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Conversion of pentynol to pentanone catalysed by Pd(II) metal centres

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Abstract

The cyclization of 3- or 4-pentyn-1-ol is catalysed by $PdCl_2$ or *trans*-$[PdCl_2L_2]$ (L = R-camphorimine; R = Ph; Pr^i; NMe_2) complexes at room temperature affording heterocyclic compounds, respectively, 2-methyl-2-pent-3-ynyloxy-tetrahydrofuran or 2-methyl-2-pent-4-ynyloxy-tetrahydrofuran which subsequently add water to give selectively 5-(2-methyl-tetrahydrofuran-2-yloxy)-pentan-2-one from both starting materials. By hydrolysis 5-(2-methyl-tetrahydrofuran-2-yloxy)-pentan-2-one undergoes ring cleavage to form 5-hydroxy-2-pentanone. The catalytic activity and selectivity of complexes *trans*-$[PdCl_2L_2]$ (L = R-camphorimine) depend on the characteristics of the R group ($NMe_2 > Pr^i > Ph$). The catalytic activity of $PdCl_2$ is comparable to that of *trans*-$[PdCl_2L_2]$ (L = Ph-camphorimine) which is the less efficient catalyst.
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1. Introduction

Catalytic activation of unsaturated molecules by transition metals is a well-established process for the synthesis of organic species which may be difficult to prepare with classical organic strategies [1]. Cascade reactions are of particular interest since several steps can be accomplished in the same vessel this accounting for time and atom economy.

Among the unsaturated molecules, alkynes are attractive versatile species that display high coordinative ability to most the transition metals forming alkynyl, vinylidene or other type of complexes [2–5] that in same cases trigger reactions such as coupling [6] or cyclization [7–12]. The introduction of an additional alcohol group may modify well-known reaction paths leading to the syntheses of heterocyclic species such as furans [13] or less stable cyclic ketal-type species [14].

In the last decades several transition metals were studied as catalysts for promotion of cyclization of alkynes [15,16] due to the relevance of these processes for syntheses of natural products or biological active species.

The search for more active or/and selective catalysts to promote the formation of aromatic or heterocyclic systems continues to be a challenge to fulfil more economical and environmental friendly synthetic processes.

2. Results and discussion

We started to explore the potential of alkynols for the synthesis of oxygen-containing heterocycles by studying the reactions of several {$PdCl_2$} metal centres with 3- or 4-pentyn-1-ol. In the absence of a catalyst these pentynols are stable at room temperature and no cyclization or hydration occur.

$PdCl_2$ (2–5%) catalysis the dimerization of 4-pentyn-1-ol affording 2-methyl-2-pent-4-ynyloxy-tetrahydrofuran (**1a**) as the first step within a process that undergoes the formation of 5-(2-methyl-tetrahydrofuran-2-yloxy)-pentan-2-one (**2**) followed by 5-hydroxy-2-pentanone (**3**) in mild

experimental conditions, Scheme 1. In a parallel process the catalyst also activates 3-pentyn-1-ol towards formation of 2-methyl-2-pent-3-ynyloxy-tetrahydrofuran (**1b**) which can be hydrated to **2** and hydrolysed to **3**.

The catalytic process is slow, a fact that is inconvenient for synthetic purposes but was very useful to get details on the activation of pentynols by {PdCl$_2$} species. At the process, the aprotic solvent (CH$_2$Cl$_2$ or CHCl$_3$) conceivably plays a key role since former studies [17,18] made in protic solvents did not allow the identification of species of type **1** in the conversion of 3- or 4-pentyn-1-ol to 5-hydroxy-2-pentanone.

Following by ^{1}H NMR the reaction of 4-pentyn-1-ol with PdCl$_2$ we first observed the decrease of intensity followed by the disappearance of the signal assigned to the terminal proton of the alkyne group, in agreement with coordination through the alkyne such as reported for Pt(II) [17], Ru [19] or Pd [18] but in contrast with reported for Rh(I) [20] that was found to involve coordination of the alcohol group. The different characteristic of the metal centres conceivably account for different intermediates and mechanism.

The study of the mechanism of cyclization of 4-pentyn-1-ol [21] promoted by W(0) showed that the coordination of the alkyne is followed by the intramolecular attack of the alcohol group to the *exo* carbon atom affording a heterocyclic species that rearranges to the final furan product.

The results herein show that {PdCl$_2$} catalysts promote further reactivity, *i.e.* addition of the alcohol moiety of a second alkynol molecule to the *exo* carbon atom of the coordinated heterocyclic species (conceivably similar to that in [21]) affording the ketal-alkyne species **1a** or **1b** that undergo hydration to **2** followed by hydrolysis to 5-hydroxy-2-pentanone.

In dichloromethane, at 10 °C, in the absence of added water, under catalytic conditions, compound **1a** is the only product detected by ^{13}C NMR until consumption of 4-pentyn-1-ol (*ca.* 50%). Longer reaction times allow addition of traces of water (in the solvent or alkynol) to the triple bond of the alkyne moiety of species **1** affording the ketone-ketal species **2**.

In chloroform the formation of **2** accompanies that of **1**, almost since the beginning of the reaction. Increasing the temperature to 25 °C the formation of **2** becomes faster,

either in dichloromethane or chloroform. Traces of moisture in the reagents account for the hydration process.

Controlled addition of water to **1a**, in the presence of catalytic amounts of PdCl$_2$ (<2%) affords **2** as the only ketone species. A large excess of H$_2$O leads to hydrolysis and formation of 5-hydroxy-2-pentanone (**3**) plus some starting 4-pentyn-1-ol (due to reverse reaction). A similar, step by step process is observed in the case of **1b**.

The hydration of 4-pentyn-1-ol catalysed by Hg(II) is known to afford 5-(2-methyl-tetrahydrofuran-2-yloxy)-pentan-2-one [22]. The process involves a Markovnikov type mechanism that is very selective in the case of terminal alkynes. However, the hydration of internal alkynes using the mercury catalyst is a random non-selective process, forming different *regio*-isomers with respect to the position of the carbonyl group in the chain, unless the alkyne is symmetric.

The results now reported show that the hydration of 3-pentyn-1-ol catalysed by PdCl$_2$ is more selective than that with mercury catalyst leading exclusively to **2** (no other cyclic ketal-ketone isomer was detected by ^{13}C NMR). The final 5-hydroxy-2-pentanone forms by hydrolysis of **2** conceivably through a linear ketal species. No experimental evidence could be obtained by NMR for such a linear species which is expected to be unstable and undergo C–O bond breaking (Scheme 2).

Compounds **1a**, **1b** and **2** were characterized by NMR and FT/IR data (see Section 4).

Up to now we demonstrated that the commercially available PdCl$_2$ catalyses the conversion of terminal or internal pentynols into 5-hydroxy-2-pentanone by a slow process that generates two reasonably stable cyclic ketal species which are hydrolysed to 5-hydroxy-2-pentanone.

In order to try to increase the low reaction rates induced by PdCl$_2$ we started the evaluation of *trans*-[PdCl$_2$(L)$_2$] (L, R = Ph (**A**); Pr^i (**B**); NMe$_2$ (**C**), see Fig. 1 for L) as catalysts for the dimerization of 3- or 4-pentyn-1-ol, since the camphorimine derived complexes *trans*-[PdCl$_2$(L)$_2$] are known to catalyse the cyclotrimerization of alkynes [7,8].

Following the reaction by NMR, we verify that *trans*-[PdCl$_2$L$_2$] (1–2%) react with 3- or 4-pentyn-1-ol affording species **1** such as observed by reaction with PdCl$_2$. The selectivity and kinetics of the process depends on L.
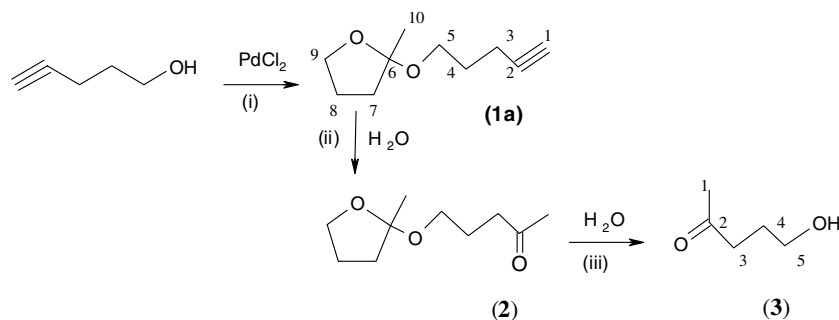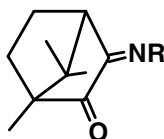

Scheme 1.
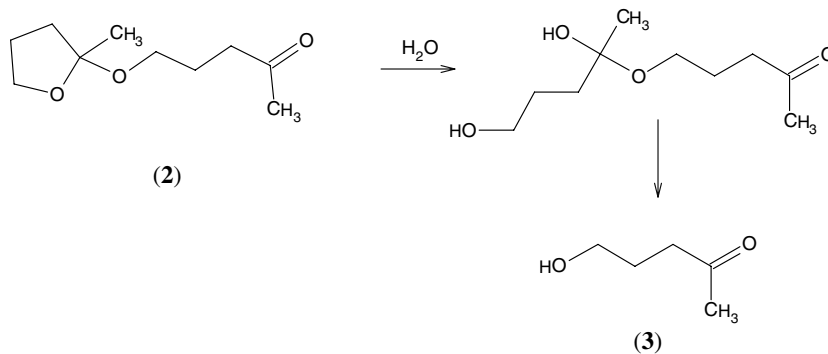
Scheme 2.

Fig. 1. Camphor type ligands (L).

At room temperature, in CHCl₃ complex **A** (R = Ph) takes 5 h to convert 20% of 4-pentyn-1-ol into **1a** (75%) and **2** (25%) the kinetics being comparable to reaction with PdCl₂. In the same experimental conditions, using complex **B** (R = Pr^i) the reaction is *ca.* two times faster on formation of **1a** and is much more selective (just traces of species **2** were obtained). Increasing the temperature (50 °C) the catalytic process becomes slightly faster (*ca.* 1.2×) but less selective (**1a**, 70%; **2**, 30%).

Complex **C** (R = NMe₂) is the most efficient catalyst, since, in less than half one hour, it selectively converts 4-pentyn-1-ol (50%) into **1a** (no traces of **2**). A similar trend was observed in the reaction with 3-pentyn-1-ol, *i.e.* complex **C** reacts faster and more selectively than **B** or **A** towards formation of **1b**. However, in this case the reaction rate is lower than with 4-pentyn-1-ol, since just 20% of 3-pentyn-1-ol were converted to **1b** in half an hour.

The catalytic properties of poor soluble PdCl₂ (in chlorinated solvents) and high soluble complex **A** are identical. Thus, faster kinetics can not be attributed to higher solubility of the Pd-camphorimine complexes. Moreover, complexes **A**, **B** or **C** display similar solubility and rather different reaction rates pointing to being steric and/or electronic factors responsible for their reactivity pattern.

The results herein show that the catalytic activity of *trans*-[PdCl₂L₂] complexes towards heterocyclic dimerization of internal or terminal pentynols follows the trend **C > B > A**, such as observed in the cyclotrimerization of 3-phenyl-1-propyne [8]. The two sets of results confirm that the camphor ligand derived from dimethylhydrazine activates better the {PdCl₂} metal centre for catalysis.

Investigations to tune the catalytic properties by modification of the characteristics of the coordination sphere of the catalysts or the experimental conditions are in progress

in order to extend this synthetic procedure to other heterocycles.

3. Conclusions

The conversion of 3- or 4-pentyn-1-ols to 5-hydroxy-2-pentanone is catalysed by metal centres having in common the {PdCl₂} unit. In the process, cyclization of the alkynol followed by addition to the coordinated heterocycle of a second alkynol molecule affords moderate stable cyclic ketal species (**1**) that still keep the alkyne function. These alkyne-ketal species undergo catalytic hydration without ring cleavage forming selectively a methyl ketal-ketone (**2**) that can be hydrolysed to the final ketone product (**3**). The process is highly selective in the case of the internal alkynol which is an advantage compared to former catalysts. The ketal-alkyne and ketal-ketone species are promising building blocks for organic syntheses.

The {PdCl₂} metal centre is necessary to promote the dimerization of the alkynol to the alkyne-ketal species **1** but camphorimine complexes *trans*-[PdCl₂L₂] enhance the selectivity by enabling higher reaction rates. The activity and selectivity of the {PdCl₂} catalysts are tuned by the electronic and steric properties of the camphorimine ligands.

4. Experimental section

The experiments were carried out under inert atmosphere by using vacuum and the Schlenck techniques. Complexes *trans*-[PdCl₂L₂] were prepared by published methods [8]. Solvents were purchased from Aldrich, purified by conventional techniques and distilled before use. PdCl₂ was purchased from Riedel-de Haën.

The NMR samples were prepared in CD₂Cl₂ or CDCl₃ using screw-cap NMR tubes and spectra were obtained on a Varian 300 spectrometer. The IR spectra were obtained in a JASCO FT/IR 4100 spectrometer.

4.1. Catalysis

The amount of PdCl₂ or *trans*-[PdCl₂L₂] catalysts varied from 2% to 5%. The reactions were carried till completion (confirmed by NMR) typically as follows:

4.2. 2-Methyl-2-pent-4-ynyloxy-tetrahydrofuran (1a) or 2-methyl-2-pent-3-ynyloxy-tetrahydrofuran (1b)

PdCl$_2$ (5 mg, 0.028 mmol) was added to a solution of 4-pentyn-1-ol (100 μl, 1.07 mmol) or 3-pentyn-1-ol (100 μl, 1.08 mmol) in CH$_2$Cl$_2$ (10 cm^3) and the mixture stirred for 2 days. After partial evaporation of the solvent followed by addition of Et$_2$O (ca. 5 cm^3) the catalyst was separated from the red–brown solution by filtration. Full evaporation of the solvent afforded yellow oil (1a, 145 mg; 80% conversion; $v_{C\equiv C} = 2119$ cm^{-1}; ^{1}H NMR (CD$_2$Cl$_2$): $\delta = 1,34$ (s, 3H, CH$_3$), 1.6–2.0 (m, 10H, H-2,4,6,7,8), 1.7–1.8 (m, 1H, CH, 1-H), 2.18 (td, 2H, $J = 7.0$ and $J = 2.2$ Hz, H-3), 3.3–3.4 (m, 2H, H-5), 3.7–3.8 (m, 2H, H-9) ppm; ^{13}C NMR (CD$_2$Cl$_2$): $\delta = 16.11$ (C-3), 22.10 (C-10), 25.43 (C-4), 30.15 (C-8), 38.85 (C-7), 59.88 (C-5), 68.24 (C-9), 68.98 (C-1), 85–06 (C-2); 108.1 (C-6) ppm) or (1b, 140 mg; 77% conversion; $v_{C\equiv C} = 2061$ cm^{-1}, ill defined; ^{1}H NMR, (CDCl$_3$): $\delta = 1,38$ (s, 3H, CH$_3$), 1.6–2.4 (m, 10H, H-2,4,6,7,8), 1.70 (t, 3H, $J = 3.3$ Hz, CH$_3$), 3.3–3.5 (m, 2H, H-5), 3.82 (t, 2H, $J = 6.6$, H-9) ppm; ^{13}C NMR (CDCl$_3$): $\delta = 3.33$(C-1), 20.58 (C-4), 21.79 (C-10), 24.29 (C-8), 38.87 (C-7), 59.85 (C-5), 67.37 (C-9), 76.17 (C-2), 76.23 (C-3), 107.4 (C-6) ppm) (see Scheme 1 for labelling).

4.3. Synthesis of 2-methyl-2-pent-4-ynyloxy-tetrahydrofuran (2)

PdCl$_2$ (5 mg, 0.028 mmol) was added to a solution of 4-pentyn-1-ol (100 μl, 1.07 mmol) in CH$_2$Cl$_2$ (10 cm^3) and the mixture stirred for 2 days. Then, H$_2$O (20 μl) was added and the mixture stirred for more 4 h. Partial evaporation of the solvent and addition of Et$_2$O followed by filtration over celite to separate the catalyst afforded a solution that was dried under vacuum to an orange oil (2, 140 mg; 77% conversion; $v_{CO} = 1716$ cm^{-1}; ^{1}H NMR (CD$_2$Cl$_2$): $\delta = 1.32$ (s, 3H, CH$_3$), 1.6–2.0 (m, 10H, H-2,4,6,7,8), 2.04 (s, 1H, CH, 1-H), 2.40 (t, 2H, $J = 7.3$ Hz, H-3), 3.3–3.4 (m, 2H, H-5), 3.7–3.8 (m, 2H, H-9) ppm; ^{13}C NMR (CD$_2$Cl$_2$): $\delta = 22.64$ (C-10), 25.38 (C-4), 30.45 (C-8 and C-1), 38.84 (C-7), 41.35 (C-3), 60.66 (C-5), 68.98 (C-9), 108.1 (C-6), 209.1 (C-2) ppm) (see Scheme 1 for labelling).

Further addition of H$_2$O or exposition to air led quantitatively to 3, ^{1}H NMR, (CDCl$_3$): $\delta = 2.03$ (s, 3H, CH$_3$), 1,66 (q, 2H, $J = 6.6$ Hz, H-4), 2.43 (t, 2H, $J = 7.1$ Hz, H-3), 3.46 (t, 2H, $J = 6.0$ Hz H-5) ppm; ^{13}C NMR (CDCl$_3$): $\delta = 29.54$(C-1), 26.26 (C-4), 61.36 (C-5), 209.6 (C-2), 39.98 (C-3) ppm) (see Scheme 1 for labelling).

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