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Note

One pot conversion of acetyl chloride to dehydroacetic acid and its coordination in a ruthenium(II) arene complex

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A R T I C L E I N F O

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A B S T R A C T

The reaction of [(η^6-*p*-cymene)RuCl(κ^2*N,O*-L-serinate)], **1**, with $CH_3C(O)Cl/NEt_3$, in chloroform at reflux temperature, led to the serendipitous isolation of the dehydroacetate complex [(η^6-*p*-cymene)RuCl(κ^2*O,O′*-dha)], **2**, in low amount. Then, dehydroacetic acid (dhaH) was prepared in one pot by self condensation of acetyl chloride in the presence of NEt_3 at room temperature, this reaction being unusual in the landscape of the chemistry of acyl chlorides. Complex **2** was synthesized in 89% yield from [(η^6-*p*-cymene)$RuCl_2$]$_2$ and dhaH, and fully characterized by means of X-ray diffraction, IR and NMR spectroscopy. Complex **2** underwent fast and extensive dissociation of the dehydroacetate ligand in dmso/water solution, the degree of dissociation being substantially higher than that observed for the acetylacetonate ligand from [(η^6-*p*-cymene)RuCl(κ^2*O,O′*-acac)], **3**.

1. Introduction

Ruthenium(II) arene compounds have been intensively investigated for their anticancer properties [1] (Fig. 1), and a common strategy aimed to enhance their cytotoxic activity consists in the incorporation of compounds with a known biological function [2]. A series of bioactive carboxylic acids have been introduced by esterification reaction of suitable ligands, these ligands being usually modified before coordination to the ruthenium centre [3]. However, the direct esterification of coordinated hydroxo-substituted triphenylphosphine [4] and tiophenolate [5] ligands has been also realized.

In this framework, we investigated the reaction of the complex [(η^6-*p*-cymene)RuCl(κ^2*N,O*-L-serinate)], **1** [6], containing a α-amino acidate ligand with a hydroxyl group in the side chain, with acetyl chloride in the presence of triethylamine, as a model for esterification reactions. This reaction led to the serendipitous finding of the one pot conversion of acetyl chloride to dehydroacetic acid.

Dehydroacetic acid (dhaH, red compound in Scheme 1) and sodium dehydroacetate (Na[dha]) are commercially available chemicals, known for their antifungal and antibacterial activity [7]. Dehydroacetic acid is also a useful starting material for the preparation of heterocyclic compounds of biological interest, including the veterinary drug Clopidol [8]. Several synthetic procedures are available to access dhaH, making use of ethyl acetoacetate [9], dimethyl 3-oxoglutarate [10] or triacetic acid lactone [11] as precursors. On the industrial scale, dhaH is produced with the base-catalyzed dimerization of diketene. This is the product of the spontaneous 2 + 2 cycloaddition of ketene (Scheme 1d) [12], which in turn is usually obtained through gas-phase thermal decomposition of acetic acid or acetone (Scheme 1a–b) [13]. An alternative preparation of diketene (via ketene) from acetyl chloride has been reported too [14], finally affording diketene in *ca.* 50% yield after distillation from the reaction mixture (Scheme 1c).

It should be remarked that the direct transformation of acetyl chloride to dhaH has not been reported heretofore. More in general, although acyl chlorides are versatile reagents hugely employed in organic and organometallic synthesis [16], self-condensation reactions of these substrates are not trivial tasks. To the best of our knowledge, the only conclusive report in the literature regards the synthesis of 4-hydroxy-2-pyrones mediated by strong Lewis acids (e.g. $AlCl_3$), via dehydroalogenative C–C bond coupling [17]. Anyway, it should be noted that a poor level of regiochemical control may be observed under these conditions [18].

Herein, we describe the one pot self condensation reaction of acetyl chloride to dhaH promoted by triethylamine, and the incorporation of dha$^-$ as a bidentate ligand in a Ru(II) *p*-cymene

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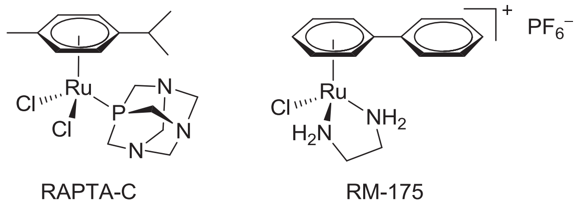
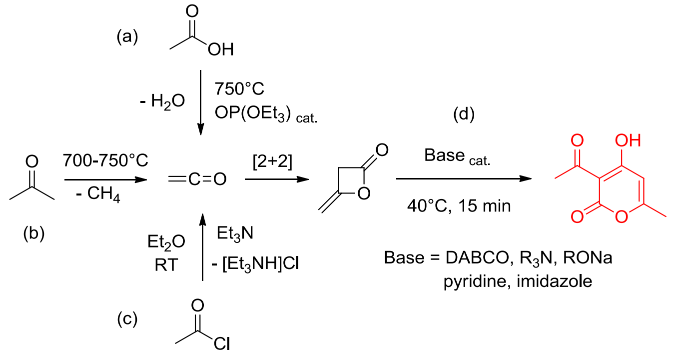


Fig. 1. Most prominent anticancer ruthenium(II) arene compounds.



Scheme 1. Preparation of dehydroacetic acid (dhaH) from C2-C3 feedstocks [15].

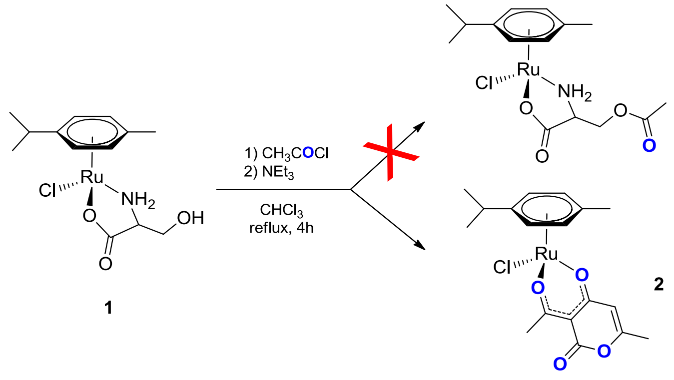
complex. The structural characterization of this complex and the behavior in aqueous medium, investigated to assess the suitability to biological studies, will be discussed.

2. Results and discussion

The reaction of the ruthenium(II) *p*-cymene α-serinate complex **1** with an excess of CH_3COCl/NEt_3 led to the isolation of few crystals of an orange solid after work-up. Surprisingly, the product was identified as the dehydroacetate complex **2** by X-ray single crystal diffraction and elemental analysis (Scheme 2).

A view of the ORTEP molecular structure of **2** is shown in Fig. 2, while relevant bonding parameters are given in Table 1.

Compound **2** comprises the expected three-leg piano-stool geometry typical of other Ru(II)-arene compounds and the bonding parameters around the Ru(II) center are similar to those reported for related [Ru(O^O)(*p*-cymene)Cl] structures (O^O = bidentate mono-anion with two O-donor atoms) [2b,d,19].



Scheme 2. Designed synthesis of [(η^6-*p*-cymene)RuCl(κ^2*N*,*O*-$O_2CCH(NH_2)CH_2OC$-OCH_3)], and serendipitous formation of [(η^6-*p*-cymene)RuCl(κ^2*O*,*O*′-dha)], **2**.

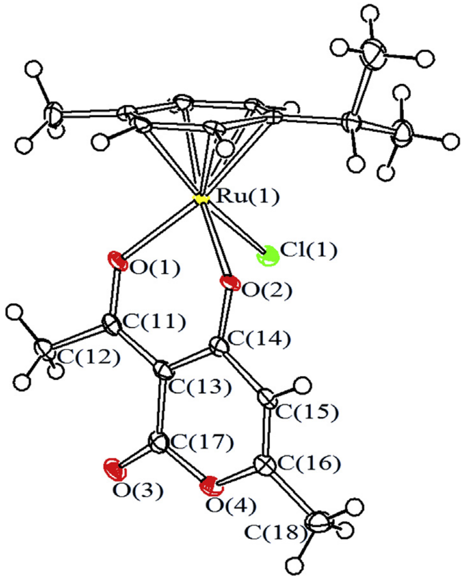


Fig. 2. Molecular structure of [(η^6-*p*-cymene)RuCl(κ^2*O*-OC(Me)CC(O)CHC(Me)OC=O)], **2**. Displacement ellipsoids are at the 50% probability level.

Table 1
Selected bond distances (Å) and angles (°) for **2**.

Ru(1)–(η^6-*p*-cymene)$_{av}$	2.178(7)	Ru(1)–Cl(1)	2.4112(9)
Ru(1)–O(1)	2.089(2)	Ru(1)–O(2)	2.079(2)
C(11)–O(1)	1.259(4)	C(14)–O(2)	1.280(4)
C(11)–C(12)	1.510(4)	C(11)–C(13)	1.440(5)
C(13)–C(14)	1.429(5)	C(13)–C(17)	1.446(5)
C(14)–C(15)	1.439(5)	C(15)–C(16)	1.337(5)
C(16)–C(18)	1.481(5)	C(16)–O(4)	1.369(4)
C(17)–O(4)	1.396(4)	C(17)–O(3)	1.217(4)
O(1)–Ru(1)–O(2)	83.74(9)	Ru(1)–O(1)–C(11)	130.1(2)
Ru(1)–O(2)–C(14)	125.4(2)	O(1)–C(11)–C(13)	123.6(3)
C(11)–C(13)–C(14)	121.6(3)	C(13)–C(14)–O(2)	125.9(3)
C(13)–C(14)–C(15)	117.8(3)	C(14)–C(15)–C(16)	120.8(3)
C(15)–C(16)–O(4)	121.6(3)	C(16)–O(4)–C(17)	122.0(3)
O(4)–C(17)–C(13)	117.6(3)	C(17)–C(13)–C(14)	119.4(3)

The dehydroacetate anion is coordinated as a chelating *O*,*O*′ β-diketonate ligand, while the ester moiety is not involved in coordination. The same coordination fashion of dha^- has been already observed in a variety of complexes with general formula [$M^{(II)}(dha)_2L_2$] (M = Cu [20], Co [21], Zn [22], Cd [22], Mn [23], Ni [24]) or [$M^{(III)}Cl_2(dha)L_2$] (M = Ru [33], Re [25]). Bonding parameters within the dha^- ligand in **2** are similar to those reported for the related complexes, showing a slightly shorter exocyclic C–O bond [C(11)-O(1) 1.259(4) Å] within the β-diketonate moiety, compared to the endocyclic C–O [C(14)-O(2) 1.280(4) Å]. A reverse situation is observed for the Ru–O bond distances [Ru(1)-O(1): 2.089(2) Å; Ru(1)-O(2): 2.079(2) Å]. A comparison of bonding lengths is given in Table 2 concerning **2**, dehydroacetic acid, sodium dehydroacetate and the previously reported complex [(η^6-*p*-cymene)RuCl(κ^2*O*,*O*′-acac)], **3**, differing from **2** in the presence of a symmetric *O*,*O*′ β-diketonate ligand (acetylacetonate).

The serendipitous formation of **2** suggested a possible route to the one pot synthesis of dehydroacetic acid (dhaH) from acetyl chloride (Scheme 1). Therefore, despite dhaH is a low-cost, commercial product, we did an investigation to reproduce the synthesis of dhaH from CH_3COCl/NEt_3.

An excess of triethylamine in chloroform was treated with acetyl chloride at room temperature, leading to the formation of dhaH (Scheme 3). Despite several byproducts were present in the crude reaction mixture, dhaH was isolated in 17% yield after