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A new method for the synthesis of mixed orthoesters from *O*-allyl acetals

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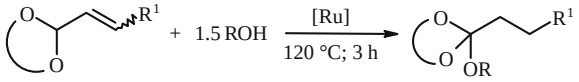
ABSTRACT

Two new methods for the synthesis of orthoesters and compounds containing an orthoester moiety (dihydroisoxazoles) are presented. Mixed orthoesters of general formulas $RC(OR^1)(OR^2)_2$ and $RC(OR^1)(OR^2)(OR^3)$ were prepared via addition of ROH (R = Bu or *m*-methylphenyl) to *O*-allyl acetals (acrolein acetals: diethyl or cyclic, i.e., 2-vinyl-1,3-dioxanes or dioxolanes). The catalytic systems for these reactions were generated from $[RuCl_2(PPh_3)_3]$ and Na_2CO_3; $\{[RuCl_2(COD)]_x\}$ or $\{[OsCl_2(1,5\text{-}COD)]_x\}$, PPh_3, and Na_2CO_3. Compounds containing an orthoester moiety (dihydroisoxazoles) were prepared *via* tandem isomerization of *O*-allyl acetals (to *O*-vinyl acetals) catalyzed by ruthenium complexes followed by cycloaddition to in situ-generated 2,6-dichlorophenylnitrile oxide.

Orthoesters are well-known compounds, and have many applications. They are used in organic synthesis as protected forms of carboxylic acids,[1–3] as endosome permeation agents,[4,5] as detergents,[6,7] and in polymer synthesis.[8] The synthesis of symmetric orthoesters (formally, acetals of esters) is simple and well known. A selective synthesis of mixed orthoesters of the general types $RC(OR^1)(OR^2)_2$ and $RC(OR^1)(OR^2)(OR^3)$ has not been described previously. The synthetic methods described in the literature always lead to the formation of a mixture of all the possible symmetric and mixed orthoesters. Herein, we describe two routes for the synthesis of mixed orthoesters from *O*-allyl acetals (particularly, cyclic or acyclic acetals of acrolein). The first route for the synthesis of mixed orthoesters involves the addition of ROH (1-butanol or *m*-cresol) to acrolein acetals, for example, acrolein cyclic acetal, Scheme 1. The most effective catalysts for this transformation were ruthenium complexes and an osmium complex generated in situ from $\{[OsCl_2(1,5\text{-}COD)]_x\}$ and PPh_3.

Conversion of the allylic systems was practically quantitative, and reaction selectivity was excellent. All possible stereoisomers of the orthoesters were formed. The structures of the orthoesters prepared from 2-vinyldioxanes and 2-vinyldioxolanes (acrolein cyclic acetals) are presented in Figure 1.

Previously, we found that the catalytic systems generated in situ from Ru or Os complexes, external ligands (particularly, phosphines), and base (Na_2CO_3, *t*-BuOK) were very effective for the addition of ROH to allyl ethers.[9] It is worth emphasizing that



Scheme 1. Synthesis of mixed orthoesters via addition of 1-butanol or *m*-cresol to *O*-allyl acetals catalyzed by 1% mol $[RuCl_2(PPh_3)_3]$ and 5% mol Na_2CO_3.

the precursors (for example, $[Ru_3(CO)_{12}]$, $\{[RuCl_2(COD)]_x\}$) used without additives were active, while the addition of base increased the selectivity by suppressing transacetalization. In the present work, we investigated the activity of several catalytic systems studied previously for the synthesis of acetals[9] in the model addition reaction of *m*-cresol to 5,5-dimethyl-2-vinyl-1,3-dioxane (see Scheme 2 and Table 1).

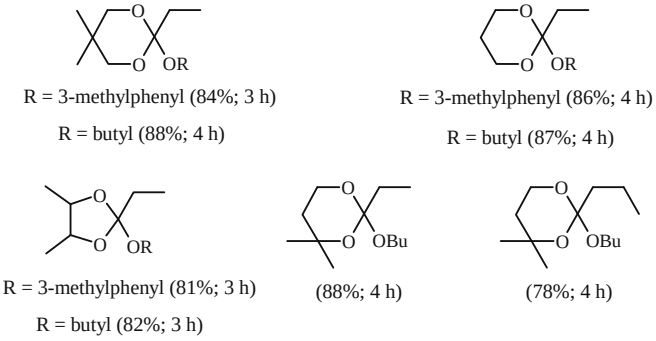


Figure 1. The structures of the orthoesters synthesized from 2-vinyldioxanes and 2-vinyldioxolanes according to Scheme 1 (isolated yields and reaction times are given in parentheses).

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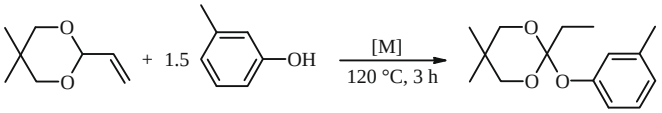


Scheme 2. Addition of *m*-cresol to 5,5-dimethyl-2-vinyl-1,3-dioxane catalyzed by ruthenium and osmium complexes ([M]) with Na_2CO_3.

Table 1
Catalytic systems for the addition of *m*-cresol to 5,5-dimethyl-2-vinyl-1,3-dioxane. COD—1,5-cyclooctadiene (120 °C, 3 h, without solvent)

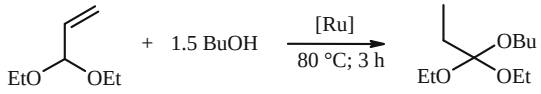
Entry	[M][a]	Yield[b] (%)
1	$[RuCl_2(PPh_3)_3]$	94
2	$\{[RuCl_2(1,5\text{-}COD)]_x\}$	0
3	$\{[RuCl_2(1,5\text{-}COD)]_x\}$ + PPh_3	94
4	$\{[RuCl_2(1,5\text{-}COD)]_x\}$ + *rac*-BINAP	0
5	$\{[OsCl_2(1,5\text{-}COD)]_x\}$	0
6	$\{[OsCl_2(1,5\text{-}COD)]_x\}$ + PPh_3	96
7	$[Ru_3(CO)_{12}]$	44
8	$[Ru_3(CO)_{12}]$ + $3PPh_3$	0

[a] All catalytic systems contained 5 mol % Na_2CO_3.
[b] Yield determined by ^1H NMR spectroscopy.

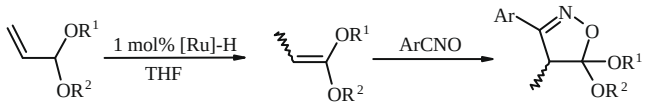
The results were quite different from those obtained in the addition of ROH to allyl ethers leading to acetals.[9] The polymeric complexes of Ru and Os (entries 2 end 6) were highly active in the synthesis of acetals, but in the synthesis of orthoesters they were inactive unless triphenylphosphine was added. Furthermore, the system $\{[RuCl_2(1,5\text{-}COD)]_x\}$/*rac*-BINAP/$Na_2CO_3$ was not active for orthoester synthesis, while it catalyzed the acetalization of allyl ethers very effectively.[9] In contrast to the polymeric precursors, $[Ru_3(CO)_{12}]$ catalyzed the addition poorly, and the system $[Ru_3(CO)_{12}]$/$3PPh_3$/$5Na_2CO_3$ was not active at all. On the other hand, both $[Ru_3(CO)_{12}]$ and $[Ru_3(CO)_{12}]$/$3PPh_3$/base were very active catalysts in the addition of ROH to allyl ethers.[9] We conclude that the addition of ROH to cyclic acrolein acetals is much more sensitive to steric hindrance than the synthesis of acetals from allyl ethers. It seems that the polymeric complexes of Ru and Os and the complexes formed from $\{[RuCl_2(1,5\text{-}COD)]_x\}$ and *rac*-BINAP or $[Ru_3(CO)_{12}]$ with PPh_3 are too bulky, hence the reaction does not take place.

We carried out a test reaction in order to prove our hypothesis of steric hindrance as a limiting factor, which involved the addition of *n*-BuOH to the diethyl acetal of acrolein. This reaction proceeded quantitatively at 80 °C, Scheme 3. Replacement of the rigid 2-vinyl-dioxane or dioxolane cyclic systems with a much more flexible acyclic acetal eliminates steric hindrance, thus lowering the activation energy.

Using the same *O*-allyl acetals, we synthesized a series of dihydroisoxazoles containing an orthoester moiety *via* tandem isomerization (*O*-allyl acetals to *O*-vinyl acetals) cycloaddition (nitrile oxide to *O*-vinyl acetals), see Scheme 4. This novel approach enables the synthesis of new functionalized dihydroisoxazoles. Many isoxazolines[10–13] and their aromatic homologs and analogs, that is, isoxazoles[14,15] serve as drugs or as potential drugs with, for example, anti-inflammatory,[16] antiplatelet[17], or antidepressant[18] activity.



Scheme 3. Addition of 1-butanol to acrolein diethyl acetal catalyzed by 1 mol % $[RuCl_2(PPh_3)_3]$ and Na_2CO_3 (80 °C, 3 h without any solvent).



[Ru]-H = $[RuClH(CO)(PPh_3)_3]$; R^1, R^2 = alkyl; Ar = 2,6-dichlorophenyl

Scheme 4. One-pot tandem isomerization (of *O*-allyl acetals to *O*-vinyl acetals)—1,3-dipolar cycloaddition (nitrile oxide to *O*-vinyl acetals).

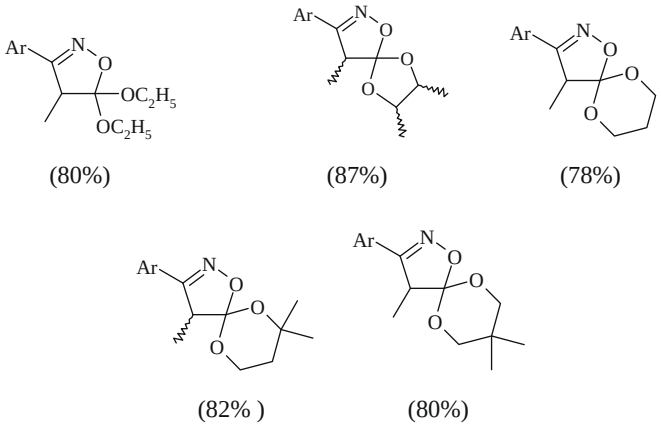
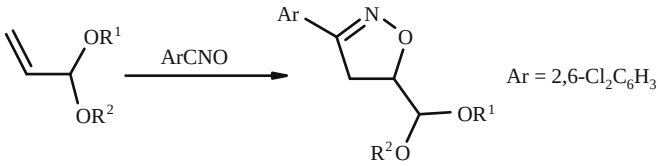


Figure 2. Structures of the dihydroisoxazoles containing an orthoester moiety synthesized according to Scheme 4 (isolated yields in parentheses).[20,21]



Scheme 5. 1,3-Dipolar cycloaddition of 2,6-dichlorobenzonitrile oxide to *O*-allyl acetals.

It is important to note that as in the cycloaddition of nitrile oxides to *O*-vinyl ethers,[19] the reaction is completely regioselective: orthoesters are the only products. The alternative regioisomer, the acetal did not form at all. The structures of the 4,5-dihydroisoxazoles synthesized according to Scheme 4 are presented in Figure 2.

We checked whether the appropriate *O*-allyl systems would cyclize; however the dihydroisoxazoles formed do not belong to the orthoester class.

New possibilities of the application of *O*-allyl acetals for the synthesis of dihydroizoxazoles are described. In the tandem reaction: isomerization of *O*-allyl acetals (to *O*-vinyl acetals)—1,3-cycloaddition (of a nitrile oxide to the *O*-vinyl acetals), dihydroxazoles, which are formally orthoesters, are formed. On the other hand, in the 1,3-cycloaddition of a nitrile oxide to *O*-allyl acetals, dihydroisoxazoles containing an acetal group are formed (see Scheme 5).

Acknowledgments

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20. Standard reaction procedure. *Isomerization of allyl systems:* Isomerization was carried out in screw-capped ampoules, under an argon atmosphere: a mixture of allyl substrate (3 mmol), catalyst (1 mol % [$RuClH(CO)(PPh_3)_3$]), and THF (1 cm^3 per 1 mmol) was stirred for a given period of time (2–4 h). After cooling, the solvent was evaporated and the residue was used in the cycloaddition reaction without additional purification. *Cycloadditions:* To a stirred solution of 1.3 mmol of 2,6-dichlorobenzaldoxime in 10 ml of CH_2Cl_2 at room temperature, 1.4 mmol of solid NCS was added. The reaction was initiated by the addition of one drop of conc. hydrochloric acid. After stirring for 4 h, the obtained solution of 2,6-dichlorobenzohydroximoyl chloride in CH_2Cl_2 was added to the isomerization product, at 0–5 °C, followed by dropwise addition of a solution of triethylamine (3.9 mmol) in CH_2Cl_2 (at 0–5 °C). The mixture was stirred for 24 h at room temperature. The reaction mixture was washed with water (3 × 10 ml), dried over Na_2SO_4, and dissolved in hexane or in benzene–hexane mixture. The resulting solution was passed through a short column filled with amino functionalized mesoporous silica-foam (1 g MCF per 20 mg of Ru-complex), and the ruthenium complexes were quantitatively adsorbed. Isoxazolines–orthoesters were eluted with hexane or benzene-hexane mixtures. The volatile fractions were evaporated on a rotary evaporator, and pure products were obtained.*Addition of ROH to O-allyl acetals*: 2-Vinyl-1,3-dioxane, 2-vinyl-1,3-dioxolane or acrolein diethyl acetal, ROH (1-butanol, *m*-cresol), catalyst (1 mol %), and Na_2CO_3 (5 mol %) in a glass screw-capped ampoule, purged with argon, then tightly capped, were heated in an oil bath for the given period of time. Molar ratios of the reaction mixture components and the temperatures are shown in Figure ure1 and Schemes 1–3. The orthoester products were separated by distillation. When ROH was *m*-cresol, the excess was removed, before distillation, by extraction with 1 M NaOH.
21. *Selected spectral data*: 3-(2,6-Dichlorophenyl)-4-methyl-1,6,10-trioxa-2-azaspiro[4.5]dec-2-ene: IR (film) 3061, 2979, 2933, 2862, 1734, 1560, 1432, 1148, 788, 741. HRMS (FAB): calcd for $C_{13}H_{14}NO_3Cl_2$ $(M+H)^+$ 302.035074; found, 302.03508. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.05 ppm (d, J = 7.1 Hz, 3H, CH_3CH); 1.79 (t, J = 5.9 Hz, 2H, $CH_2CH_2CH_2$); 3.61 (t, J = 5.9 Hz, 2H, $CH_2CH_2CH_2$); 4.15 (t, J = 6.0 Hz, 2H, $CH_2CH_2CH_2$); 4.37 (q, J = 7.1 Hz, 1H, CH_3CH); 7.26–7.32 (m, 3H, C_{Ar-H}) ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.8 ppm (CH_3CH); 25.2 ($OCH_2CH_2CH_2O$); 52.0 (CH_3CH); 61.3 ($OCH_2CH_2CH_2O$); 120.5 (CH_3CHC); 159.2 (C=N); 129.6; 131.3; 132.4; 135.6 (C_{Ar}) MS (ESI) *m/z* 329.1 $[M+4H+Na]^{2+}$. 2-Butoxy-2-ethyl-5,5-dimethyl-1,3-dioxane: IR (film) 2957, 2875, 2734, 1744, 1469, 1364, 1251, 1211, 1149, 1072. CHN: calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.58; H, 11.21. ^1H NMR ($CDCl_3$, 600 MHz) δ = 1.16 (s, 3H, $-CH_3$), 0.95 (t, J = 7.3 Hz, 3H, $-CH_2CH_3$), 0.96 (t, J = 7.5 Hz, 3H, $-OCH_2CH_2CH_2CH_3$), 1.16 (s, 3H, $-CH_3$), 1.41–1.47 (m, 2H, $-OCH_2CH_2CH_2CH_3$), 1.58–1.63 (m, 2H, $-OCH_2CH_2CH_2CH_3$), 1.75 (q, J = 7.5 Hz, 2H, $-CH_2CH_3$), 3.24 (d, J = 10.4 Hz, 6.6 Hz, 2H, $-OCH^aH^bC(CH_3)_2CH^aH^bO-$), 3.40 (t, J = 6.6 Hz, 2H, $-OCH_2CH_2CH_2CH_3$), 3.80 (d, J = 10.4 Hz, 2H, $-OCH^aH^bC(CH_3)_2CH^aH^bO-$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 7.4 ($-OCH_2CH_3$), 14.0 ($-OCH_2CH_2CH_2CH_3$), 19.7 ($-OCH_2CH_2CH_2CH_3$), 22.1 ($-CH_3$), 22.7 ($-CH_3$), 28.5 ($-CH_2CH_3$), 29.1 ($-OCH_2CH_2CH_2O-$), 32.0 ($-OCH_2CH_2CH_2CH_3$), 62.0 ($-OCH_2CH_2CH_2CH_3$), 69.7 ($-OCH_2CH_2CH_2O-$), 111.9 (C^{IV}). GC–MS (70 eV), *m/z* (int [%]): 216 (<1), 187 (6), 144 (12), 143 (69), 131 (60), 75 (70), 69 (52), 56 (100).