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A selective and convenient ruthenium mediated method for the synthesis of mixed acetals and orthoesters

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Abstract—Addition of alcohols and phenols to *O*-allyl compounds (allyl ethers and acrolein acetals), catalyzed by $[RuCl_2(PPh_3)_3]$, was examined. Intramolecular addition of an OH group, leading to the formation of cyclic acetals and orthoesters, was also investigated. As a result, a new, selective and convenient method for the synthesis of symmetrical and unsymmetrical (mixed) acetals and orthoesters was developed.

Mixed (unsymmetrical) acetals are widely used in synthetic organic chemistry.[1–3] Also, in the fragrance[4,5] and pharmaceutical[6] industries, acetals are used both as intermediates and as end products. Acetals are recognized as good carbonyl protecting groups.[7,8] There are many methods for the synthesis of acetals[9–11] and orthoesters[12] in the literature. However, selective syntheses of mixed acetals of type $RCHOR^1(OR^2)$ and orthoesters of type $RC(OR^1)_2(OR^2)$ is still difficult. Application of classical methods for the synthesis of these compounds is not satisfactory, as a concomitant transacetalization reaction leads to a mixture of symmetrical and unsymmetrical acetals and orthoesters, which can be difficult to separate. So far, only one report describing a selective method for the preparation of several mixed acetals[13] has been published. These compounds were obtained by reaction of dimethyl (or diethyl) acetals of type $R^1CH(OMe)_2$ with TESOTf and 2,4,6-collidine and then by treating the salt obtained with R^2OH.[13] A few attempts using transition metal complexes for the synthesis of mixed acetals have not been successful.

Chang obtained various symmetrical and unsymmetrical acetals, in the reactions of $R^1OCH_2CH{=}CHR^2$ with methanol, catalyzed by cobalt complexes generated from $[Co_2(CO)_8]$ in the presence of hydrogen and carbon monoxide.[14] However, the syntheses of unsymmetrical acetals of type EtCH(OMe)(OR) in reactions of allyl ethers with MeOH were very unselective (transacetalization was observed).[14] A symmetrical diethyl acetal was also obtained by reaction of allyl ether (n-C_6H_{13}-$COCH{=}CHCH_2OMe$) with 95% EtOH in the presence of $[RhCl(PPh_3)_3]$.[15] Moreover, a synthesis of acrolein cyclic acetals via cyclization reactions of allyloxyalcohols of type $RCH{=}CRCHROCH_2CH(OH)(CH_2)_nH$ (R=H or Me; $n = 0$, 1, 2) catalyzed by 'conventional hydrogenation catalysts' (heterogeneous nickel, platinum and palladium catalysts) was also reported.[16]

Herein, we present a new, simple and in most cases, highly selective method for the synthesis of symmetrical and unsymmetrical acetals of type $RCH(OR^1)(OR^2)$ and orthoesters of type $RC(OR^1)_2(OR^2)$, in an addition reaction of alcohols and phenols to allyl ethers or acrolein acetals, catalyzed by $[RuCl_2(PPh_3)_3]$. The method is a development of our research published earlier[17] on isomerization of monoallyl ethers of diols.

Addition of phenols and alcohols to allyl ethers of type ROAllyl is a useful and simple method for acetal synthesis, including mixed acetals, see Scheme 1 and Table 1. The non-hydride ruthenium complex $[RuCl_2(PPh_3)_3]$, was an effective precursor of the reaction catalyst. In the presence of hydride complexes, for example, $[RuClH(CO)(PPh_3)_3]$ or $[RuCl_2(PPh_3)_3] + NaBH_4$, mainly, or

Keywords: *O*-Allyl compounds; Addition; Ruthenium complexes; Mixed acetals; Orthoesters.
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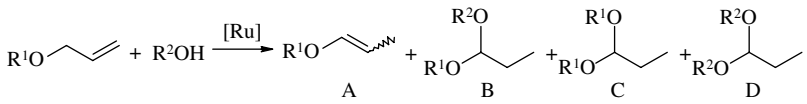


[Ru] = $[RuCl_2(PPh_3)_3]$ (with or without Na_2CO_3)

Scheme 1. Addition of alcohols or phenols to allyl ethers, catalyzed by $[RuCl_2(PPh_3)_3]$.

Table 1. Synthesis of acetals via addition of alcohols or phenols to allyl ethers[a,b]

R^1	R^2	[Ru]	α[c] (%)	A[d] (%)	B[d] (%)	C[d] (%)
n-Bu	$PhCH_2$	Ru^1	100	11	83	6
n-Bu	*n*-Bu	Ru^1	100	0	100	—
n-Bu	$CH_3CH{=}CHOCH_2CH_2$	Ru^1	100	10	90	0
n-Bu	*p*-HOC_6H_4	Ru^1	100	66	44	0
n-Bu	Ph	Ru^1	100	5	88	7
n-Bu	Ph	Ru^2	100	1	98	1
n-Bu	$PhCH_2CH_2$	Ru^2	100	15	85	0
$PhCH_2$	Ph	Ru^1	85	0	96	0
$PhCH_2$	$PhCH_2$	Ru^1	100	24	76	—
$PhCH_2$	*n*-Bu	Ru^1	100	65	35	0

Ru^1 = 1 mol % $[RuCl_2(PPh_3)_3]$; Ru^2 = 1 mol % $[RuCl_2(PPh_3)_3]$ + 5 mol % Na_2CO_3; ROAllyl/ROH = 1:1.5; without solvent; 3 h; 120 °C.

[a] The reactions were carried out according to the typical procedure.[21,22]

[b] Product D was not observed (see Scheme 1).

[c] Allyl ether conversion determined by ^1H NMR.

[d] All yields were determined by ^1H NMR and GC–MC analyses of crude mixtures.

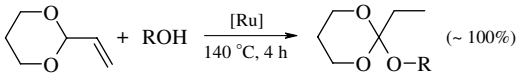
only isomerization products of allyl ethers (i.e., 1-propenyl ethers) were formed. It was shown that hydride ruthenium complexes, for example, $[RuClH(CO)(PPh_3)_3]$ and generated in situ from non-hydride precursors, (e.g., $\{[RuCl_2(1,5\text{-cod})]_x\}$, $[RuCl_2(PPh_3)_3]$) and hydride ligand donors (e.g., CaH_2, $NaBH_4$) were very effective catalysts of double bond migration.[18–20]

Reactions of ROAllyl with alcohols and phenols led to acetals (symmetrical when $R^1 = R^2$, or unsymmetrical when $R^1 \neq R^2$), and sometimes to 1-propenyl ethers (ROAllyl isomerization products). However, separating the isomerization product from the addition product was in most cases easy (distillation). Due to the presence of Na_2CO_3 in the catalytic system, we have managed to limit or practically eliminate the transacetalization.

We also ascertained that the reaction in Scheme 1 did not occur for allyl aryl ethers (R^1 = Ph, *m*-ClC_6H_4, (*p*-$CH_3O)C_6H_4$) and when R^2 was very bulky (R^2 = *t*-Bu). It was also interesting to note that addition of ROH to an ether of type $ROCH_2CH{=}CHR$ was possible, Scheme 2.

We did not observe any transacetalization during this reaction and the isomerized product could be separated from the addition product by simple distillation.

This method for acetal synthesis can also be applied to prepare unsymmetrical orthoesters, Scheme 3. Addition



R = *n*-Bu, *m*-$CH_3C_6H_4$

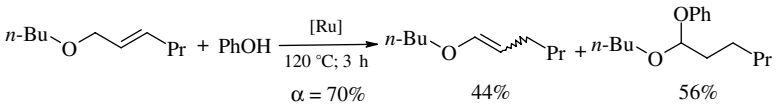
Scheme 3. Addition of *n*-butanol or *m*-cresol (ROH) to 2-vinyl-1,3-dioxane (D) catalyzed by 0.5 mol % $[RuCl_2(PPh_3)_3]$ + 5 mol % Na_2CO_3, D/ROH = 1:1.5.

of *n*-butanol or *m*-cresol to 2-vinyl-1,3-dioxane occurred practically quantitatively, and no formation of other products was observed.[23]

Addition of an OH group from alcohols or phenols to an *O*-allyl system (ethers or acetals), can also be carried out as an intramolecular reaction. In the reaction of mono- and diallyl triol ethers in the presence of $[RuCl_2(PPh_3)_3]$, we obtained cyclic acetals as dioxolane and/or dioxane derivatives, Table 2.

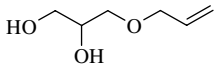
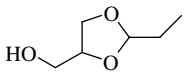
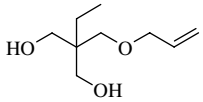
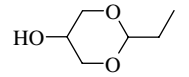
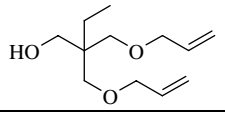
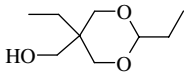
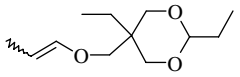
The mixture of dioxolane and dioxane derivatives, formed in the isomerization reaction of 3-allyloxy-1,2-propandiol, was separated by selective tritylation, then by distillation of **1** and crystallization of **2**, Scheme 4.

In the case of 2-vinyl-4-hydroxymethyl-4-ethyl-1,3-dioxane, intramolecular addition of the OH group to the allylic system occurred particularly easily, Scheme 5.



Scheme 2. Addition of phenol to *n*-butyl [(*E*)-(2-hexenyl)]ether, catalyzed by 1 mol % $[RuCl_2(PPh_3)_3]$ + 5 mol % Na_2CO_3.

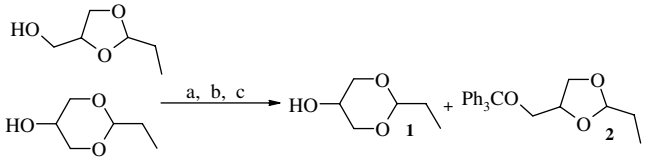
Table 2. Isomerization of mono- and diallyl ethers of triols to the cyclic acetals[a] catalyzed by 0.2–1 mol % $[RuCl_2(PPh_3)_3]$[b]

Allyloxyalcohol	Cyclic acetal
	
	
	
	

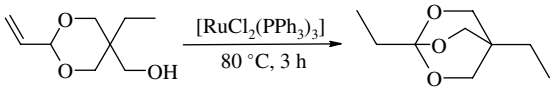
[a] Conversion and selectivity were quantitative.
[b] Reaction conditions: 120 °C, 2 h, without solvent.

We also investigated the mechanism of OH addition to *O*-allylic systems, using the model addition reaction of benzyl alcohol to benzyl-α,α-dideuteroallyl ether, Scheme 6. The only products of this reaction were acetals **3** and **4**, formed in a 1:1 ratio. We ascertained also that in the presence of $[RuCl_2(PPh_3)_3]$, addition of ROH (R=*n*-Bu or Ph) to *n*-BuOCH=CH_2 did not occur, and 2-vinyloxyethanol did not undergo cyclization. Thus, addition of the OH group (both intra- and intermolecular) to *O*-vinylic systems did not occur. However, *O*-(1-propenylic) systems undergo such a reaction, even if significantly slower than *O*-allylic systems.

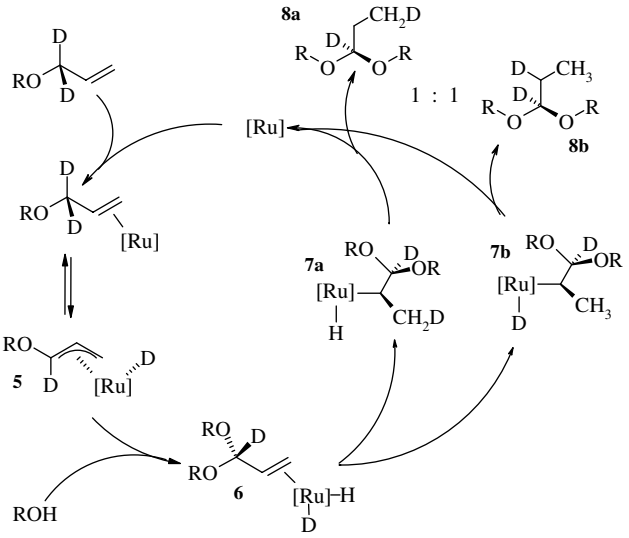
The data obtained thus far indicate that the examined reaction is a nucleophilic addition of OH (intra- or intermolecular) to a hydrido-π-allyl complex. The complex forms as a result of an oxidative addition of ROAllyl to the non-hydride ruthenium complex, Scheme 7.



Scheme 4. Separation of the mixture of dioxolane and dioxane. Reagents and conditions: (a) Ph_3CCl + py, 5 d, rt; (b) vacuum distillation **1**, 60% and (c) Crystallization **2**, 52%.



Scheme 5. Intramolecular addition of an OH group to the *O*-allylic system.



Scheme 7. Proposed sequence of intra- or intermolecular addition of hydroxy group to the double bond in *O*-allylic systems.

In the key stage of the reaction, ^{2}H-hydrido-π-allyl complex **5** undergoes a nucleophilic attack by the OH group (intra- or intermolecular). The formed ^{2}H,^{1}H-dihydrido-π-alkene complex then undergoes typical transformations leading to **8a** and **8b** products, and to regeneration of the non-hydride [Ru] complex.

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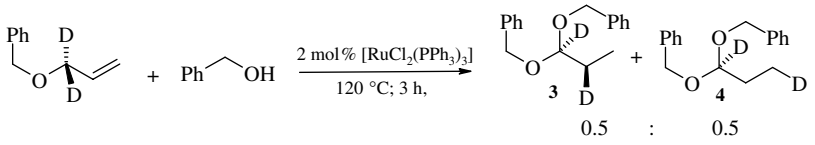

Scheme 6. Addition of benzyl alcohol to benzyl-α,α-dideuteroallyl ether.

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21. *Standard reaction procedure*: Allyl ether (or 2-vinyl-1,3-dioxane), ROH (alcohol or phenol for intermolecular reaction), $[RuCl_2(PPh_3)_3]$ and Na_2CO_3 (if applicable) in a glass screw-capped ampoule, purged with argon, and tightly capped were vigorously stirred and heated in an oil bath for a given period of time. Molar ratios of the reaction mixture components and the temperature are shown in the Tables and Schemes. Acetals and orthoesters were separated by distillation. When ROH was a phenol, the excess was removed, before distillation, by extraction with 1 M NaOH.
22. Selected spectral data: *1-n-butoxy-1-phenoxypropane* bp = 96–97 °C (5 mmHg) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.3$, 3H, $-OCH_2CH_2CH_2CH_3$), 0.98 (t, $J = 7.5$, 3H, $-CH_2CH_3$), 1.26–1.32 (m, 2H, $-OCH_2CH_2CH_2CH_3$), 1.50–1.59 (m, 2H, $-OCH_2CH_2CH_2CH_3$), 1.83 (dqd, $J = 13.0$, 7.5, 5.6, 1H, $-CH^aH^bCH_3$), 1.86 (dqd, $J = 13.0$, 7.5, 5.6, 1H, $-CH^aH^bCH_3$), 3.49 (dt, $J = 9.4$, 6.7, 1H, $-OCH^a H^bCH_2CH_2CH_3$), 3.71 (dt, $J = 9.4$, 6.7, 1H, $-OCH^aH^bCH_2CH_2CH_3$), 5.16 (t, $J = 5.6$, 1H, $-OCH(CH_2CH_3)O-$), 6.94–7.03 (m, 3H, Ph), 7.23–7.29 (m, 2H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.7$ ($-CH_2CH_3$), 13.7 ($-OCH_2CH_2CH_2CH_3$), 19.2 ($-OCH_2CH_2CH_2CH_3$), 26.9 ($-CH_2CH_3$), 31.7 ($-OCH_2CH_2CH_2CH_3$), 65.6 ($-OCH_2CH_2CH_2CH_3$), 104.0 ($-OCH(CH_2CH_3)O-$), 117.4 (C_{Ph}[2,3]), 121.7 (C_{Ph}[6]), 129.5 (C_{Ph}[4,5]), 157.4 (C_{Ph}[1]). GC–MS (EI, 40 eV), *m*/*e* (int (%)): 208 (<1), 135 (48), 115 (54), 114 (58), 94 (80), 77 (26), 59 (100), 57 (68).
23. Selected spectral data: *2-n-butoxy-2-ethyl-1,2-dioxane* bp = 73–74 °C (5 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.5$ Hz, 3H, $-CH_2CH_3$), 0.95 (t, $J = 7.2$ Hz, 3H, $-OCH_2CH_2CH_2CH_3$), 1.29–1.33 (m, 1H, $-OCH_2CH^aH^bCH_2O-$), 1.71 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 1.33–1.43 (m, 2H, $-OCH_2CH_2CH_2CH_3$), 1.52–1.59 (m, 2H, $-OCH_2CH_2CH_2CH_3$), 1.65 (q, $J = 7.5$ Hz, 2H, $-CH_2CH_3$), 1.90–2.04 (m, 1H, $-OCH_2CH^aH^bCH_2O-$), 3.41 (t, $J = 6.5$ Hz, 2H, $-OCH_2CH_2CH_2CH_3$), 3.63–3.68 (m, 2H, $-OCH^aH^bCH_2CH^aH^bO-$), 4.03–4.10 (m, 2H, $-OCH^aH^bCH_2CH^aH^bO-$). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 7.0$ ($-OCH_2CH_3$), 13.7 ($-OCH_2CH_2CH_2CH_3$), 19.4 ($-OCH_2CH_2CH_2CH_3$), 24.2 ($-CH_2CH_3$), 28.5 ($-OCH_2CH_2CH_2O-$), 31.7 ($-OCH_2CH_2CH_2CH_3$), 59.2 ($-OCH_2CH_2CH_2CH_3$), 61.7 ($-OCH_2CH_2CH_2O-$), 112.4 (C). GC–MS (EI, 40 eV), *m*/*e* (int (%)): 187 (<1), 159 (4), 115 (100), 103 (42), 75 (22), 57 (64).