Journal of Organometallic Chemistry 819 (2016) 1–10

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Nucleophilic substitution reactions of $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CO}_2\text{H})]^+$: Synthesis, characterization and cytotoxicity of organoruthenium ester and amide complexes

Bradley T. Loughrey [a, *], Michael L. Williams [a], Peter G. Parsons [b], Peter C. Healy [a]

[a] Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, Australia
[b] Drug Discovery Group, Queensland Institute of Medical Research, Brisbane, Australia

ARTICLE INFO

Article history:
Received 21 February 2016
Received in revised form
1 May 2016
Accepted 5 June 2016
Available online 7 June 2016

Keywords:
Anti-cancer
Arene
Cyclopentadienyl
Organometallic
Ruthenium
Sandwich complex

ABSTRACT

This article outlines the synthesis of an electrophilic organoruthenium carboxylic acid of the structure $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CO}_2\text{H})]^+$ and explores the behavior of this molecule under a variety of nucleophilic substitution conditions using a range of oxygen and nitrogen based nucleophiles including alcohols, primary and secondary amines and aromatic sulfonamides. The resulting organoruthenium ester $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{COOR})]^+$ and amide $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CONHR})]^+$ or $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CONR})]^+$ complexes are additionally reported. All prepared complexes have been fully characterized using Fourier-transform IR and NMR spectroscopy and electrospray mass spectrometry with single-crystal X-ray structural determinations reported for three complexes: $3[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CO}_2\text{H})]\text{B}(\text{C}_6\text{H}_5)_4.[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CO}_2)].\text{H}_2\text{O}$, $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CONHCH}_2\text{Ph})]\text{PF}_6$ and $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-C}_6\text{H}_5\text{CONHSO}_2\text{C}_6\text{H}_4\text{-COMe})]\text{PF}_6$. Complexes were also evaluated for *in vitro* cytotoxic activity against the MCF7 (hormone-dependant breast cancer), MDA-MD-231 (hormone-independent breast cancer), MM96L (human melanoma) tumourigenic cell lines and the normal NFF (neonatal foreskin fibroblasts) human cell line.

1. Introduction

Group 8 sandwich complexes of the structure $[(\eta^5\text{-Cp})\text{Ru}(\eta^6\text{-Arene})]^+$ (where $\text{Cp} = (\text{C}_5\text{H}_5)$ or $\text{Cp}^* = (\text{C}_5(\text{CH}_3)_5)$) have been studied now for a number of years, with the first such ruthenium derivative $[(\eta^5\text{-Cp})\text{Ru}(\eta^6\text{-benzene})]\text{Cl}$ prepared as early as 1973 by Baird et al. [1] Through the combination of a wide range of synthetic procedures, structurally diverse libraries of $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-Arene})]^+$ complexes have been prepared with the $[(\eta^5\text{-Cp}^*)\text{Ru}]^+$ moiety in particular demonstrating a strong areneophilic nature. This organoruthenium cation displays the capability of selectively coordinating to the aromatic ring of a wide array of functionalized arene ligands. This potential for structural diversity means that $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-Arene})]^+$ complexes have shown promise in such areas as natural product synthesis [2], radioisotopic labeling of biomolecules [3], crystal engineering [4], preparation of charge-transfer materials [5], incorporation as supramolecular anion receptors [6] and as precursors to organoruthenium species which are known to catalyze a variety of organic transformations [7]. Work by our research group in 2008 demonstrated that these molecules may also show promise as anticancer agents, with structurally diverse variations of $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-Arene})]^+$ complexes exhibiting potent and selective cytotoxic activity towards a diverse range of cancerous cell lines during *in vitro* study [8].

This finding was significant as research into ruthenium based cancer chemotherapeutic agents (Fig. 1) was highly topical owing to the success of the ruthenium(III) complexes KP1019 (a potent cytotoxic agent) [9] and NAMI-A (an inhibitor of metastatic forms of disease) [10]. These compounds, in addition to NKP-1339 (the Na^+ adduct of KP1019) have now successfully completed phase I clinical trials and have progressed onto phase II [11–13].

Organoruthenium(II) half-sandwich (piano-stool) complexes have also demonstrated promising *in vitro* and *in vivo* anticancer activity with the $[\text{Ru}(\eta^6\text{-arene})(\text{en})\text{L}]^+$ (en = ethylenediamine, and L = monodentate anion) and RAPTA $[\text{Ru}(\eta^6\text{-arene})(\text{YZ})\text{PTA}]$ (PTA = 1,3,5-triaza-7-phospha-adamantane) series of complexes proving to be potent cytotoxic and antimetastatic agents, respectively [14–18].

Over recent years our research group has continued to investigate the structure activity relationship of $[(\eta^5\text{-Cp}^*)\text{Ru}(\eta^6\text{-Arene})]^+$

* Corresponding author.
E-mail address: bradley.loughrey@griffithuni.edu.au (B.T. Loughrey).

http://dx.doi.org/10.1016/j.jorganchem.2016.06.012
0022-328X/

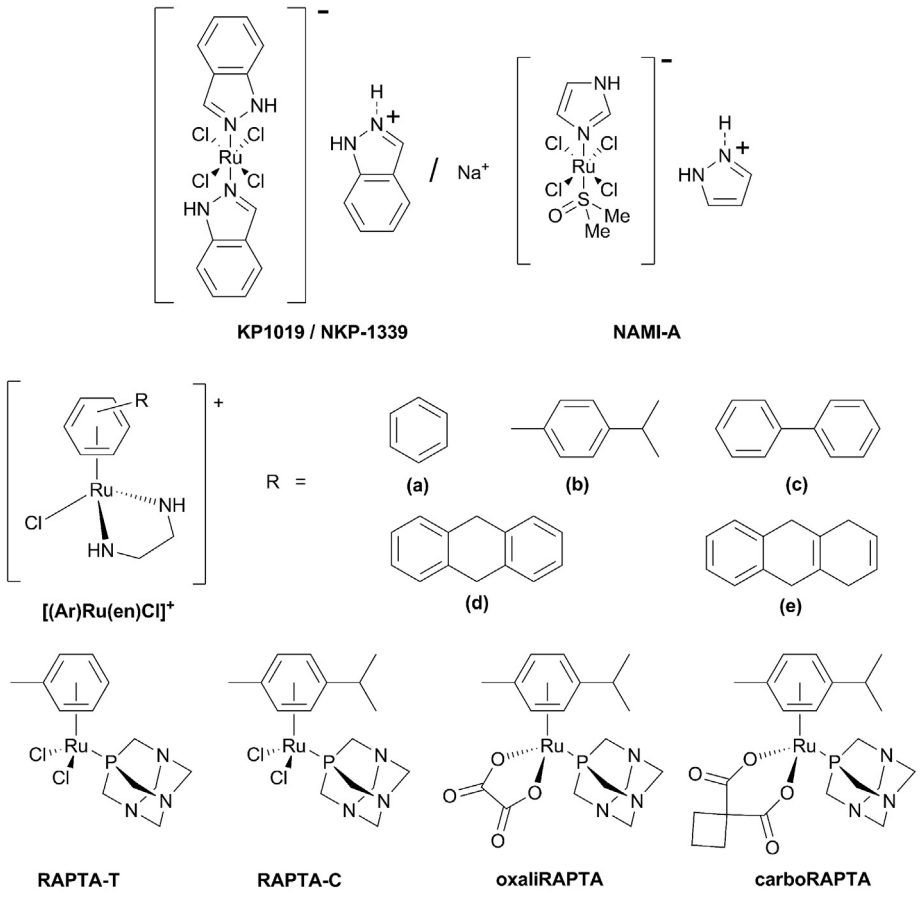

Fig. 1. Ruthenium(III) compounds currently progressing through clinical trials (KP1019, NKP-1339 and NAMI-A) and prominent examples of organoruthenium(II) piano-stool compounds; $[Ru(\eta^6\text{-arene})(en)L]^+$ (where R includes aromatic ligands such as benzene (a), *p*-cymene (b), biphenyl (c), dihydroanthracene (d) and tetrahydroanthracene (e) and RAPTA (R = ruthenium, A = arene, PTA = 1,3,5-triaza-7-phospha-adamantane) complexes.

complexes (Fig. 2 – series A) and have revealed that cytotoxicity is dependent on both the size and lipophilicity of the attached arene and/or Cp group respectively [19–21], with complexes incorporating large, lipophilic arene ligands such as naphthalene.

phenanthrene and pyrene achieving IC_{50} values over an order of magnitude more potent than cisplatin *in vitro* [21]. It was also demonstrated that the presence of a cationic charge is essential for cytotoxic activity with structurally diverse series of ruthenocenyl complexes displaying relative inactivity in comparison to their charged brethren [22,23]. Recent international studies support these results, demonstrating that series of ruthenium naphthalene complexes with amino acid esters substituted off the Cp* group (Fig. 2 – series B) achieve comparable IC_{50} values to cisplatin *in vitro* [24], while organoruthenium 2-formyl-naphthalene and 9-formyl-anthracene Cp complexes (Fig. 2 – series C) induce significant supercoiling and kinking of free DNA under atomic force microscopy [25].

As a means of continuing to enhance and optimize the cytotoxic profile of $[(\eta^5\text{-Cp}^*)Ru(\eta^6\text{-Arene})]^+$ full-sandwich complexes it was of interest to develop a synthetic method that would afford convenient structural modification of the η^6-arene ligand post ruthenium complexation. We therefore set out to prepare a labile, electrophilic $[(\eta^5\text{-Cp}^*)Ru(\eta^6\text{-Arene})]^+$ starting material which would be eligible for participation in a range of nucleophilic

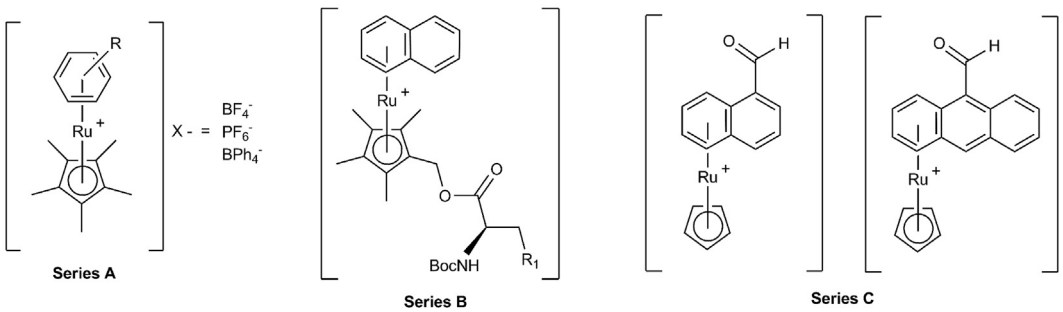

Fig. 2. A diverse library of cytotoxic organoruthenium full-sandwich complexes; R = a range of aromatic systems incorporating substituted benzenes (functional groups include alkyls, amines, carbamates, esters, ketones, and sulphonamides) and polycyclic aromatic systems (naphthalene, phenanthrene, pyrene); R_1 = phenyl and 2-indolyl.