Ruthenium catalysed formation of 2-alkoxy-5-methylenetetrahydropyrans

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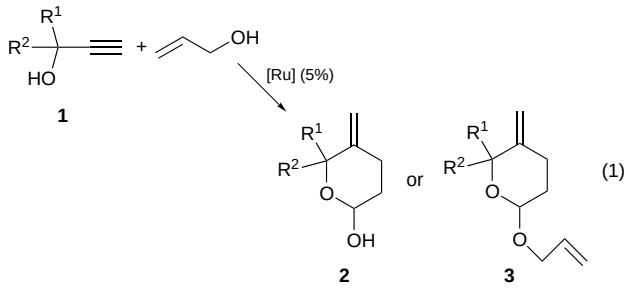
The regioselective carbon–carbon coupling of prop-2-yn-1-ols with allyl alcohol is achieved in the presence of the ruthenium(II) catalyst RuCl(cod)(C_5Me_5) and leads to either 2-hydroxy- or 2-allyloxy-5-methylenetetrahydropyrans.

The tetrahydropyran skeleton is a key structure in intermediates for the synthesis of natural products such as terpenoids, pheromones, antibiotics and other biologically active compounds.[1] The 2-alkoxy-5-methylenetetrahydropyrans have been used to give access to 3-hydroxypyran-4-ones, flavouring components,[2] aggregation pheromones,[3] members of the tricothecanes[4] and to precursors of cytotoxic and antitumour active vernolepin.[5] The 2-alkoxytetrahydropyrans are usually conveniently constructed from sugars.[3,4]

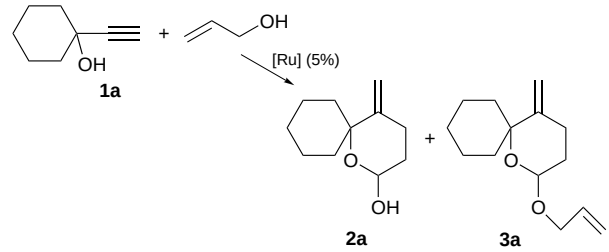
We now report a novel, general method leading to new 2-hydroxy- or 2-alkoxy-5-methylenetetrahydropyrans. It is based on a regioselective ruthenium catalysed C–C coupling of prop-2-yn-1-ols with allyl alcohol, with atom economy, according to eqn. (1).



The carbon–carbon bond coupling of C≡C and C=C bonds on a ruthenium(II) centre has already been reported to preferentially lead to linear derivatives[6] and we have shown by contrast that the reaction of terminal alkynes with allyl alcohol in the presence of ruthenium(IV) and ruthenium(II) catalyst precursors led to γ,δ-unsaturated aldehydes[7] with a branched/linear ratio up to 4 : 1.

The reaction of the prop-2-yn-1-ol **1a** (2.5 mmol) with 3 equiv. of allyl alcohol, in the presence of 5 mol% of RuCl(cod)(C_5Me_5) catalyst[8] (cod = cycloocta-1,5-diene) affords a mixture of **2a** and **3a** below 90 °C. However, when a large excess of allyl alcohol is used (5 ml) the same reaction, performed above 45 °C, leads to the selective formation of the mixed acetal **3a** (Scheme 1). The latter was obtained after 1 h at 80 °C in 80% yield; by contrast, when the reaction was performed at 25 °C (30 min), only the hemiacetal **2a** (80%) was obtained.

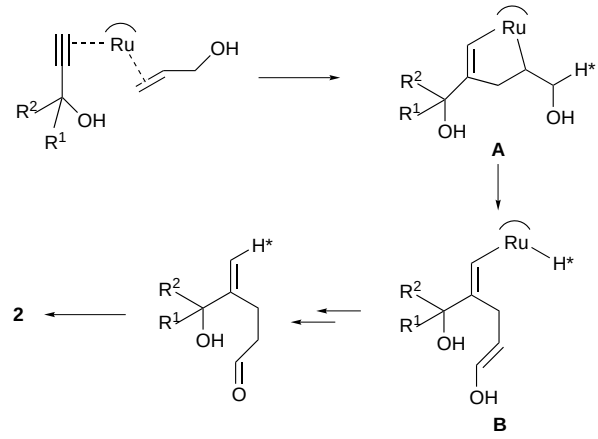
These results show that the hemiacetal **2a** is first selectively produced and that further heating in an excess of allyl alcohol selectively leads to the 2-allyloxy acetal **3a**. The reaction corresponds, after displacement of the cod ligand, to the *regioselective* oxidative coupling of the alkyne C≡C and allyl alcohol C=C bonds on the ruthenium centre, leading to **A**, followed by β-elimination involving the exocyclic methylene group, giving the intermediate **B** (Scheme 2). The latter, on reductive elimination, should form a branched γ,δ-unsaturated aldehyde which cyclises into the six-membered hemiacetal **2**. It is noteworthy that the presence of a hydroxy group at the α-position of a terminal C≡CH bond allows the regioselective coupling leading only to the branched isomer, a regioselectivity phenomenon not observed before.[6,7] A ruthenium allenylidene intermediate (Ru=C=C=CR_2) usually produced by metal activation of prop-2-yn-1-ols (HC≡CR_2OH) followed by water elimination[9] can be ruled out. Indeed the reaction of MeC≡C-CH_2OH with allyl alcohol according to the conditions shown in Table 1 also affords the cyclic hemiacetal of type **2** with an exocyclic ethylidene group.



allyl alcohol: 3 equiv.	90 °C, 5 h	—	30%
allyl alcohol: 5 ml	45 °C, 3 h	45%	35%
	45 °C, 20 h	—	77%
	80 °C, 1 h	—	80%
	room temp., 30 min	80%	—

Scheme 1

The conditions in Table 1, applied to a variety of prop-2-yn-1-ols with an excess of allyl alcohol, can be used to produce selectively either the corresponding 2-hydroxy- **2** or 2-allyloxy-tetrahydropyrans **3**, respectively. Prop-2-ynyl alcohol **1b** leads to a low yield of **2b** (42%) but **1c** affords selectively **2c** (70%) or **3c** (55%). When unsymmetrically substituted derivatives **1d**–**f** ($R^1 \neq R^2$) were used, diastereoisomers were formed in good yields (51–78%) in the ratio 60 : 40 for both **2d**–**f** and **3d**–**f**



Scheme 2

Table 1 Results of reaction of **1** and allyl alcohol to give **2** and **3**[a]

			Reaction at room temp.		Reaction at 80 °C	
Alkynol	R^1	R^2	*t*/h	Product (% yield)[b]	*t*/h	Product (% yield)[b]
1a	$-[CH_2]_5-$		0.5	**2a** (80)	1	**3a** (80)
1b	H	H	1	**2b** (42)	7	**2b** (28) **3b** (15)
1c	Me	Me	2	**2c** (70)	1	**3c** (55)
1d	Me	Et	2	**2d** (64)[c]	4	**3d** (61)[c]
1e	Me	CH_2CHMe_2	2	**2e** (78)[c]	5	**3e** (51)[c]
1f	Me	$[CH_2]_2CH{=}CMe_2$	2	**2f** (68)[c]	3	**3f** (72)[c]
1g	Me	Ph	3	**2g** (73)	5	**2g** (60) **3g** (11)

[a] Reaction conditions: **1** (2.5 mmol) in allyl alcohol (5 ml) was treated with [RuCl(cod)(C_5Me_5)] (0.125 mmol, 5 mol%) under the conditions shown. [b] Isolated yields after silica gel chromatography. All compounds were fully characterised by spectroscopic methods. [c] Diastereomeric ratio of 60 : 40 determined by ^{1}H NMR.

derivatives. This ratio corresponds to the anomer ratio usually obtained from sugar derivatives. However, from the phenyl derivative **1g** only one diastereoisomer **2g** was obtained either at 25 °C (3 h) in 73% yield or at 80 °C (5 h) in 60% yield. In that case the presence of the aryl group slowed down the formation of the allyloxy acetal, and the derivative **3g** could only be observed in 11% yield at 80 °C for 5 h. NOE experiments showed the relative *trans* arrangement of the phenyl group and the OH group of **2g**.

This one-pot ruthenium catalysed regioselective C–C coupling reaction followed by cyclisation takes place with atom economy,[10] and offers a new route to functional tetrahydropyran derivatives. On the basis of the known reactions involving 2-alkoxytetrahydropyrans obtained from sugars,[1] this selective catalytic formation of 2-alkoxy-5-methylenetetrahydropyrans has potential for organic synthesis.

Footnote

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