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Preliminary Communication

Synthesis of the new organometallic carboxylic acid complexes $[(\eta^5\text{-}C_5H_4COOH)M(CO)_nMe]$ (M = Mo, $n = 3$; M = Fe, $n = 2$) and their potential as bioconjugates

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Abstract

The new compounds $[(\eta^5\text{-}C_5H_4COOH)M(CO)_nMe]$ [M = Mo, $n = 3$ (**2**); M = Fe, $n = 2$ (**5**)] were synthesized in 61% and 63% yields, respectively, and treated with *N*-hydroxysuccinimide to yield the corresponding activated ester derivatives $[(\eta^5\text{-}C_5H_4COONS)M(CO)_nMe]$ [M = Mo, $n = 3$ (**3**); M = Fe, $n = 2$, (**6**)]. The metal-activated ester complex, $[(\eta^5\text{-}C_5H_5)Mo(CO)_3(CH_2COONS)]$ (**8**) was obtained similarly, the ester unit being bonded directly to the metal rather than to the π-bonded cyclopentadienyl. The reactivity and potential of the above species as labelling agents for amino-acids is discussed.

Key words: Iron; Molybdenum; Carboxylic acid derivatives; Cyclopentadienyl derivatives

The labelling of specific sites of proteins by organometallic units is an area of burgeoning interest [1]. In this context, it is essential to design selective labelling agents and to examine their reactivity. With these objectives in mind, we have explored several reported synthetic pathways in order to prepare stable (η^5-cyclopentadienyl)metallo-carbonyl labelling agents. The ability of cyclopentadienyl to stabilize and coordinate various organometallic moieties is now well documented, but the π-bonded cyclopentadienyl group attached to an activated succinimidyl ester function has attracted less interest.

Rausch and co-workers discovered a general route of great utility for the formation of a wide variety of functionally (η^5-cyclopentadienyl)metallo-carbonyl compounds [2]. The synthetic procedure consists of treating the substituted cyclopentadienide reagents C_5H_4RTl, C_5H_4RNa or C_5H_4RLi [3] with the metal carbonyl species $M(CO)_n$ (M = Cr, Mo or W), followed by alkylation to yield the desired functionally-substituted cyclopentadienylmetal carbonyl compound [4]. Thus complexes of type (I) (Fig. 1) were prepared in good yield depending on the metal and on the functional group "R". In particular, the organometallic carboxylic acid complexes $[(\eta^5\text{-}C_5H_4COOH)ML_n]$ (M = Co or W) were obtained by saponification of the corresponding ester derivatives with aqueous potassium hydroxide in methanol, followed by acidification with hydrochloric acid. However, the experimental conditions described have been shown to be unsuccessful for preparing the compound $[(\eta^5\text{-}C_5H_4COOH)Mo(CO)_3Me]$ (**2**). The authors attributed this to the instability of **2** in basic media [5].

In this communication we report for the first time a facile synthesis [1] of $[(\eta^5\text{-}C_5H_4COOH)Mo(CO)_3Me]$ (**2**)

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[1] Satisfactory C and H analyses were obtained for **2**, **3**, **5**, **6** and **8**. Spectroscopic data for new compounds:

2: IR ν (cm^{-1}) (KBr) M–CO 2025, 1950, 1917; C=O 1680; ^1H NMR ($(CD_3)_2CO$) δ 5.90 (t, $J_{H-H} = 2.5$ Hz, 2H, $-C_5H_4$), 5.68 (t, $J_{H-H} = 2.5$ Hz, 2H, $-C_5H_4$) 0.44 (s, 3H, $-CH_3$); ^{13}C NMR ($(CD_3)_2CO$) δ 239, 227 (M–CO), 165.40 (C=O), 99.33, 96.15, 95.99 ($-C_5H_4$), −19.60 ($-CH_3$).

3: IR ν (cm^{-1}) (KBr) M–CO 2028, 1936, C=O, 1802, 1769, 1736; ^1H NMR ($(CD_3)_2CO$) δ 6.10 (t, $J_{H-H} = 2.5$ Hz, 2H, $-C_5H_4$), 5.83 (t, $J_{H-H} = 2.5$ Hz, 2H, $-C_5H_4$), 2.92 (s, 4H, $-CH_2-CH_2-$, -NS) 0.55 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2CO$) δ 235.71, 223.15 (M–CO), 166.76, 160.38 (C=O), 95.94, 94.60, 90.47 ($-C_5H_4$), 25.50 ($-CH_2-CH_2-$, -NS), −19.36 ($-CH_3$).

5: IR ν (cm^{-1}) (KBr) M–CO 2012, 1951, C=O, 1676; ^1H NMR ($(CD_3)_2CO$) d 5.43 (t, $J_{H-H} = 2.5$ Hz, 2H, $-C_5H_4$), 5.13 (br, 2H, $-C_5H_4$), 0.25 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2CO$) δ 216.75 (M–CO), 166.22 (C=O), 91.50, 87.96, 85.96 ($-C_5H_4$), −21.41 ($-CH_3$).

6: IR ν (cm^{-1}) (KBr) M–CO 2024, 1970, C=O, 1811, 1780, 1738; ^1H NMR ($CDCl_3$) d 5.50 (t, $J_{H-H} = 2.0$ Hz, 2H, $-C_5H_4$), 5.03 (t, $J_{H-H} = 2.0$ Hz, 2H, $-C_5H_4$), 2.89 (s, 4H, $-CH_2-CH_2-$, -NS), 0.46 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2CO$) δ 213.76 (M–CO), 168.58, 160.70 (C=O), 91.44, 85.10, 78.15 ($-C_5H_4$), 25.29 ($-CH_2-CH_2-$, -NS), −20.70 ($-CH_3$).

8: ν (cm^{-1}) (KBr) M–CO 2031.85, 1965, 1954, 1927, C=O 1791, 1731; ^1H NMR ((CD_3Cl) δ 5.54 (s, 5H, $-C_5H_5$), 2.82 (s, 4H, $-CH_2-CH_2-$, -NS), 1.92 (s, 2H, $-CH_2-$); ^{13}C NMR ($(CD_3)_2CO$) δ 228.24 (M–CO), 177.16, 171.39 (C=O), 95.36 ($-C_5H_4$), 26.23 ($-CH_2-CH_2-$, -NS), −9.51 ($-CH_2-$).

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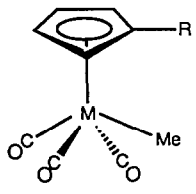


R = -COH, -COMe, -COOMe or -COOEt

M = Cr, Mo or W.

(I)

Fig. 1.

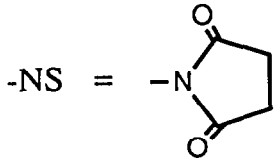


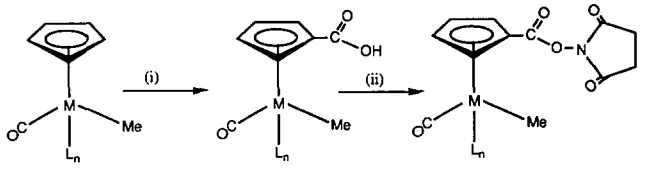
Fig. 2.

and $[(\eta^5\text{-}C_5H_4COOH)Fe(CO)_2Me]$ (**5**). The reactivity of the acid derivatives **2** and **5** to give the corresponding metal-succinimidyl esters $[(\eta^5\text{-}C_5H_4COONS)M(CO)_nMe]$ (M = Mo, $n = 3$ (**3**); M = Fe, $n = 2$) (**6**) is also described. These last species can be used as labelling agents for amines and amino acids (for simplicity the abbreviation -NS is used to denote the succinimidyl fragment of the ester unit in Fig. 2).

The fact that metallocenes of molybdenum and iron are known to be inert in physiological media and have been used for pharmacological purposes [5] has prompted us to examine the behaviour of the activated esters **3** and **6**.

Treatment of $[(\eta^5\text{-}C_5H_5)Mo(CO)_3Me]$ (**1**) with Li^{s}Bu in THF at −78°C for 15 min followed by addition of solid CO_2 and subsequent acidification followed by dichloromethane extraction afforded $[(\eta^5\text{-}C_5H_4COOH)Mo(CO)_3Me]$ (**2**) in 61% yield, as a yellow microcrystalline solid. Care should be taken to avoid purification in a basic medium [2] (Scheme 1). Similarly, $[(\eta^5\text{-}C_5H_4COOH)Fe(CO)_2Me]$ (**5**) was obtained as a yellow-orange microcrystalline solid in 63% yield from $[(\eta^5\text{-}C_5H_5)Fe(CO)_2Me]$ (**4**) (Scheme 1). Compounds **2** and **5** can also be obtained by using Li^{n}Bu instead of Li^{2}Bu but the yields are lower.

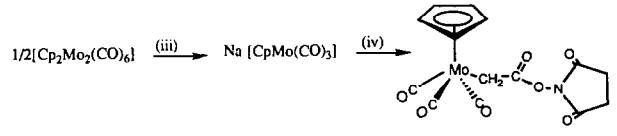
Compared to the tungsten derivative $[(\eta^5\text{-}C_5H_4COOH)W(CO)_3Me]$, the compounds **2** and **5** are stronger acids [6]. Table 1 shows the pK_a values of these acids obtained by titration [2]. The acid strength of these species can be correlated with the electron-attracting effect of the metal carbonyl moieties towards the functionalized cyclopentadienyl unit which decrease in the order $Mo(CO)_3Me > Fe(CO)_2Me > W(CO)_3Me$.



M = Mo, L = CO, n = 2; (2) M = Mo, L = CO, n = 2; (3)

M = Fe, L = CO, n = 1; (5) M = Fe, L = CO, n = 1; (6)

Scheme 1. (i) a-THF, Li^{s}Bu (1.7 equiv.), −78°C, 15 min b-THF, dry ice (excess), −30°C, 10 min c-HCL (10%), THF, r.t.; (ii) CH_3CN, Disuccinimidylcarbonate (DSC) (1 equiv.), pyridine (1 equiv.), r.t.



Scheme 2. (iii) THF, Na/Hg. 2h, r.t.; (iv) THF, $ClCH_2COONS$ (1 equiv.), −78°C, 5 min, then 1h, r.t.

When **2** was treated with 1 equiv of hydroxysuccinimide in the presence of dicyclohexyl carbodiimide (DCC) in THF for 12 h, the activated ester derivative $[(\eta^5\text{-}C_5H_4COONS)Mo(CO)_3Me]$ (**3**) was obtained in low yield. We found that **3** can be also prepared in 57% yield when **2** is treated with succinimidyl carbonate in CH_3CN. In a similar fashion the activated ester of the iron system $[(\eta^5\text{-}C_5H_4COONS)Fe(CO)_2Me]$ (**6**) was prepared in 62% yield from the corresponding acid $[(\eta^5\text{-}C_5H_4COOH)Fe(CO)_2Me]$ (**5**) and *N*-hydroxysuccinimide with DCC in THF. In general the iron compounds **5** and **6** exhibit higher stability in solution than do the molybdenum derivatives **2** and **3**.

On the other hand, we have prepared another type of metal-activated ester, in which the ester unit is bonded directly to the metal and not to the cyclopentadienyl fragment. Thus $[(\eta^5\text{-}C_5H_5)Mo(CO)_3(CH_2COONS)]$ (**8**) was obtained in 45% yield by a one-pot-

[2] The titrations were performed using a solution cell designed so that the contents were always protected with argon. Measurements were done on a CG817 pH meter (Schott Gerate) with a combination glass electrode. A typical experiment involved titrating 0.2 mmol of the organometallic acid in 15 ml (EtOH:H_2O 1:1) with 0.1 N NaOH solution at room temperature. Compound **2** decomposed after standing for several minutes in base (pH = 11–12). However, this did not affect the determination of pK_a.

TABLE 1. pK_a values of acids **2–5**

Acid	pK_a	Reference
$[(\eta^5\text{-}C_5H_4COOH)W(CO)_3Me]$	4.5	4
$[(\eta^5\text{-}C_5H_4COOH)W(CO)_3Me]$	4.5	This work
$[(\eta^5\text{-}C_5H_4COOH)Fe(CO)_2Me]$	4.4	This work
$[(\eta^5\text{-}C_5H_4COOH)Mo(CO)_3Me]$	4.2	This work

reaction by cleavage of the dimer $[Cp_2Mo_2(CO)_6]$ (**7**) with Na/Hg followed by addition of 2 equivalents of $ClCH_2CONHS$ in THF.

Preliminary results on labelling amino acids have shown that both Mo- and Fe-activated succinimidyl esters **3** and **6** react with β-alanine ethylester during 12 h to form stable conjugates. Compound **8**, where the activated ester unit is bonded to the metal has proved to be inactive. Furthermore, it has been found that the analogous Fe-activated succinimidyl ester $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(CH_2COONS)$ (**9**) requires one week to react with amino acids. This difference in reactivity between the two families **3** and **6** (η^5-Cp-bonded activated ester complexes) and **8** and **9** (metal-bonded activated ester complexes) may be related to the pK_a values of the parent acids. Thus compounds of the type $[(\eta^5\text{-}C_5H_5)M(CO)_n(CH_2COOH)]$ (M = Mo, $n = 3$; M = Fe, $n = 2$) possess pK_a values in the range of 8.2–8.7 [7] and are weaker acids than $[(\eta^5\text{-}C_5H_4COOH)M(CO)_nMe]$ (M = Mo, $n = 3$ (**2**); M = Fe, $n = 2$ (**5**)) with pK_a values of 4–4.5 (vide supra), and hence are less reactive. In general the trend is also valid for the corresponding succinimidyl esters. Hence activated ester complexes, for instance $[(\eta^5\text{-}C_5H_4COONS)M(CO)_nMe]$ (M = Mo, $n = 3$ (**3**); M = Fe, $n = 2$, (**6**)) should be more reactive towards the addition-elimination reaction that takes place during the labelling process of amino acids.

The biochemical properties of the above complexes are currently under investigation and will be the subject of future reports.

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