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Preparation and characterization of d^6 tungsten compounds with amino acid derivatized diimine ligands and preparation of dipeptide derivatives using peptide coupling agents

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Abstract

Attempts to prepare dipeptide compounds from organometallic N-substituted amino acids are reported. Condensation of pyridine-2-carboxaldehyde, α-amino acids (H-L-Ala-OH or H-L-Asp-OH) and $W(CO)_4(pip)_2$ leads to formation of $W(CO)_4$(pyca-Et) (**1**) (pyca refers to the α-diimine fragment, $C_5H_4NCH{=}N$) following decarboxylation of one or two equivalents of CO_2. This decarboxylation does not occur for β-alanine or GABA (γ-aminobutyric acid). Coupling of [Hpip][$W(CO)_4$(pyca-β-Ala-O)] (**2**) or [Hpip][$W(CO)_4$(pyca-GABA-O)] (**3**) to amino acid esters, H-L-Ala-OEt, or H-L-Val-OMe, using the standard 1,3-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt) procedure produced four new dipeptide compounds, **4**–**7**. The reactions proceed in good yield and compounds were characterized spectroscopically. The dipeptide complex, $W(CO)_4$(pyca-Ala-Ala-OMe) (**8**), was prepared by reaction of $W(CO)_4(pip)_2$ with H-L-Ala-L-Ala-OMe and pyridine-2-carboxaldehyde. In addition the molecular structure of $W(CO)_4$(pyca-β-Ala-Val-OMe) (**5**) is reported.

Keywords: Amino acid; Crystal structure; Diimine; Tungsten

1. Introduction

Incorporation of biological ligands [1–3], especially amino acids or peptides [4,5], into organometallic systems has become a focus of chemists in recent years. The motivations for this focus range from the excitement of creating organometallic compounds with unusual ligands containing multiple and diverse functional groups, to the search for biological and medical applications [6,7].

Our group has concentrated on incorporating amino acid esters in diimine ligands as a way to create tightly binding ligands for organometallic centers. The first report of this chemistry focused on $M(CO)_4$(pyca-R) compounds (M = Cr, Mo, W; pyca refers to the pyridine-2-carbaldehyde imine fragment, $C_5H_4NCH{=}N$; R refers to the amino acid ester) such as $Mo(CO)_4$(pyca-Val-OMe) [8]. This work demonstrated that the α-diimine ligand, with the nitrogen of the amino acid ester contributing to the formation of the exocyclic imine, produces stable group 6 d^6 compounds. The pyca-R amino acid ester ligand set was also successfully utilized to make $Re(CO)_3Cl$(pyca-R) compounds. When chiral amino acid esters were employed, diastereomers in unequal populations were produced because of the presence of a stereogenic metal center [9]. We recently extended this work to molybdenum and tungsten compounds with corresponding diazabutadiene ligands created from the condensation of glyoxal and an amino acid ester [10]. It was observed that employing NEt_3 to remove HCl from the amino acid ester during the synthesis

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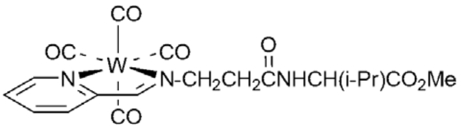
led to racemization of the α-carbon. Crystal structures of two diastereomers of $Mo(CO)_4$(dab-Asp(OMe)-OMe) supported this observation. Other researchers have examined organometallic compounds with pyridine-based diimine ligands for the possible development of metal-based pharmaceuticals. In particular thiosemicarbazones derived from 2- or 4-acetylpyridine, 2-pyridineformamide and 2,2′-dipyridyl ketone have been used in the creation of a variety of monomeric and dimeric compounds utilizing the $M(CO)_3^+$ (M = Tc, Re) fragment [11–14].

We were interested in extending these studies to examine whether group 6 compounds using the pyridine-2-carbaldehyde imine ligand with amino acids instead of amino acid esters could be created. The ultimate goal was to determine if dipeptide compounds could be prepared via standard peptide coupling methods with the $W(CO)_4$(pyca) moiety as an organometallic N-protecting group. Organometallic N-protecting groups have been the subject of previous studies because of the possible advantages they can offer including the color or lipophilic character of the protecting group. The ferrocenyl methyl (Fem) residue has been the most extensively studied [15,16]. It can be introduced without racemization of the amino acid, it survives peptide coupling reactions, and the yellow color of the protecting group is an aid to chromatographic separation. Some group 6 d^6 compounds have been examined as protecting groups as well. Aminocarbene compounds are formed by aminolysis of $[(CO)_5M{=}CR(COCH_3)]$ (M = Cr, W) with amino acid esters [17] and *cis*-$(OC)_4Re(CH_3CO)_2H$ condenses with amino acid esters to create the corresponding β-ketoimine derivatives [18,19].

Herein we report that the initial attempt to prepare diimine ligands based on α-amino acids led to decarboxylation. Reactions of mixtures of $W(CO)_4(pip)_2$ (pip = piperidine) and pyridine-2-carboxaldehyde with alanine or aspartic acid each gave $W(CO)_4$(pyca-Et) (**1**) due to loss of one or two molecules of CO_2, respectively. This was confirmed independently by creation of **1** using H_2NEt. A recent report of similar decarboxylation reactions has been published for the corresponding molybdenum compounds [20]. The reactions using the β- and γ-amino acids, β-alanine and GABA (γ-aminobutyric acid), showed that piperidinium salts with a pendant carboxylic acid, [Hpip][$W(CO)_4$(pyca-$(CH_2)_n$-CO_2)] ($n = 2$ or 3, compounds **2** and **3**, respectively), could be obtained under the same conditions in good yield without loss of CO_2.



5 = $W(CO)_4$(pyca-β-Ala-Val-OMe)

Fig. 1. Representative structure of **5**.

The N-protected amino acid piperidinium salts, **2** and **3**, were successfully coupled with L-alanine ethyl ester or L-valine methyl ester to create four new single enantiomer organometallic dipeptide compounds, **4**–**7** (see Fig. 1 and Scheme 1). In addition $W(CO)_4$(pyca-Ala-Ala-OMe) (**8**) was prepared as a single enantiomer by direct reaction of the dipeptide, H-L-Ala-L-Ala-OMe, with $W(CO)_4(pip)_2$ and pyridine-2-carboxaldehyde. Finally we report the structural characterization of **5**. Preliminary accounts of the decarboxylation [21] and peptide coupling [22] processes were presented previously.

2. Results and discussion

2.1. Attempted syntheses of $W(CO)_4$(pyca-Ala-OH) and $W(CO)_4$(pyca-Asp-OH): preparation of $W(CO)_4$(pyca-Et) (1)

Reflux of one equivalent each of $W(CO)_4(pip)_2$, pyridine-2-carboxaldehyde and alanine in methanol led to the rapid change in solution color from light-yellow to a deep, red color. Column chromatography followed by removal of the solvent led to a reddish-brown solid. Elemental analysis and spectroscopic characterization were consistent with formulation of this compound as **1**. The reaction using aspartic acid as the amino acid was also attempted. Isolation and purification again resulted in a compound with spectroscopic properties consistent with those expected for **1**.

To verify that these compounds were indeed **1**, this compound was prepared using H_2NEt as the added amine. The

$$[\mathrm{Hpip}][\mathrm{W(CO)_4(pyca\text{-}(CH_2)_nCO_2)}] \xrightarrow[\mathrm{H_2NCHRCO_2R'\cdot HCl}]{\mathrm{DCC,\ HOBt,\ NEt_3}} \mathrm{W(CO)_4(pyca\text{-}(CH_2)_nCONHCHRCO_2R')}$$

No.	n =	Comp.
2	2	[Hpip][$W(CO)_4$(pyca-β-Ala-O]
3	2	[Hpip][$W(CO)_4$(pyca-GABA-O]

No.	n =	R =	R' =	Comp.
4	2	Me	Et	$W(CO)_4$(pyca-β-Ala-Ala-OEt)
5	2	i-Pr	Me	$W(CO)_4$(pyca-β-Ala-Val-OMe)
6	3	Me	Et	$W(CO)_4$(pyca-GABA-Ala-OEt)
7	3	i-Pr	Me	$W(CO)_4$(pyca-GABA-Val-OMe)

Scheme 1. General reaction scheme and numbering system for compounds **2**–**7**.