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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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ABSTRACT

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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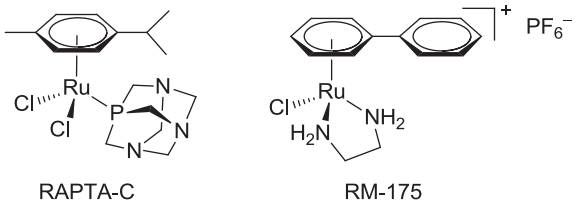
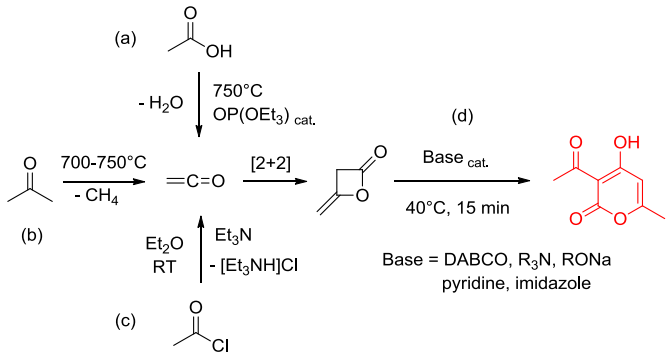


Fig. 1. Most prominent anticancer ruthenium(II) arene compounds.



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.

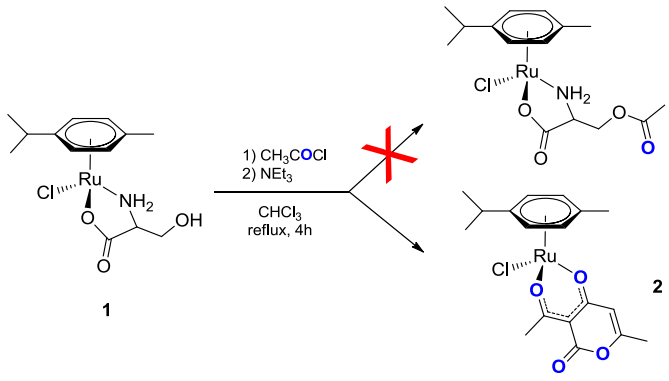
2. Results and discussion

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].

The dehydroacetate anion is coordinated as a chelating *O,O′* β-diketonate ligand, while the ester moiety is not involved in



Scheme 2. Designed synthesis of [(η⁶-*p*-cymene)RuCl(κ²*N,O*-$O_2CCH(NH_2)CH_2OCOCH_3$)], and serendipitous formation of [(η⁶-*p*-cymene)RuCl(κ²*O,O′*-dha)], **2**.

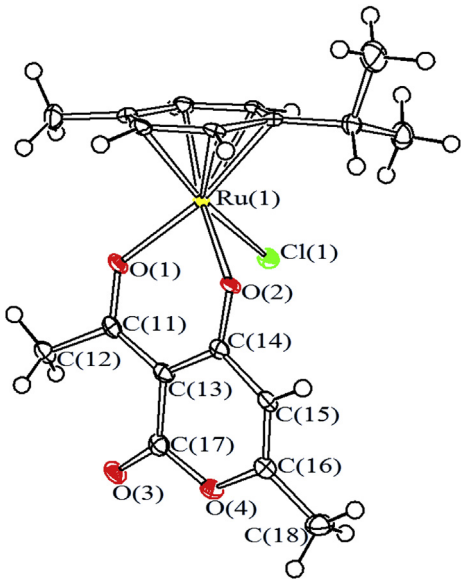


Fig. 2. Molecular structure of [(η⁶-*p*-cymene)RuCl(κ²*O*-OC(Me)CC(O)CHC(Me)OC=O)], **2**. Displacement ellipsoids are at the 50% probability level.

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

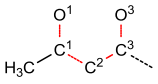
Ru(1)–(η⁶-*p*-cymene)$_{av}$	2.178(7)	Ru(1)–Cl(1)	2.4112(9)
Ru(1)–O(1)	2.089(2)	Ru(1)–O(2)	2.079(2)
C(11)–O(1)	1.259(4)	C(14)–O(2)	1.280(4)
C(11)–C(12)	1.510(4)	C(11)–C(13)	1.440(5)
C(13)–C(14)	1.429(5)	C(13)–C(17)	1.446(5)
C(14)–C(15)	1.439(5)	C(15)–C(16)	1.337(5)
C(16)–C(18)	1.481(5)	C(16)–O(4)	1.369(4)
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)

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 [(η⁶-*p*-cymene)RuCl(κ²*O,O′*-acac)], **3**, differing from **2** in the presence of a symmetric *O,O′* β-diketonate ligand (acetylacetonate).

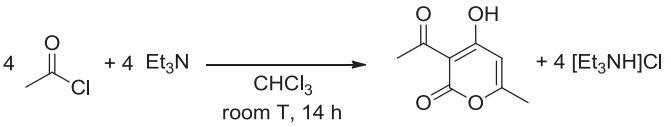
The serendipitous formation of **2** suggested a possible route to the one pot synthesis of dehydroacetic acid (dhaH) from acetyl chloride (Scheme 1). Therefore, despite dhaH is a low-cost, commercial product, we did an investigation to reproduce the synthesis of dhaH from CH_3COCl/NEt_3.

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

Table 2
Comparison of C–C and C–O bond distances in the β-diketonate moiety of dhaH, Na[dha]·H_2O and [(η^6-*p*-cymene)RuCl(L)] (L = acac, dha).

Reference structure	Compound	Bond length/Å					Ref.
		C^1-O^1	C^1-C^2	C^2-C^3	C^3-O^3	C=O lactone	
	dhaH[a]	1.244(4)	1.432(5)	1.398(4)	1.305(3)	1.204(4)	[15b]
		1.240(4)	1.452(5)	1.404(4)	1.305(3)	1.206(4)	
	Na[dha]·H_2O[a]	1.222(4)	1.448(4)	1.437(4)	1.253(3)	1.210(4)	[26]
		1.241(3)	1.451(4)	1.430(4)	1.260(2)	1.225(4)	
	2	1.259(4)	1.440(5)	1.429(5)	1.280(4)	1.217(4)	*this work*
	3	1.275(3)	1.387(3)	1.394(3)	1.271(3)	–	[27]

[a] Two crystallographically-independent molecules in the asymmetric unit.



Scheme 3. One-pot synthesis of dehydroacetic acid (dhaH) from acetyl chloride and triethylamine.

dichloromethane/water extraction and silica chromatography. The formation of dhaH probably proceeds via (di)ketene, according to the known mechanism (see Introduction).

The direct acetyl chloride to dhaH conversion was found to be very sensitive to the experimental conditions, strictly requiring the use of dry triethylamine (stored over pre-activated MS-4A) in a dilute reaction mixture (see Experimental). It should be mentioned here that former studies on the ketene dimerization (polymerization) pointed that different self-condensation products could be generated, the presence of H_2O traces being responsible for the formation of fused-ring systems [28]. The reactions of CH_3COCl with NEt_3, conducted in the presence of variable amounts of ruthenium(II) *p*-cymene compounds (**1** or [(η^6-*p*-cymene)$RuCl_2$]$_2$), did not result in any increase of yield/selectivity; this fact suggests that ruthenium does not probably participate to the formation of dhaH, even though it may stabilize the anion dha^- by coordination (formation of **2**, Scheme 2).

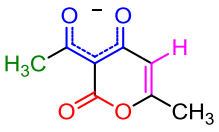
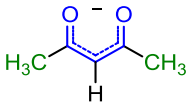
In order to obtain larger amounts of **2** for full characterization, the reaction between [(η^6-*p*-cymene)$RuCl_2$]$_2$ and dhaH was performed in methanol at room temperature in the presence of NaOH. Thus, **2** was finally isolated as a yellow-brown solid in 89% yield and then characterized by analytical and spectroscopic (IR/NMR) techniques. A comparative view of IR and NMR data for **2** and related compounds is supplied in Table 3.

Compound **2** is a racemate in $CDCl_3$ solution, containing a stereogenic Ru center. As a consequence, distinct resonances for otherwise equivalent isopropyl/methyl groups of the *p*-cymene ligand can be found in the ^1H and ^{13}C NMR spectra. In the ^1H spectrum of **2**, the dha^- ligand gives rise to three singlets at 5.80, 2.59 and 2.15 ppm, assigned to the vinyl proton and the two methyl groups, respectively. In the ^{13}C spectrum, the β-diketonate moiety is featured by resonances at 196.7, 180.6 and 101.9 ppm, while the lactone resonance has been found at 163.8 ppm. These chemical shift values are reminiscent of those of sodium dehydroacetate.

The IR spectrum of dehydroacetic acid shows four strong bands in the 1700-1500 cm^{-1} region, due to the stretching of the ketone (1730 cm^{-1}) and lactone (1708 cm^{-1}) carbonyls and two C=C stretching of the aromatic system (1638 and 1547 cm^{-1}). In the IR spectrum of **2** (solid state), two strong bands at 1650 and 1567 cm^{-1} have been attributed to the ν(C-C-O) stretchings of the β-diketonate ligand. As a comparison, the corresponding absorptions fall at 1574 and 1521 cm^{-1} in the IR spectrum of **3**. The lactone stretching in **2** occurs at 1694 cm^{-1}, showing minor variation with respect to non-coordinated dhaH.

In the light of the biological properties of dehydroacetic acid (see Introduction), a number of dehydroacetate metal complexes

Table 3
Comparison of selected IR and NMR data for **2**, **3**, dhaH and Na[dha].

Compound	IR (solid state) : $\tilde{\nu}$/cm^{-1}				^{13}C NMR ($CDCl_3$) : δ/ppm		^1H NMR ($CDCl_3$) : δ/ppm	
	ν(C=O) lactone	ν(C-C-O) 1,2-diketonate		ν(C=C)	CO_2 lactone	1,2-diketo moiety	CH_3-C=O	H-C=C
dhaH [a]	1708s	1730s-sh [b]	1638s [b]	1547s	161.4	205.4, 181.2, 100.0	2.66	5.93
Na[dha] [c]	1676s	1659s	1604s	1538s	159.1	196.7, 181.0, 102.3	2.30	5.44
2	1694s	1650s	1567s	1567s	163.8	197.6, 180.6, 101.9	2.59	5.80
3 [d]	-	1574s	1521s	-	-	186.4, 98.7	1.96	-
Reference structures and color code								

[a] IR assignments from Ref. [29].
[b] Corresponding to ν(C=O) and ν(C=C) in the α-ketoenol structure of dhaH (see Scheme 1, red compound).
[c] NMR data in DMSO-d_6 from Ref. [30].
[d] ^{13}C NMR data from Ref. [43a].

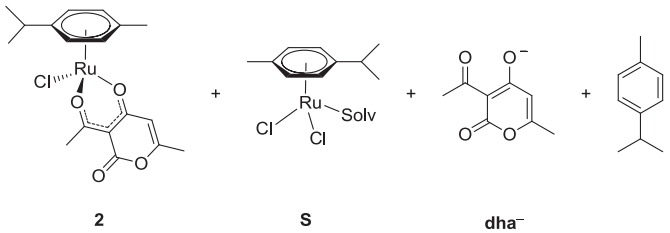
have been investigated for their possible biological applications [31]. In particular, Cu(II) [32], Ru(II) [33], Zn(II) and Sn(II) [34] compounds have been demonstrated to exhibit antifungal, antimicrobial or antibacterial activity, the activity being sometimes enhanced compared to that of dhaH itself. It should be noticed also that structurally-related pyrones have been conjugated to Pt(II) or Ru(II) arene scaffolds with the aim of obtaining a synergic effect in terms of anticancer activity [35].

In order to assess the suitability of **2** to cytotoxicity studies, we investigated the stability of this compound in aqueous medium at 37 °C along 72 h. Due to insolubility in water, the stability of **2** was evaluated by ^{1}H NMR in a DMSO:D_2O 9:1 *v*/*v* solution, being DMSO a solvent of choice in drug research [36]. NaCl 0.11 M was added to the solution, thus matching the chloride concentration normally employed for *in vitro* tests. Under these conditions, rapid release of dha^- from **2** took place, with only minor amounts (<10%) of the starting material still in solution from 7 h onwards (see Scheme 4 and Table 4). On the other hand, the analogous acetylacetonate compound **3** resulted significantly more inert toward ligand dissociation, as *ca.* 70% of Ru-acac persisted in solution after 72 h (see Scheme 5 and Table 5).

Earlier studies on the behavior of ruthenium arene complexes in aqueous solution evidenced that N,N- and N,O-bidentate ligands usually remained bound to the metal centre [1f,37]. In contrast with this general trend, a significant release over time has been reported for a variety of O,O-ligands, including fluoro-substituted diketonates [38], quinolones [19a], maltolate [39] and 3-hydroxy-4-pyr(id)ones [35]. For instance, ca. 40% release of quinolone ligands was detected after 24 h in aqueous solution. It is noteworthy that a high degree of dissociation may correlate with a low cytotoxicity against a panel of cancer cell lines [35]. On account of these considerations, we decided not to proceed with biological assays on compound **2**.

3. Conclusions

In the course of our studies on the structural modification of Ru(II) arene complexes for medicinal purposes, we have serendipitously found that acetyl chloride can be converted into dehydroacetic acid in one pot, in the presence of triethylamine. This reaction, albeit occurring in low yield, represents an unusual case of acyl chloride self condensation. A Ru(II) arene - dehydroacetate conjugate has been prepared and structurally characterized. This compound manifests fast and extensive release of the bidentate O,O-ligand in aqueous medium, the degree of dissociation being superior to that exhibited by acetylacetonate in an analogous system. This observation resembles previous reports on the relative lability, in aqueous environment, of various bidentate O,O-donors coordinated to Ru(II) arene complexes.



Scheme 4. NMR detected species as a function of time in the dmso/H_2O/NaCl solution of **2** at 37 °C.

4. Experimental

4.1. General experimental details

$RuCl_3 \cdot xH_2O$ (99.9%) was purchased from Alfa Aesar, then [(η^6-*p*-cymene)$RuCl_2$]$_2$ [40] and [(η^6-*p*-cymene)RuCl(κ^2*N*,*O*-L-serinate)], **1** [6], were prepared according to the literature. The organic reactants and solvents were obtained from Alfa Aesar, Sigma Aldrich or TCI Europe, and were of the highest purity available. Acetyl chloride and Et_3N (over 4 Å MS) were stored under nitrogen as received. 1.0 M NaOH solution in water was prepared from Normex solution (Carlo Erba) and standardized by potassium hydrogen phthalate titration before use. The synthesis of dehydroacetic acid (dhaH) and the reaction of **1** with MeCOCl/Et_3N were performed under a nitrogen atmosphere using standard Schlenk techniques and solvents distilled from appropriate drying agents. All the other operations were carried out in air with common laboratory glassware. NMR spectra were recorded at 298 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. Chemical shifts (expressed in parts per million) are referenced to the residual solvent peaks (^{1}H, ^{13}C) [41]. Spectra were assigned with the assistance of DEPT-135, ^{1}H-^{1}H (COSY) and ^{1}H-^{13}C (*gs*-HSQC and *gs*-HMBC) correlation experiments [42]. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer, equipped with a UATR sampling accessory. Carbon, hydrogen and nitrogen analyses were performed on a Carlo Erba mod. 1106 instrument.

4.2. Synthesis and characterization of compounds

4.2.1. Reaction of [(η^6-*p*-cymene)RuCl(κ^2*N*,*O*-L-serinate)], **1**, with $CH_3C(O)Cl/NEt_3$

In a 25-mL Schlenk tube, Et_3N (1.1 mL, 7.9 mmol) was added to a mixture of **1** (58 mg, 0.16 mmol) and acetyl chloride (55 μL, 0.77 mmol) in $CHCl_3$ (8 mL). The resulting yellow solution was stirred at reflux temperature for 4 h then at room temperature overnight. The mixture was then extracted with H_2O (3 × 15 mL) and volatiles were removed under vacuum from the organic phase, affording a yellow-orange solid. X-ray quality crystals of **2** were collected from a $CHCl_3$ solution of this solid layered with hexane and settled aside at −20 °C. Anal. Calcd. for $C_{18}H_{21}ClO_4Ru$: C, 49.37; H, 4.83. Found: C, 4; 49.84, 4.70.

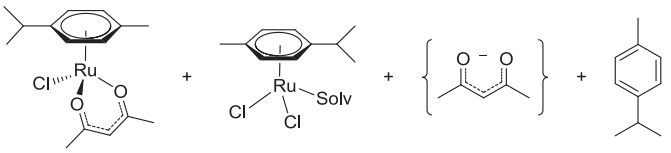
4.2.2. Dehydroacetic acid (dhaH)

In a 25-mL Schlenk tube, acetyl chloride (0.10 mL, 1.4 mmol) was added dropwise to a solution of Et_3N (0.40 mL, 2.9 mmol) in $CHCl_3$ (9 mL) and the resulting colorless solution ($c_{MeCOCl} = 0.15$ mol L^{-1}) was stirred at room temperature for 15 h. A pale yellow solution was obtained, thus volatiles were removed under vacuum and the residue was re-dissolved in CH_2Cl_2. The organic phase was extracted with H_2O (x3) and then loaded on top of a silica column. The title compound was obtained as a colorless solid following elution with EtOAc:hexane 2:1 *v*/*v* and solvent removal under vacuum (40 °C). Yield: 11 mg, 19%. Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.79. Found: C, 57.22; H, 4.65. IR (solid state): $\tilde{\nu}/cm^{-1} = 3087w, 2962w, 2927w, 1730s-sh (\nu_{C7=O}), 1708s (\nu_{C5=O}), 1638s (\nu_{C1=C6}), 1611m-sh, 1547s (\nu_{C2=C3}), 1449 m, 1429m-sh, 1416m-sh, 1371 m, 1349 m, 1254s, 1170w, 1031 m, 1008m-sh, 995s, 963 m, 923 m, 856s, 806w, 778 m, 711w, 704w. ^{1}H NMR ($CDCl_3$): δ/ppm = 16.69 (s, 1H, OH), 5.93 (s, 1H, C2-H), 2.66 (s, 3H, C8-H), 2.27 (s, 3H, C4-H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 205.4 (C7), 181.2 (C1), 169.2 (C3), 161.4 (C5), 101.6 (C2), 100.0 (C6), 30.2 (C8), 20.8 (C4). See Chart 1 for structure and atom numbering.

A comparable yield of dhaH was obtained when the reaction was performed under protection from the light or with 10 eq. of Et_3N. The development of a red color with massive precipitation of

Table 4
NMR detected species as a function of time in the dmso/H_2O/NaCl solution of **2** at 37 °C.

time/hours		0	7	25	47	72
% NMR	2 *vs.* internal standard	73	9	8	7	5
	2	73	6	5	4	3
	S	14	48	45	41	38
	dha^-	13	43	43	43	43
	p-cymene	0	3	7	12	16



3 S

Scheme 5. NMR detected species as a function of time in the dmso/H_2O/NaCl solution of **3** at 37 °C.

$[NEt_3H]Cl$ was observed when the reaction was performed in more concentrated solutions (c_{MeCOCl} = 0.5, 1.0 mol L^{-1}). In these cases, no dhaH was identified in the crude reaction mixture by ^1H NMR. When the reaction was performed with c_{MeCOCl} = 0.5 mol L^{-1} at 0 °C, a yellow solution not containing dhaH was obtained.

4.2.3. *[(η^6-p-cymene)RuCl(κ^2O,O′-dha)],* ***2***

A brick red solution of $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (302 mg, 0.493 mmol) and dhaH (167 mg, 0.993 mmol) in MeOH (20 mL) was treated with 1.0 M NaOH (1.0 mL, 1.0 mmol). The resulting yellow-orange solution was stirred at room temperature overnight, therefore volatiles were removed under vacuum. The residue was suspended in CH_2Cl_2 and filtered. The filtrate solution was taken to dryness under vacuum affording a yellow-brown solid, which was washed with hexane and dried under vacuum (50 °C). Yield: 396 mg, 89%. Compound **2** is soluble in DMSO, MeOH and CH_2Cl_2, poorly soluble in Et_2O and insoluble in hexane and H_2O. Anal. Calcd. for $C_{18}H_{21}ClO_4Ru$: C, 49.37; H, 4.83. Found: C, 49.22; H, 4.75. IR (solid state): $\hat{u}/cm^{-1}$ = 3062w, 3002w, 2961w, 2922w, 2869w, 1694s ($\nu_{C12=O}$), 1650s ($\nu_{C13\text{-}C14\text{-}O}$), 1567s ($\nu_{C13\text{-}C8\text{-}O} + \nu_{C9=C10}$), 1471s, 1421s, 1396s, 1378s, 1363s, 1349s, 1280w, 1264w, 1238 m, 1201w, 1165 m, 1114w, 1092w, 1066 m, 1056w-sh, 1033 m, 1023w-sh, 1003 m, 970 m, 947 m, 882 m, 844 m, 806w, 780 m, 728w, 718w, 687w, 668w. ^1H NMR ($CDCl_3$): δ/ppm = 5.80 (s, 1H, C9-H), 5.53 (pseudo-t, $^3J_{HH}$ = 5.0 Hz, 2H, C4-H + C4′-H), 5.27 (d, $^3J_{HH}$ = 6.0 Hz, 2H, C3-H + C3′-H), 2.89 (hept, $^3J_{HH}$ = 7.0 Hz, 1H, C6-H), 2.59 (s, 3H, C15-H), 2.24 (s, 3H, C1-H), 2.04 (s, 3H, C11-H), 1.33 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H + C7′-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 197.6 (C14), 180.6 (C8), 163.8 (C12), 163.4 (C10), 106.5 (C9), 101.9 (C13), 100.2 (C5), 97.4 (C2), 82.8, 82.6 (C4 + C4′), 79.5, 79.5 (C3 + C3′), 31.9 (C15), 30.9 (C6), 22.4, 22.3 (C7 + C7′), 19.9 (C11), 18.0 (C1). See Chart 2 for structure and atom numbering. A clean recovery of the starting materials was obtained when the reaction was performed in refluxing CH_2Cl_2 without the addition of a base.

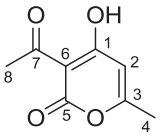


Chart 1. Structure of dhaH (numbering refers to carbon atoms) [15].

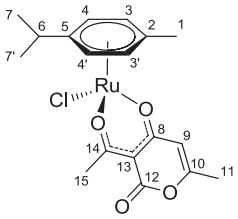


Chart 2. Structure of [(η^6-*p*-cymene)RuCl(κ^2O,O′-dha)], **2** (numbering refers to carbon atoms).

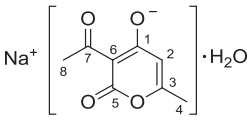


Chart 3. Structure of Na[dha] (numbering refers to carbon atoms) [26].

4.2.4. *Sodium dehydroacetate monohydrate, Na[dha]·H_2O*

NaOH (1.0 M, 0.64 mL, 0.64 mmol) was added dropwise to a suspension of dhaH (107 mg, 0.636 mmol) in water (3 mL). The resulting pale yellow solution (pH = 8) was stirred at room temperature for 2.5 h. Therefore volatiles were removed under vacuum and the residue was suspended in Et_2O. The suspension was filtered and the resulting colorless solid was washed with Et_2O and dried under vacuum (40 °C). Yield: 123 mg, 93%. Anal. Calcd. for $C_8H_9NaO_5$: C, 46.16; H, 4.36. Found: C, 46.30; H, 4.29. IR (solid state): $\hat{u}/cm^{-1}$ = 3400w-br (ν_{OH}), 3077w, 2994w, 2965w, 2927w, 1711m-sh, 1676s ($\nu_{C5=O}$), 1659s ($\nu_{C6\text{-}C7\text{-}O}$), 1604s ($\nu_{C6\text{-}C1\text{-}O}$), 1538s ($\nu_{C2=C3}$), 1444m-sh, 1401s, 1382s-sh, 1358s, 1343s, 1263 m, 1221w, 1203w, 1165 m, 1112w, 1061w, 1022 m, 1000s, 952 m, 898 m, 833 m, 776 m, 723w, 698 m.

See Chart 3 for structure and atom numbering.

Table 5
NMR detected species as a function of time in the dmso/H_2O/NaCl solution of **3** at 37 °C.

time/hours		0	5.75	24	48	72
% NMR	3 *vs.* internal standard	97	80	78	72	69
	3	97	62	59	56	52
	S	3	19	18	17	16
	acac-derivative	0	17	16	16	16
	p-cymene	0	2	7	11	16

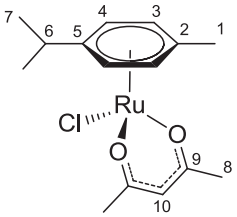


Chart 4. Structure of [(η^6-*p*-cymene)RuCl(κ^2*O*,*O*′-acac)], **3** (numbering refers to carbon atoms).

4.2.5. [(η^6-*p*-cymene)RuCl(κ^2*O*,*O*′-acac)], **3** [43]

The title compound was prepared as described for [(η^6-*p*-cymene)RuCl(κ^2*O*,*O*′-dha)], using [(η^6-*p*-cymene)RuCl$_2$]$_2$ (123 mg, 0.200 mmol), acetyl acetone (45 μL, 0.44 mmol) and 1.0 M NaOH (0.45 mL, 0.45 mmol) in MeOH (4 mL). Reaction time = 2 h. Yield: 123 mg, 83% (ocher-yellow solid). Compound **3** is soluble in MeOH and CH_2Cl_2, poorly soluble in Et_2O and insoluble in hexane. Anal. Calcd. for $C_{15}H_{21}ClO_2Ru$: C, 48.71; H, 5.72. Found: C, 48.84; H, 5.75. IR (solid state): $\tilde{\nu}$/cm^{-1} = 3066w, 3030w, 2962 m, 2918w, 2873w, 1574s ($\nu_{C10\text{-}C9\text{-}O}$), 1521s ($\nu_{C10\text{-}C9\text{-}O}$), 1469 m, 1427 m, 1386s, 1324 m, 1300w, 1269 m, 1198 m, 1161w,1145w, 1115w, 1095 m, 1055 m, 1018 m,932 m, 904w, 881 m, 794 m, 779m-sh, 677w, 657w. ^{1}H NMR ($CDCl_3$): δ/ppm = 5.43 (d, $^3J_{HH}$ = 5.9 Hz, 2H, C4-H), 5.18 (d, $^3J_{HH}$ = 5.9 Hz, 2H, C3-H), 5.12 (s, 1H, C10-H), 2.84 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, C6-H), 2.24 (s, 3H, C1-H), 1.96 (s, 6H, C8-H), 1.28 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H).

See Chart 4 for structure and atom numbering.

4.3. Stability of Ru compounds in dmso/water solutions

4.3.1. General procedure

A stock DMSO-d_6/D_2O 9:1 *v*/*v* solution containing NaCl (0.11 mol L^{-1}) and dimethyl sulfone ($5.6\cdot10^{-3}$ mol L^{-1}) as reference for ^{1}H NMR spectra (δ/ppm = 2.97 (s, 6H) in DMSO-d_6/D_2O 9:1 *v*/*v*) was used for the following experiments. Complexes **2** and **3** were dissolved in the DMSO-d_6/D_2O solution (0.6 mL; [Ru] = $1.5\cdot10^{-2}$ mol L^{-1}) and the resulting solution was maintained at 37 °C for 72 h and analyzed by ^{1}H NMR spectroscopy as a function of time. Percent values of compounds in solution are based on ^{1}H NMR spectroscopy and refer to identified compounds only (indicated as "*% NMR*") or refer to dimethyl sulfone used as internal standard (indicated as "*% NMR vs internal standard*").

4.3.2. Reference data

NMR spectra of the following compounds dissolved in the DMSO-d_6/D_2O solution were recorded and used for comparison for NMR assignments. ***p*-cymene**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 7.12–7.03 (m, 4H), 2.80 (hept, *J* = 6.9 Hz, 1H), 2.23 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 6H). **Na[dha]·H$_2$O**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.47 (s, 1H), 2.28 (s, 3H), 1.96 (s, 3H). **acacH**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.68 (s, 0.2H*), 3.63 (s, 0.5H), 2.10 + 1.96 (s, 6H). **Na[acac]**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 4.77 (s, 1H*), 1.65 (s, 6H). *H/D exchange with the solvent lowers the integral value. **[(η^6-*p*-cymene)RuCl$_2$]$_2$**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.79 (d, *J* = 6.3 Hz, 2H), 5.74 (d, *J* = 6.3 Hz, 2H), 2.79 (hept, *J* = 6.9 Hz, 1H), 2.07 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 6H). This set of signals was attributed to the formation of a solvato-complex [(η^6-*p*-cymene)RuCl$_2$(Solv)], **S** [4].

4.3.3. Stability studies: compound **2**

Red-brown solution (0–7 h), yellow-brown solution (7–72 h). Data are reported in Table 4 while NMR detected species are shown in Scheme 4. **2.** ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.90 (s, 1H), 5.74 (d, *J* = 5.5 Hz, 2H), 5.47 (d, *J* = 5.8 Hz, 2H), 2.77 (hept, *J* = 6.7 Hz, 1H), 2.42 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H).

Table 6
Crystal data and measurement details for **2**.

Formula	$C_{18}H_{21}ClO_4Ru$
FW	437.87
T, K	100(2)
λ, Å	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
a, Å	7.0011(6)
b, Å	9.5431(8)
c, Å	14.1615(12)
α,°	109.268(2)
β,°	98.744(2)
γ,°	95.998(2)
Cell Volume, Å^3	870.57(13)
Z	2
D_c, g·cm^{-3}	1.670
μ, mm^{-1}	1.072
F(000)	444
Crystal size, mm	0.15 × 0.13 × 0.09
θ limits,°	1.554–26.997
Reflections collected	11305
Independent reflections	3768 [R_{int} = 0.0413]
Data/restraints/parameters	3768/0/222
Goodness on fit on F^2	1.125
R_1 ($I > 2\sigma(I)$)	0.0403
wR_2 (all data)	0.0736
Largest diff. peak and hole, e Å^{-3}	1.030/−1.232

4.3.4. Stability studies: compound **3**

Yellow-brown solution. Data are reported in Table 5 while NMR detected species are shown in Scheme 5. **3.** ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.55 (d, *J* = 5.9 Hz, 2H), 5.29 (d, *J* = 5.9 Hz, 2H), 5.09 (s, 1H*), 2.70 (hept, *J* = 6.7 Hz, 1H), 1.83 (s, 6H), 1.21 (d, *J* = 6.9 Hz, 6H). *H/D exchange with the solvent lowers the integral value. **Acac-derivative**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 1.75 + 1.72 (s, 6H). **Other species**. ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 5.24 (d), 5.02 (d), 2.33 (m), 2.21 (m), 2.05 (m), 1.97 (s), 1.08–1.02 (m).

4.4. X-ray crystallography

Crystal data and collection details for **2** are reported in Table 6. Data were recorded on a Bruker APEX II diffractometer equipped with a PHOTON100 detector using Mo–Kα radiation. Data were corrected for Lorentz polarization and absorption effects (empirical absorption correction SADABS) [44]. The structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2 [45]. Hydrogen atoms were fixed at calculated positions and refined by a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters.

Supporting information

CCDC contain the supplementary crystallographic data for the X-ray study reported in this paper. CCDC 1564132 (**2**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1016/j.jorganchem.2017.08.003.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2017.08.003.

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