.
(31) Compound **16**: yellow oil. ^{1}H NMR (400 MHz, C_6D_6): δ = 6.00 (ddd, 1 H, $^3J_{trans}$ = 17.4 Hz, $^3J_{cis}$ = 10.6 Hz, ^3J = 6.1 Hz), 5.32 (br dt, 1 H, $^3J_{trans}$ = 17.2 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz), 5.06 (ddd, 1 H, $^3J_{cis}$ = 10.6 Hz, ^2J = 1.8 Hz, ^4J = 1.4 Hz), 4.57 (qt, 1 H, ^3J = 6.1 Hz, ^4J = 1.3 Hz), 3.79 (dd, 1 H, ^2J = 9.7 Hz, ^3J = 6.1 Hz), 3.62 (dd, 1 H, ^2J = 9.7 Hz, ^3J = 5.9 Hz), 3.20 (s, 3 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 3.16 (s, 3 H), 1.42 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 138.7, 128.9, 115.4, 114.8, 72.6, 66.0, 49.8, 49.7, 49.6, 49.5, 20.8, 19.4. MS (ESI): m/z = 287 $[M + Na]^+$. HRMS (ESI, +ve): m/z $[M + Na]^+$ calcd for $C_{12}H_{24}O_6$: 287.1470; found: 287.1454.
(32) In a typical experiment, ketene dimethyl acetal (3 mmol per hydroxyl group) was added cautiously to the anhyd alcohol (1 mmol) and stirred rapidly at r.t. under argon for 30 min. The reaction was followed by neutral alumina TLC. After complete conversion into the mixed ortho ester, the excess ketene dimethyl acetal was removed in vacuo resulting in pure mixed ortho ester in quantitative yield. Toluene-d_8 and C_6D_6 were used for most NMR samples because trace amounts of HCl in $CDCl_3$ resulted in decomposition of the mixed ortho ester.[33]
(33) All compounds synthesised were characterised by ^{1}H, ^{13}C NMR and/or HRMS and elemental analysis.