Journal of Organometallic Chemistry 807 (2016) 22–28

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Synthesis and characterization of ruthenium compounds incorporating keto-amine ligands. The applications of catalytic transfer hydrogenation and cancer cell inhibition

Tzung-Han Lin [a], Kuheli Das [a], Amitabha Datta [a], Wohn-Jenn Leu [c], Hung-Chang Hsiao [a], Chia-Her Lin [b], Jih-Hwa Guh [c], Jui-Hsien Huang [a, *]

[a] Department of Chemistry, National Changhua University of Education, Changhua, 50058, Taiwan
[b] Department of Chemistry, Chung-Yuan Christian University, Chun-Li, 320, Taiwan
[c] School of Pharmacy, National Taiwan University, Taipei, 100, Taiwan

ARTICLE INFO

Article history:
Received 15 October 2015
Received in revised form
20 January 2016
Accepted 21 January 2016
Available online 29 January 2016

Keywords:
Transfer hydrogenation
Keto-amine
Ruthenium
Hormone-refractory prostate cancer

ABSTRACT

A series of keto-amine bidentate precursors **1**–**5**, $OCCH_3CHCCH_3NHR$ (where **1**, R = C_6H_3-2,6-$^iPr_2$; **2**, R = C_6H_2-2,4,6-Me_3; **3**, R = C_6H_4-2-^{t}Bu; **4**, R = C_6H_4-2-OMe; **5**, R = C_6H_4-2-OMe-5-Me) were synthesized and combined with $[Ru(\eta^6$-*p*-cymene$)Cl_2]_2$ to generate the monomeric arene-Ru derivatives, $[Ru(\eta^6$-*p*-cymene$)(OCCH_3CHCCH_3NR)Cl]$ (where **6**, R = C_6H_3-2,6-$^iPr_2$; **7**, R = C_6H_2-2,4,6-Me_3; **8**, R = C_6H_4-2-^{t}Bu; **9**, R = C_6H_4-2-OMe; **10**, R = C_6H_4-2-OMe-5-Me) in moderate yield. The ruthenium derivatives effectively catalyzed the conversion rate in transfer hydrogenation of substituted acetophenone. The molecular structures of **2**, **6**–**10** were determined by single crystal X-ray diffractometry in the solid state, revealing a four-coordination environment around the Ru atom. The potential anti-cancer activity of ruthenium derivatives against human hormone-refractory metastatic prostate cancer (HRMPC) cell lines was also studied.

1. Introduction

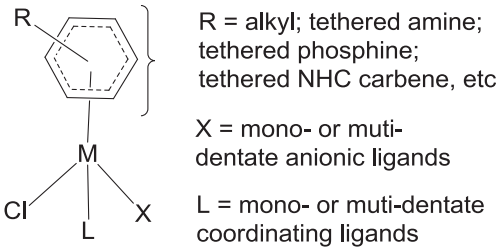
The chemistry of η^6-arene ruthenium compounds has received considerable attention in recent years, since a large number of applications in supramolecular [1–5] and medicinal chemistry [6–11] have been developed with excellent or promising results. Ruthenium arene-chloride dimeric complexes, $[(\eta^6$-arene$)RuCl_2]_2$ [12–14], are good starting materials that could generate a variety of ruthenium derivatives to be used as anti-cancer drugs [15–24] and homogeneous catalysts [25–27]. The distinctive features of the ruthenium arene compounds include (i) the variability of η^6-arene fragments, (ii) substitution of the chloride with mono- or multi-dentate anionic ligands, and (iii) the ability to adjoin mono- or multi-dentate ligands to arene ruthenium compounds as shown in Scheme 1. The η^6-arene fragment in ruthenium compounds includes alkyl substituted arenes [28], tethered amines, phosphines, and NHC carbine arenes [29,30], etc. Similarly, mono- and multi-dentate anionic ligands as well as neutral ligands have been applied to form new organo-ruthenium derivatives (see Scheme 1).

Catalytic asymmetric transfer hydrogenation of ketones has recently emerged as a viable means for synthesizing chiral alcohols [31]. Due to its operational simplicity, the easy availability of reductants, and the high enantioselectivities, the catalytic enantioselective reduction of ketones has been extensively studied during the last decade. The $[Ru(\eta^6$-arene$)$-(chelating-ligand)Cl]-type compounds exhibit the characteristic "piano stool" structure, with the unreactive arene as a "spectator ligand" in the metal coordination sphere and the chloride as a suitable "leaving group" [32]. These structural features seem favorable to afford sequential reactions involved in catalysis. Recently, Williams et al. [33] reported the synthesis of water-soluble aminosulfonamide ligands and their applications in the Ru(II)-catalyzed enantioselective transfer hydrogenation of aromatic ketones.

In the search for new organo-ruthenium compounds, we developed a series of bidentate keto-amine ligands and have subjected these precursors into $[Ru(\eta^6$-*p*-cymene$)Cl_2]_2$ to form new monomeric ruthenium derivatives. By changing the sterically hindered alkyl substituents on the keto-amine moiety, we are able to tune the stereogeometries of the ruthenium compounds and to

* Corresponding author.
E-mail address: juihuang@cc.ncue.edu.tw (J.-H. Huang).

http://dx.doi.org/10.1016/j.jorganchem.2016.01.029
0022-328X/



Scheme 1. The variation of η^6-arene ruthenium complexes.

study the Ru-catalyzed transfer hydrogenation. We also investigated the potential of the Ru derivatives as anticancer agents against HRMPC PC-3 and DU-145 cells.

2. Results and discussion

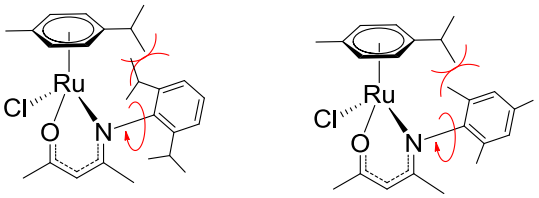
2.1. Synthesis and characterization of compounds *1*–*10*

A series of keto-amine ligands **1**–**5**, $OCCH_3CHCCH_3NHR$ (where **1**, R = C_6H_3-2,6-^{i}Pr$_2$; **2**, R = C_6H_2-2,4,6-Me$_3$; **3**, R = C_6H_4-2-^{t}Bu; **4**, R = C_6H_4-2- OMe; **5**, R = C_6H_4-2-OMe-5-Me) were synthesized according to a modified procedure [34] by the reaction between an arylamine and 2,4-pentanedione in methanol with a small amount of formic acid (Scheme 2). The amine N*H* protons for compounds **1**–**5** were involved in intramolecular hydrogen bonding with the keto (C=O) oxygen to form a six-membered chelate ring and the ^{1}H NMR spectra were relatively similar, showing broad *NH* signals at ca. δ 12.0. The methine protons of the keto-amine backbone for compounds **1**–**5** all displayed characteristic sharp singlets at *ca.* δ 4.7–5.1. In the ^{1}H NMR spectrum, the chemical shift of the methine proton is usually monitored to screen for the complexation of keto-amine ligands with metals. The keto-amine ligands **1**–**5** were converted to their corresponding lithium salts by adding one equivalent of Li^{n}Bu and then were subjected to a THF solution of [Ru(η^6-*p*-cymene)Cl$_2$]$_2$ [35] at 0 °C. After workup, complexes [Ru(η^6-*p*-cymene)($OCCH_3CHCCH_3NR$)Cl] (where **6**, R = C_6H_3-2,6-^{i}Pr$_2$; **7**, R = C_6H_2-2,4,6-Me$_3$; **8**, R = C_6H_4-2-^{t}Bu; **9**, R = C_6H_4-2-OMe; **10**, R = C_6H_4-2-OMe-5-Me) were isolated in moderate yield (see Scheme 2) and characterized by ^{1}H and ^{13}C NMR spectra. The characteristic methine proton for the keto-amine backbone of complexes **6**–**10** showed the typical ^{1}H NMR signal at ca. δ 4.66–4.77, a more up-field shifted signal than observed for the corresponding keto-amine ligands. This upfield shift was presumably due to the electron shielding from the ruthenium atom. It is worth noting that the steric hindrance between the cymene isopropyl group [36] and the substituted aryl group of the keto-amine ligands resulted in a slow rotation of the amine-aryl C–N bond as shown in Scheme 3. This criterion is quite distinct for larger steric hindrance among aryl rings of the keto-amine for compounds **6** and **7**. At room temperature, *i.e.*, the slow limit, compound **6** showed two septets (δ 3.78 and 3.09) and four doublets (δ 1.42, 1.31, 1.29, and 1.27) for the two corresponding isopropyl fragments. Compound **7** likely displayed two singlets (δ 2.37 and 2.14) for two methyl groups at *ortho* positions of the 2,4,6-trimethylphenyl fragment. These resonances were broadened when the ^{1}H NMR spectra were taken at elevated temperature (see Supporting information). The energy barriers for C–N bond rotation of compounds **6** and **7** were estimated at 60.9 and 59.8 kJ/mol, respectively [37]. For compounds **8**–**10**, the ^{1}H and ^{13}C NMR spectra corresponded well with the predicted molecular geometries.

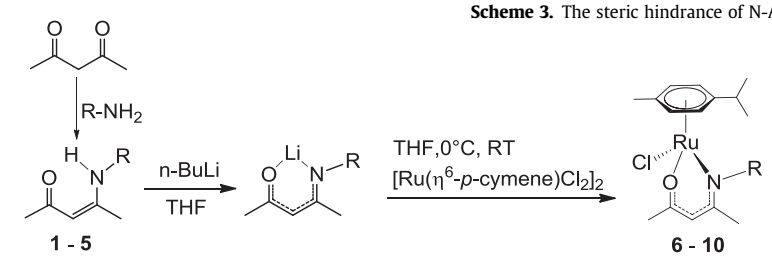
2.2. Molecular geometries of compounds *2* and *6*–*10*

The summary of X-ray crystal data collection and the selected bond lengths and angles for compounds **2** and **6**–**10** are shown in Tables 1 and 2, respectively. The crystals of organic keto-amine compound **2** were obtained from a saturated methylene chloride solution at −20 °C and its molecular geometry is depicted in Fig. 1. Compound **2** showed a planar keto-amine backbone architecture with conjugated bond lengths [38,39]. The corresponding bond lengths for C=O and C–N were 1.2438(15) and 1.3409(15) Å, respectively. Crystals of compounds **6**–**10** were obtained from concentrated toluene solutions at −20 °C. The molecular geometries of **6**–**10** are depicted in Figs. 2–6 and could be best described as three-legged piano stool structures with the cymene as the base and the oxygen and nitrogen atoms from the keto-amine frame and the chloride serving as the three legs.

The corresponding bond lengths between ruthenium and the center of the cymene ring belong at ca. 1.67 Å [40–43]. In general, the keto-amine backbone was coordinated with the ruthenium atom to form a six-membered chelated ring where the ruthenium atom deviated from the keto-amine plane at ca. 0.53 Å. The Ru-



Scheme 3. The steric hindrance of N-Aryl bond rotation of compounds **6** and **7**.



compound	1, 6	2, 7	3, 8	4, 9	5, 10
R				OMe	OMe

Scheme 2. Synthesis of compounds **1**–**10**.