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Inorganic Chemistry Communications

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

Synthesis and characterization of the first examples of ferrocene and $[\eta^5-CpCo(\eta^4-C_4Ph_4)]$ derived 2-pyridones



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A R T I C L E I N F O

ABSTRACT

Article history: Received 10 May 2013 Accepted 20 July 2013 Available online 1 August 2013

Keywords: Ethynyl ferrrocene Pyridone Alkynyl aldehyde Cobalt sandwich

A major development in the area of bio-organometallic chemistry has been the introduction stable organometallic units onto a drug molecule thereby enhancing its activity many-fold. The most well known examples for such compounds are ferroquine and ferrocifen wherein ferrocenyl replaces an alkyl or aryl unit of a known drug. Ferroquine, an organometallic variant of the antimalarial drug chloroquine, wherein an alkyl fragment of chloroquine has been replaced by ferrocene was found to be very efficient even against chloroquine resistant malaria. Ferrocifen, another drug molecule where ferrocenyl group replaces an arvl group of the well known breast cancer drug tamoxifen has shown enhanced activity than the latter [1,3]. 2-Pyridones, a well known class of organic heterocycles are an important constituent of many drugs and biologically active natural products [4]. Due to their dual properties as an aromatic compound and an amide, they have the tendency to interact and bind with many biological sites [2]. Fig. 1 lists a few of the well known biologically active 2-pyridone derivatives which are multidrug resistance (MDR) modulators [4], antileukemic and antitumor agents [6,7] as well as acetyl cholinesterate inhibitors [8]. The effectiveness of improving the properties and activity of many drugs as well as the use of such molecules as organometallic tags

prompted us to attempt the synthesis of air and moisture stable organometallic sandwich derivatives of 2-pyridones. Although examples of 2-pyridones with a variety of alkyl and aryl substituents have been reported [4,5], no examples of metal sandwich substituted 2-pyridones are known till to date. The very high air

and moisture stability of ferrocene and the relatively lesser known

 $(\eta^5$ -cyclopentadienyl) $(\eta^4$ -tetraphenylcyclobutadiene)cobalt, η^5 -CpCo $(\eta^4$ -C₄Ph₄) prompted us to use these sandwich compounds in this study. Unlike ferrocene, direct derivatization of the sterically bulky η^5 -CpCo $(\eta^4$ -C₄Ph₄) has been found to be difficult [9]. However, by using substituted sodium cyclopentadienyls as precursors in the sandwich synthesis, we as well as others have reported methods to prepare a range of potential derivatives of η^5 -CpCo $(\eta^4$ -C₄Ph₄) [10–13]. As ethynyl ferrocene and ethynyl derived η^5 -CpCo $(\eta^4$ -C₄Ph₄) are air and water stable compounds which can be synthesized in a few steps [14,15], we were keen to see the possibility of using these compounds as precursors for realizing metal sandwich derived alkynyl imines.

Reactions of ferrocene and $(\eta^{5}$ -cyclopentadienyl) $(\eta^{4}$ -tetraphenylcyclobutadiene)cobalt derived alkynylaldehydes

with p-anisidine gave the corresponding metal sandwich based alkynylimines, 4-methoxy-N-(3-ferrocenylprop-

2-ynylidene)aniline and 4-methoxy-N-[3-(η^5 -cyclopentadienyl)(η^4 -tetra-phenylcyclobutadiene)cobalt prop-2-

ynylidene]aniline. The 1,4-nucleophilic addition of sodium methylmalonate with these alkynylimines gave the first examples of metal sandwich substituted 2-pyridones, [methyl 1-(4-methoxyphenyl)-2-oxo-4-ferrocenyl

1,2-dihydropyridine-3-carboxylate and methyl 1-(4-methoxyphenyl) 2-oxo-4- $(\eta^5$ -cyclopentadienyl)(η^4 -

tetra-phenylcyclobutadiene)cobalt 1,2-dihydropyridine-3-carboxylate in good yields. Reaction of sodium

ethylmalonate with the ferrocene derived alkylimine gave the stable ferrocene derived 2-pyridone, ethyl 1-(4-

methoxyphenyl)-2-oxo-4-ferrocenyl 1,2-dihydropyridine-3-carboxylate which was also structurally characterized.

A reaction of aryl alkynyl carboxaldehyde with *p*-anisidine has been found to form a Schiff's base which when further treated with dialkyl malonate under basic conditions yielded a substituted 2-pyridone [5]. Here 1,4- addition reaction of dialkyl sodiomalonate to alkynylimine generates an allenamine which in turn isomerizes to an enamine and finally undergoes cyclization to give the 2-pyridone (Fig. 2). We were keen to see the possibility of using this procedure to prepare ferrocene and the bulky cobalt sandwich compound, η^5 -CpCo(η^4 -C₄Ph₄) substituted 2-pyridones.

Reaction of ferrocenyl(formyl) acetylene with a *p*-anisidine gave a carbinolamine intermediate which underwent dehydration to give a substituted imine **1** in 52% yield. A similar reaction of the cobalt sandwich derivative of alkynyl carboxaldehyde with *p*-anisidine gave the substituted alkynyl imine **2** in 67% yield (Scheme 1).

A reaction of the in-situ generated dimethyl sodiomalonate with ethynylferrocene substituted imine **1** gave the 2-pyridone derivative **3** in 50% yield. A similar reaction of the dimethyl sodiomalonate derivative with ethynyl cobalt sandwich derived imine **2** gave an orange-yellow

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Fig. 2. Synthesis of aryl substituted 2-pyridones by 1,4 addition reaction.

colored 2-pyridone, **4** in 48% yield (Scheme 1) [16]. However, repeated efforts to obtain suitable crystals of **3** and **4** for single crystal X-ray structural characterization were unsuccessful. We therefore attempted the synthesis of an analogous ethyl derivative starting from ethyl malonate in place of methyl malonate. A 1:1 reaction of diethylmalonate with sodium hydride in THF as a solvent gave the diethyl sodiomalonate. Reaction of this compound with the imine **1** under basic conditions gave the cyclized 2-pyridone **5** in 54% yield (Scheme 2) [17].

Interestingly, the $\nu_{C=C}$ infrared stretching bands of the alkynyl units of compounds **1** and **2** and its parent (formyl) acetylene derivative were found to be highly dependent on the type of substitution around the alkynyl unit. For example the ferrocenyl(formyl)acetylene showed a band at 2179 cm⁻¹ while the same vibrational band was found at 2191 cm⁻¹ for its alkynylimine derivative **1**. Similar variation for $\nu_{(C=C)}$ bands was also observed on formation of the cobalt sandwich substituted alkynylimine **2** from its parent (formyl) acetylene

derivative. The cause of this variation is the substitution of a more electronegative carbonyl group by a less electronegative aldimine group. Similar variations in the $v_{C=C}$ infrared stretching bands were observed in the case of formation of the aldimine derivative of phenyl propionaldehyde. While phenyl propionaldehyde shows a $v_{C=C}$ infrared stretching band at 2190 cm⁻¹, the same has been found to shift to 2200 cm⁻¹ after aldimine formation [5].

¹H NMR spectra of the compounds **1**, **3** and **5** exhibited three sets of peaks for the ferrocene moiety. The protons attached to the substituted cyclopentadienyl units in these compounds were found to resonate in the range of 4.24-4.51 ppm. A deshielded peak at 9.22 and 8.74 in case of 3-ferrocenyl-2-propynal and $[\eta^5-C_5H_4(C=C)CHO]Co(\eta^4-C_4Ph_4)$ which was assigned as aldehydic protons, disappeared after formation of their respective alkynyl imines **1** and **2**. The proton signals for the cyclopentadienyl units of the cobalt sandwich compounds 2, and 4 were observed as two signals in the range of 4.74-5.21 ppm. The chemical shifts for the two pyridone protons in case of 5 were observed as doublets at 6.46 ppm and 7.29 ppm, the latter overlapping with other phenyl proton signals. Similarly, the two pyridone protons in case of **3** were observed as doublets at 6.39 ppm and at 7.23 ppm. This chemical shift is consistent with that of the analogous phenyl substituted 2-pyridone, 1-phenyl-3-methyl-4-phenyl-2(1H)-pyridone, where both the protons on the pyridone ring resonate at 6.20 and 7.25 ppm [5]. In contrast, to that of 3 and 5 in which one of the pyridone hydrogens overlap with that of the phenyl signal, the corresponding hydrogen in case of the cobalt sandwich substituted pyridone 4 was observed as two separate doublets at 6.66 and 6.98 ppm.

In the ¹³C NMR the carbon atoms of the cyclopentadiene units of the cobalt sandwich compounds, **2** and **4** were observed as three signals in the range of 86.2 to 87.4 ppm. Carbon atoms of the pyridone moiety were found to resonate in the range of 114.9 to 159.4 in case of ferrocenyl derived pyridones **3** and **5**, while it was found to resonate in between 118.3 and 148.1 ppm in case of the cobalt sandwich substituted 2-pyridone, **4**.

A CCDC search for structures of analogous 2-pyridones to compound **5** indicated that no similar pyridones have been structurally characterized so far. The only reported structure of a 2-pyridone whose features are close to that of **5** is that of compound **A** (Fig. 3) in which a phenyl group occupies the position of ferrocene of **5**, a methyl group at the sixth position replaces the ester group at the third position and the N is bonded to a 4-methoxy phenyl group instead of a benzyl group [18].

Average C–C and C–N bond distances in the pyridone moiety of **5** were found to be 1.393(3) and 1.388(3) Å which are close to the corresponding bond distances in case of the phenyl based pyridone 6-methyl-4-phenyl-1-(phenylmethyl)-2(1H)-pyridone where it was observed at 1.392(2) and 1.388(2) Å [18]. The C–O bond distance of the carbonyl group of the pyridone was found to be 1.226(3) Å which is close to 1.243(2) Å observed in the case of the structure reported for the phenyl based pyridone [18]. The dihedral angle between the plane defined by all six atoms of pyridone **5** makes an angle of



Scheme 1. Synthesis of ferrocene and cobalt sandwich derived alkynyl imines 1 and 2.



Scheme 2. Synthesis of ferrocene and cobalt sandwich based pyridones 3 and 4 and 5.



Fig. 3. Comparison of compound A with analogous compound 5.

 $62.1(1)^{\circ}$ with the phenyl group in **5**. The dihedral angle between the plane defined by all five atoms of cyclopentadiene ring of the ferrocene unit of **5** make an angle of $42.7(1)^{\circ}$ with the plane passing through all six ring atom of pyridone ring (Fig. 4).

This is in contrast to the structure reported for the phenyl substituted 2-pyridone where both phenyl and the pyridone units were found to be almost planar making an angle of 13.3 (1)[°]. The planarity of

the 2-pyridone ring in both these compounds is comparable. The crystal packing diagram of the compound **5** indicated that both oxygen atoms of carbonyl group of the pyridone and ester moiety take part in hydrogen bonding resulting in a sheet-like motif (see supplementary data).

In conclusion, the first examples of air and moisture stable metal sandwich derived 2-pyridones have been synthesized by 1,4-nucleophilic addition of dialkyl sodiomalonates with the metal sandwich based alkynyl imines followed by cyclization. The novel organometallic 2-pyridones have been structurally characterized [19].

Acknowledgments

The authors thank the Department of Science and Technology (DST), India and CSIR India for financial assistance in the form of research grants to A.J.E. [DST SR/SI/IC-43/2010 and CSIR 01(2693)/12/EMR-II]. KK thanks CSIR India for the research fellowship. We thank DST-FIST and IITD for funding of the single crystal X-ray diffraction and HRMS facilities at IIT Delhi.



Fig. 4. X-ray structure of the compound **5**. Thermal ellipsoids are drawn at the 30% probability level. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg) with esd's in parenthesis. C(1)–C(11) 1.474(3); C(11)–C(12) 1.423(3); C(12)–C(13) 1.343(4); C(14)–O(3) 1.228(3); C(13)–N(1) 1.364(3); C(15)–C(11)–C(12) 118.1(2); C(11)–C(12) - C(13) 119.6(2); C(13)–N(1)–C(14) 121.7(2).

Appendix A. Supplementary materials

Experimental details of structural determination, data collection parameter and synthesis of compounds **1–5** are given as supplementary information. CCDC 936287 contains the supplementary crystallographic data for **5**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.inoche.2013.07.012.

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- [16] Synthesis of 3: To a solution of dimethyl malonate (0.13 g, 1.25 mmol) in 2.0 ml of tetrahydrofuran, 60% NaH suspension (0.03 g, 1.00 mmol) was added with constant stirring. Then a solution of ferrocenyl alkynyl imine (0.17 g, 0.50 mmol) in 2 ml was added to it. The reaction mixture was stirred under reflux for 7 hours and then brine was added. The mixture was extracted with dichloromethane and the organic layer was dried over sodium sulphate. The solvents were evaporated and the resultant residue was purified over silica gel column to give a yellow colored solid which was characterized as ferrocenyl substituted 2-pyridone 3. Yield: 0.11 g, 50%. IR (v, cm⁻¹): 1645 (C=O). Mp: 176–178 °C (dec.). Found: C, 65.11; H, 4.72; N, 3.18. Calcd. for C₂₄H₂₁FeNO₄: C, 65.03; H, 4.78; N, 3.16. ¹H NMR (δ, 300 MHz, CDCl₃): Card card (4, 5, Card), 4, Cr (50,5,7, 1, 4, 7), 4, 7), 4, 7, 10, 11, 11, 11, 11, (4, 5, 7), 4, 5, (7), 4, 5, (7), 5, 52.4 (OCH₃), 55.5 (OCH₃), 68.5, 70.1, 70.8, 71.9 (Cp), 114.3, 127.1, 136.7, 127.4, 149.4 (Ph), 117.1, 133.0, 159.3, 159.5, (C=C), 166.8 (C=O). HRMS: Calcd. for C24H22FeNO4: 444.0898, Found: 444.0904. Compound 4 was synthesized and worked up in a similar manner using dimethyl malonate (0.40 g, 2.50 mmol) and the cobalt sandwich substituted alkynyl imine (0.63 g, 1.00 mmol). Yield: 0.35 g, 48 % IR (ν , cm⁻¹): 1643 (C=O). Mp: 195-197 °C (dec.) Found: C, 76.54; H, 5.06; N, 1.92. Calcd. for C₄₇H₃₆CoNO₄: C, 76.52; H, 4.92; N, 1.90.¹H NMR (δ , 300 MHz, CDCl₃): 3.71 (3H, s, CH₃), 3.86 (3H, s, OCH₃), 4.77 (2H, s, Cp), 5.11 (2H, s, Cp), 6.65–6.68 (1H, d), 6.96–6.99 (1H, d), 7.19–7.28 (20H, m, Ar), 7.40–7.43 (8H, m, ¹³C{¹H} NMR: δ 52.3 (OCH₃), 54.5 (OCH₃), 77.6 (CbC), 86.5, 86.2, 87.1 (Cp), Ph). 114.5, 115.2, 135.6, 151.7 (C₆H₄OCH₃) 126.4, 127.9, 128.8, 134.2 (CbPh), 118.3, 131.0, 142.5, 132.4, 148.1 (C=C), 171.3 (C=O). HRMS: Calcd. for C47H36CoNO4 Na: 760.1874, Found: 760.1856.
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layer was dried over sodium sulphate. The solvents were evaporated off and the resultant residue was purified over silica gel to give a yellow colored crystalline solid sultant residue was purified over silica gel to give a yellow colored crystalline solid which was characterized as the ferrocenyl substituted 2-pyridone **5**. Vield: 0.24 g, 54 %. IR (ν , cm⁻¹): 1650 (C=O). Mp: 183–185 °C (dec.). Found: C, 65.71; H, 5.03; N, 3.14. Calcd. for C₂₅H₂₃FeNO₄: C, 65.66; H, 5.07; N, 3.06.¹H NMR (δ , 300 MHz, CDCl₃): 1.30 (3H, s, CH₃), 3.82 (2H, s, CH₂), 4.17 (5H, s, Cp), 4.33 (2H, q, -OCH₃), 4.43 (2H, s, Cp), 4.49 (2H, s, Cp), 6.45–6.47 (2H, s), 6.95–6.97 (2H, d), 7.26–7.33 (3H, m). ¹³Cl¹H} NMR: δ 13.9 (CH₃), 55.4 (OCH₂), 61.5, 68.6, 70.0, 70.6 (Cp), 114.2, 127.4, 136.6, 149.1, (Ph), 106.9, 122.4, 159.4, 159.2 (C=C), 167.3 (C=O). HRMS: Calcd. for C₂₅H₂₃FeNO₄: 457.0976, Found: 457.0996.

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