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Research paper

Cyclopentadienyl molybdenum(II) compounds bearing carboxylic acid functional group

Jiří Schejbal [a], Lucie Melounková [b], Jaromír Vinklárek [a], Martina Řezáčová [c], Zdeňka Růžičková [a], Ivana Císařová [d], Jan Honzíček [e,*]

[a] Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic
[b] Department of Analytical Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic
[c] Department of Medical Biochemistry, Faculty of Medicine in Hradec Králové, Charles University in Prague, Šimkova 870, 500 01 Hradec Králové, Czech Republic
[d] Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030/8, 128 43 Prague 2, Czech Republic
[e] Institute of Chemistry and Technology of Macromolecular Materials, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic

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ABSTRACT

This work describes a procedure giving cyclopentadienyl molybdenum(II) compounds bearing carboxylic acid function group. It involves synthesis of carboxylic acid ester functionalized cyclopentadienides, their coordination to molybdenum(II) precursor and saponification of ester function groups. The method is not limited only to compounds with the function group directly attached in the cyclopentadienyl ring but also to those functionalized in the side chain. The attempts to synthesize the indenyl analogues were only partially successful due to low stability in the saponification step. All reported structure types were elucidated from spectroscopic measurements and verified by X-ray crystallography. The second part of the work describes an effect of the outer-coordination sphere on cytotoxicity of the cationic molybdenum(II) compounds bearing *N,N*-chelating ligands. The cytotoxicity of the modified species bearing phenanthroline ligand toward human leukemia cells MOLT-4 (IC_{50} = 10.5 ± 0.5 μmol l^{-1}) is higher than reported for cisplatin (IC_{50} = 15.8 ± 1.9 μmol l^{-1}).

1. Introduction

Various transition metal complexes and organometallic compounds attract attention of biochemists and farmacochemists since cytostatic properties of cisplatin (*cis*-$[PtCl_2(NH_3)_2]$) were discovered by Rosenberg et al. [1,2]. In past decades, a large variety of transition metal compounds was scrutinized and many structural patterns with promising cytostatic properties were recognized. Nevertheless, the quest for new species with enhanced activity toward cisplatin resistant tumor cells and reduced side-effects is still ongoing [3–20].

Our ongoing development of molybdenum-based cytostatic drug [21–24] follows the fundamental work of Romão et al., who established cyclopentadienyl and indenyl molybdenum compounds $[(\eta^5\text{-Cp}')Mo(CO)_2L_2][BF_4]$ (Cp′ = C_5H_5, C_9H_7, L_2 = neutral chelating ligand) as a new class of highly cytotoxic species active against several tumor cell lines [25]. In following studies, an early insight into mechanism of their action was reported [26,27] and number of active compounds was extended with congeners bearing various substituents in the cyclopentadienyl ring and another bidentate ligands [21,22,28]. Enhanced *in vitro* cytotoxicity toward leukemia cells MOLT-4 was observed in case of water-soluble derivatives obtained by functionalization of cyclopentadienyl ring with amine function groups [24]. Another approach to reach water-soluble derivatives of $[(\eta^5\text{-Cp}')Mo(CO)_2L_2][BF_4]$ involves attachment of carboxylic acid group that is subject of present study.

The first notes about the modification of cyclopentadienyl ligand with carboxylic acid functional group are dated shortly after discovery ferrocene [29,30]. Nevertheless, a quest for such modification has emerged much later within a development of water soluble organometallic compounds designed for homogenous catalysis [31] and medicinal applications [32]. Strong hydrogen bond systems in the carboxylic acid functionalized organometallic compounds have been utilized for crystal engineering as well [33–35]. Nevertheless, the current research is focused mainly on the assembly of biomolecule conjugates suitable for target drug delivery [36–38], where acid functionalized cyclopentadienyl compounds form convenient building blocks.

Four distinct synthetic strategies are available for transition metal compounds bearing carboxylic acid functional group in the

* Corresponding author.
E-mail address: jan.honzicek@upce.cz (J. Honzíček).

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η^5-bonded cyclopentadienyl ligand. The direct coordination of Thiele's acid [$(C_5H_5COOH)_2$] is only described for technetium or rhenium carbonyls [39,40]. More convenient pathway consists of metalation/carbonation procedure [30,41,42], which is commonly used for a direct functionalization of electron-rich middle and late transition metal compounds resistant to reduction under conditions of the metalation [*e.g.* (η^5-$C_5H_5)_2$Fe, (η^5-C_5H_5)Mn(CO)$_3$, (η^5-C_5H_5)(η^7-C_7H_7)V]. Carboxylic acid group could be also generated from ester group by hydrolysis [43]. Starting ester substituted derivatives are usually accessible from functionalized alkali metal cyclopentadienides [44,45]. Such strategy has been successfully used for compounds with one or more functionalities in the cyclopentadienyl ring [43,46] as well as in the side chain [37,47]. Another approach covers oxidation of aldehyde (CHO), alcohol (CH_2OH), ketone (COR) and alkyne (CH≡CR) functionalities [48–50].

The aim of this study is to modify the outer coordination sphere of molybdenum(II) compounds with the carboxylic acid functionality in the attempt to improve their cytotoxic properties. As nature of ligand L_2 plays important role in a drug efficiency [21,25], four *N,N*-chelators of different π-system size were chosen. Cytotoxic properties of these derivatives were examined *in vitro* on human leukemia cell line MOLT-4.

2. Results and discussion

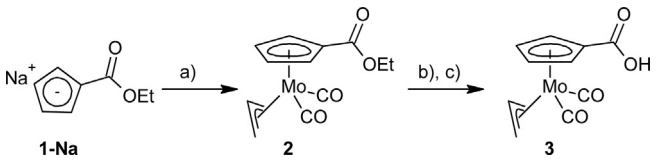
2.1. Synthesis of allyl molybdenum precursors

The target molybdenum compounds [(η^5-Cp′)Mo(CO)$_2$L$_2$][BF_4] are commonly synthesized from allyl precursors by protonation with strong acid followed with addition of appropriate chelating ligand. The starting derivative with carboxylic group directly attached in the cyclopentadienyl ring [(η^3-C_3H_5)(η^5-C_5H_4COOH)Mo(CO)$_2$] (**3**) was already reported [51,52]. Nevertheless, we decided to develop alternative synthetic pathway, using hydrolysis of ester group, which could be further applicable for congeners bearing the carboxylic group in the side chain.

Ethyl ester functionalized compound [(η^3-C_3H_5)(η^5-C_5H_4COOEt)Mo(CO)$_2$] (**2**), readily available from Na[C_5H_4COOEt] (**1-Na**) and [(η^3-C_3H_5)Mo(CO)$_2$(NCMe)$_2$Cl], undergoes saponification of ester group in the mixture NaOH/MeOH/water. The desired species bearing carboxylic group (**3**) is then obtained in high yield after acidification (Scheme 1).

Deprotonation of **3** with sodium methanolate gives stable sodium salt Na[(η^3-C_3H_5)(η^5-C_5H_4COO)Mo(CO)$_2$] (**3-Na**) in high yield. Delocalization of the negative charge over both oxygen atoms of the carboxylate is evident from low wavenumber of the antisymmetric COO stretching mode (1584 cm^{-1}). Lower wavenumbers of the carbonyl stretching modes (ν_a = 1913 cm^{-1}, ν_s = 1839 cm^{-1}) reflect a higher electron density on molybdenum available for π-backbonding than observed for **3** (ν_a = 1927 cm^{-1}, ν_s = 1861 cm^{-1}).

Cyclopentadienides **6-Na** and **7-Na**, necessary for synthesis of molybdenum compounds with the carboxylic group in the side chain of the Cp ligand, were prepared by reaction of sodium cyclopentadienide with 1.5 equivalents of dimethyl isophthalate



1-Na 2 3

Scheme 1. Synthesis of molybdenum compound **3**. Reagents: a) [(η^3-C_3H_5)Mo(CO)$_2$(NCMe)$_2$Cl]/THF, b) NaOH/MeOH/water, c) HCl (aq.).

(**4**) and dimethyl terephthalate (**5**), respectively (Scheme 2). Although such stoichiometry leads to appearance of ~25% side products (**8-Na**, **9-Na**), it prevent contamination with starting diesters (**4**, **5**). We note that 1: 1 stoichiometry does not give pure monocyclopentadienide (**6-Na**, **7-Na**) but a mixture with appropriate bis(cyclopentadienide) and unreacted diester. As both contaminants are hardly removable are by simple purification processes, we decided to use an excess of NaCp in order to prevent the contamination with diester and not separate the products in this reaction step but after coordination to molybdenum and saponification process (Scheme 2).

Cyclopentadienides **6a** and **7a** react with [(η^3-C_3H_5)Mo(CO)$_2$(NCMe)$_2$Cl] to give complexes with ester group in side chain **10** and **11**, respectively. After standard work up, these products contain about 25% of appropriate bridged compound (**12** and **13**) as evidenced by ^{1}H NMR spectroscopy. Such dinuclear complexes were isolated by long term stirring with sodium hydroxide solution in wet methanol. The mononuclear species are dissolved as the ester groups hydrolyze. Pure species **12** and **13** are then obtained after recrystallization from toluene. Infrared spectra of the compounds **12** and **13** show two CO stretching bands of the carbonyl ligand at ~1936 cm^{-1} (ν_a) and ~1845 cm^{-1} (ν_s). Stretching band of the keto group appears at ~1635 cm^{-1}. ^{1}H NMR spectra of the compounds **12** and **13** show two apparent triplets at ~5.8 and ~5.5 ppm ($^3J = {}^4J$ = 2.4 Hz) typical for monosubstituted Cp ligand. Allyl ligands give signals at 3.89, 2.80 and 1.54 ppm. The dinuclear character of the species **12** and **13** is apparent from pattern of the bridge that is, in both cases, typical for symmetrical disubstituted benzene. 1,3-disubstituted ring of the compound **12** gives two triplets at 8.08 ppm (H^2) and 7.58 ppm (H^5) and doublet of doublets at 7.93 ppm ($H^{4,6}$). In case of **13**, four equivalent protons of 1,4-disubstituted benzene give one singlet at 7.80 ppm.

Single crystals of the compound **13**, suitable for X-ray analysis, were obtained by vacuum sublimation. The molecules consist of two [(η^3-C_3H_5)Mo(CO)$_2$] fragments connected via a bridging bis(cyclopentadienyl) ligand with rigorous overall C_i symmetry (Fig. 1). The coordination sphere of both molybdenum atoms could be taken as pseudo-tetrahedral as centroids of η^3-allyl and η^5-cyclopentadienyl are considered to occupy one coordination site each. The geometric parameters, related with central metal, are given Table 1. Small dihedral angle between the Cp ring and a plane the ketone, defined by C1, C6, C7 and O1, [Pl_1–Pl_2 = 6.4(2)°] suggests more effective conjugation than between bridging benzene ring and the keto group [Pl_2–Pl_3 = 34.09(18)°]. The conjugation is also apparent from a shorter C1–C6 bond [1.471(5) Å] compared to neighboring C6–C7 bond [1.503(5) Å].

The complexes with the carboxylic group in the side chain of the cyclopentadienyl ligand **14** and **15** were prepared by saponification of aforementioned crude compounds **10** and **11**, respectively (Scheme 2). Treatment with sodium hydroxide solution in aqueous methanol leads to selective hydrolysis of the ester groups to give sodium salts of desired products. The pure species with carboxylic group (**14** and **15**) are then precipitated upon acidification.

CO stretching bands of the carboxylic group were observed in the infrared spectra of the compounds **14** and **15** at 1688 cm^{-1} and 1683 cm^{-1}, respectively. ^{1}H NMR spectra show, beside the signals of allyl and cyclopentadienyl ligand, a typical pattern of unsymmetrical 1,3- and 1,4-disubstituted benzene, respectively. Crystal structure of the compound **14**, determined by X-ray diffraction analysis, proves a similar coordination sphere of molybdenum as aforementioned for compound **13**. A strong hydrogen bonding connects the carboxylic groups of a pair of molecules **14** to give a cyclic dimer as evident from short O2···O3′ intermolecular distances [2.630(2) Å], see Fig. 2.

The assembly of the ester-functionalized indenyl molybdenum compound [(η^3-C_3H_5)(η^5-C_9H_6COOMe-2)Mo(CO)$_2$] (**18**) is summa-