First Example of Cyanohydroxycarbonylation Using the $[Fe^{II}(CN)_6]^{4-}/H_2O/CN^-/CO$ System: Synthesis of Carboxylactams in Water

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Summary: Cyanohydroxycarbonylation of α-keto alkynes in the presence of potassium ferrocyanide, carbon monoxide, and potassium cyanide in water, under moderate reaction conditions of pressure and temperature, affords unsaturated carboxylactams. The complex $[Fe^{II}(CO)_2(CN)_4]^{2-}$*, formed "in situ" from* $K_4Fe(CN)_6$*, appears to be an active species in the reaction, and a plausible mechanism was proposed for the formation of carboxylactams.*

Introduction

The use of water as a solvent in homogeneous transition-metal-catalyzed reactions for organic syntheses have been steady growing last years. Nevertheless, there is a scanty number of examples of aqueous catalytic systems with acceptable activities for the synthesis of heterocycles.[1] There are also a few reports in the literature, as a part of the syntheses of carboxylactam derivatives, but most of the processes involve condensation of preformed substrates in several steps and use of air-sensitive organometallic compounds and organic solvents with complicated workup.[2−3] To best of our knowledge cyanohydroxycarbonylation in one pot is unknown, though there are examples reported in some patents involving these processes.[4−6]

Iron cyano carbonyl complexes have become the focus of intensive experimental investigations in recent years, because iron cyanocarbonyl moieties were found to be catalytic centers in hydrogenase enzymes.[7−9] From a physiological point of view, it is remarkable to find cyano and carbonyl groups as native ligands in metallo proteins.[10−12] However, the use of these iron complexes as catalytic species in other reactions have not been documented.

Recently we reported that an anionic species of nickel(0) induces carbonylation, hydrocyanation, heterocyclization, and cyclocondensation reactions with keto alkynes in water and produces different heterocycles in very high yields.[14−18]

In our pursuit of studying cyclocarbonylation and heterocyclization reactions using water as solvent, here we wish to report the novel and facile synthesis of substituted carboxylactams from α-ketoalkynes promoted by the complex $K_4Fe(CN)_6$ in water in the presence of carbon monoxide and potassium cyanide. The cyanohydroxycarbonylation reaction using this iron complex is more convenient, as $K_4Fe(CN)_6$ is cheap and readily available and can be easily prepared.[19]

Table 1 shows the results of catalytic cyanohydroxycarbonylation of α-keto alkynes with $K_4Fe(CN)_6$ in the presence of carbon monoxide and cyanide anion in water. The conditions used for the reaction were very moderate, i.e., 5−6 atm of carbon monoxide pressure at 60−90 °C, and good yields of carboxylactam were obtained, as shown in Scheme 1.

Although the nature of the active species using $K_4Fe(CN)_6$ as a promoter for catalytic cyanohydroxycarbonylation reactions of α-keto alkynes in the presence of carbon monoxide and potassium cyanide is difficult to establish, we wish to propose the anionic species $Fe[(CN)_4(CO)_2]^{2-}$ as an active precursor intermediate. This species was generated in solution by the addition of $NaCN{\cdot}4H_2O$ to an aqueous solution of $FeCl_2{\cdot}4H_2O$ under a carbon monoxide atmosphere. In this report we propose that the anionic species $[Fe(CN)_4(CO)_2]^{2-}$ is formed in situ from $K_4Fe(CN)_6$, carbon monoxide, and

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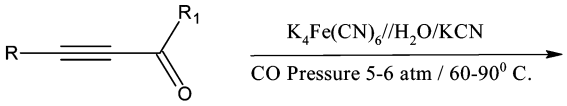
Table 1. Synthesis of Carboxylactams Catalyzed by Iron−Cyanocarbonyl Complexes in Water[a]

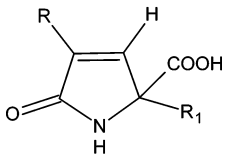
α-keto alkyne	R	R_1	reacn time (h)	pressure of CO (atm)	temp (°C)	yield (%)
1	n-C_4H_9	C_2H_5	3	5	60	73
2	n-C_4H_9	n-C_3H_7	3	5	60	69
3	C_6H_5	CH_3	3	6	75	71
4	C_6H_5	C_2H_5	3	6	80	82
5	C_6H_5	n-C_3H_7	3	6	90	80

[a] Reaction conditions: keto alkyne, 10 mmol; water, 50 mL; $K_4Fe(CN)_6$, 0.5 mmol; pressure of CO, 5−6 atm; temperature, 60−90° C; reaction time, 5−6 h.

Scheme 1. General Reaction Scheme



R = Ph, *n*-Bu.
R_1 = *n*-Bu, Et, *n*-Pr..



cyanide ion. Such ligand exchange could be formally described as

$$[Fe(CN)_6]^{4-} + 2CO \rightleftharpoons [Fe(CN)_4(CO)_2]^{2-} + 2CN^-$$
I

The IR spectra of reaction media show sharp carbonyl and cyanide stretching bands at 1990 and 2100 cm^{-1}, respectively, suggesting the formation of $[Fe(CN)_4(CO)_2]^{2-}$ in the aqueous solution, which is consistent with the previous report of Koch and Jiang.[20] A plausible dissociative pathway yielding the anionic species **II**, which seems to be responsible for the catalytic cycle, is suggested for the formation of carboxylactams, as shown in Scheme 2.

When the reactions were carried out without the presence of carbon monoxide, no products were observed. In addition, a solution of the anionic complex prepared by the method of Jiang et al. was successfully used as a catalyst in the cyanohydroxycarbonylation reaction and good conversions were obtained for carboxylactams **1** and **2**, very similar to those observed when the complex was formed in situ.

The work related to the confirmation of active species, reaction mechanism, and application of this system to other substrates is still in progress.

Experimental Section. General Procedure. A typical experiment was performed as follows: a solution of 15.0 mmol of KCN in 50 mL of water was saturated with CO by slow bubbling (5 mL min^{-1}) with stirring. To this solution was then added 0.5 mmol (5 mol %) of $K_4Fe(CN)_6$, and the stirring was continued under CO under the same conditions. After 2 h, the corresponding α-ketoalkyne was added (10 mmol). The resulting solution was then introduced into a 100 mL Parr stainless steel pressure reactor equipped with mechanical stirring and automatic temperature control. The temperature was increased, and the CO pressure was set at 5 or 6 atm. The progress of the reaction was followed by GC in a Hewlett-Packard 5890 instrument with an HP 225 (10 m × 053 mm) packed column; at the end of the reaction (3 h), ethyl acetate was used to extract the product. After the usual workup, the organic solvent was removed at reduced pressure in a rotary evaporator to give the crude product, which was crystallized from an ethyl acetate/hexane mixture.

The unsaturated carboxylactams obtained were characterized by the usual analytical spectroscopy: e.g. ^1H and ^{13}C NMR, IR, and FAB^+ mass spectrometry. In the case of 3-butyl-5-carboxy-5-ethyl-3-pyrrolin-2-one, the structure was unambiguously established by X-ray crystallography.[21]

3-Butyl-5-carboxy-5-ethyl-3-pyrrolin-2-one (1). The product was obtained as described in the general procedure in 75.2% yield as a white solid (mp 75 °C). Anal. Calcd (found) for $C_{11}H_{17}NO_3$: C. 62.54 (62.22); H. 8.11 (8.62). Mass spectrum (*m/z*): 211. IR (selected, cm^{-1}): 3388 (s, NH) 3200 (br, OH), 1720 (vs, CO, carboxy), 1689 (vs, CO amide). ^1H NMR (300 MHz, $(CD_3)_2CO$; *δ*, ppm): 0.89−0.92 (m, 6H), C*H*$_3$(CH$_2$)$_2$CH$_2$ and C*H*$_3$CH$_2$CCOOH), 1.31 (sext, 2H, $J = 7$ Hz, CH$_3$C*H*$_2$-CH$_2$CH$_2$), 1.47 (qn, 2H, $J = 6$ Hz, CH$_3$CH$_2$C*H*$_2$ CH$_2$), 1.8 (q, 2H, $J = 7$ Hz, CH$_3$C*H*$_2$CCOOH), 2.19 (q, 2H, $J =$ 2 Hz, CH$_3$(CH$_2$)$_2$C*H*$_2$), 6.66 (s, 1H, C=C*H*), 8.22 (bs, 1H, N*H*). 10.45 (s, 1H, COO*H*). ^{13}C NMR (75 MHz, $CDCl_3$; *δ,* ppm): 7.90, 13.40 (*C*H$_3$(CH$_2$)$_2$CH$_2$ and *C*H$_3$CH$_2$), 21.90, 24.51 (CH$_3$(*C*H$_2$)$_2$CH$_2$), 29.16, 32.72 (CH$_3$-(CH$_2$)$_2$*C*H$_2$ and CH$_3$*C*H$_2$COOH), 70.64 (N*C*COOH), 138.83 (*C*=CH), 142.78 (C=*C*H), 172.31 (N*C*O), 175.6 (*C*OOH).

3-Butyl-5-carboxy-5-propyl-3-pyrrolin-2-one (2). The product was obtained as described in the general procedure in 68.9% yield as a white solid (mp 120 °C). Anal. Calcd (found) for $C_{12}H_{19}NO_3$: C. 63.98 (63.68); H. 8.50 (8.57). Mass spectrum (*m/z*): 225. IR (selected, cm^{-1}): 3388 (s, NH), 3200 (br, OH), 1740 (vs, CO amide), 1680 (vs CO, carboxy). ^1H NMR (300 MHz, $(CD_3)_2CO$; *δ,* ppm): 0.87−0.90 (m. 6H, C*H*$_3$(CH$_2$)$_2$CH$_2$ and C*H*$_3$-CH$_2$CH$_2$CCOOH), 1.21−1.40 (m, 4H, CH$_3$C*H*$_2$CH$_2$CH$_2$ and CH$_3$C*H*$_2$CH$_2$CCOOH), 1.46 (qn 2H, CH$_3$CH$_2$C*H*$_2$-CH$_2$), 1.68 (t, 2H, $J = 7$ Hz, CH$_3$CH$_2$C*H*$_2$CCOOH), 2.05 (t, 2H, $J = 7$ Hz, CH$_3$-(CH$_2$)$_2$C*H*$_2$), 6.67 (s, 1H, C=C*H*), 8.26 (bs. 1H, NH), 11.0 (s 1H, COO*H*). ^{13}C NMR (75 MHz, $(CD_3)_2CO$; *δ*, ppm): 13.86, 14.12 (*C*H$_3$(CH$_2$)$_2$CH$_2$ and *C*H$_3$CH$_2$CH$_2$CCOOH), 17.68, 22.37, 24.76 (CH$_3$-(*C*H$_2$)$_2$CH$_2$ and CH$_3$*C*H$_2$CH$_2$CCOH), 29.56, 37.85 (CH$_3$-(CH$_2$)$_2$*C*H$_2$ and CH$_3$CH$_2$*C*H$_2$CCOOH), 70.25 (N*C*OOH), 138.51 (*C*=CH), 144.3 (C=*C*H), 173.45 (N*C*O), 175.44 (*C*OOH).

3-Phenyl-5-carboxy-5-methyl-3-pyrrolin-2-one (3). The product was obtained as described in the general procedure in 70.8% yield as a white solid (mp 112 °C). Anal. Calcd (found) for $C_{12}H_{11}NO_3$: C. 66.35 (66.95); H. 5.10 (5.18). Mass spectrum (*m/z*): 217. IR (selected, cm^{-1}): 3375 (s, NH), 3209 (br, OH), 1696 (vs, CO amide). 1715 (vs, CO, carboxy). ^1H NMR (300 MHz, $(CD_3)_2CO$; *δ*, ppm): 1.60 (s, 3H, C*H*$_3$), 6.95 (s, 1H, C*H*=C), 7.40−7.89 (m, 5H, C$_6$*H*$_5$), 7.69 (b, 1H, NH), 10.45 (s, 1H, O*H*). ^{13}NMR (75 MHz, $(CD_3)_2CO$; *δ,* ppm): 25.6 (*C*H$_3$), 70.35 (N*C*COOH), 128.11, 129.10, 129.31 (C$_6$H$_5$), 137.82 (C

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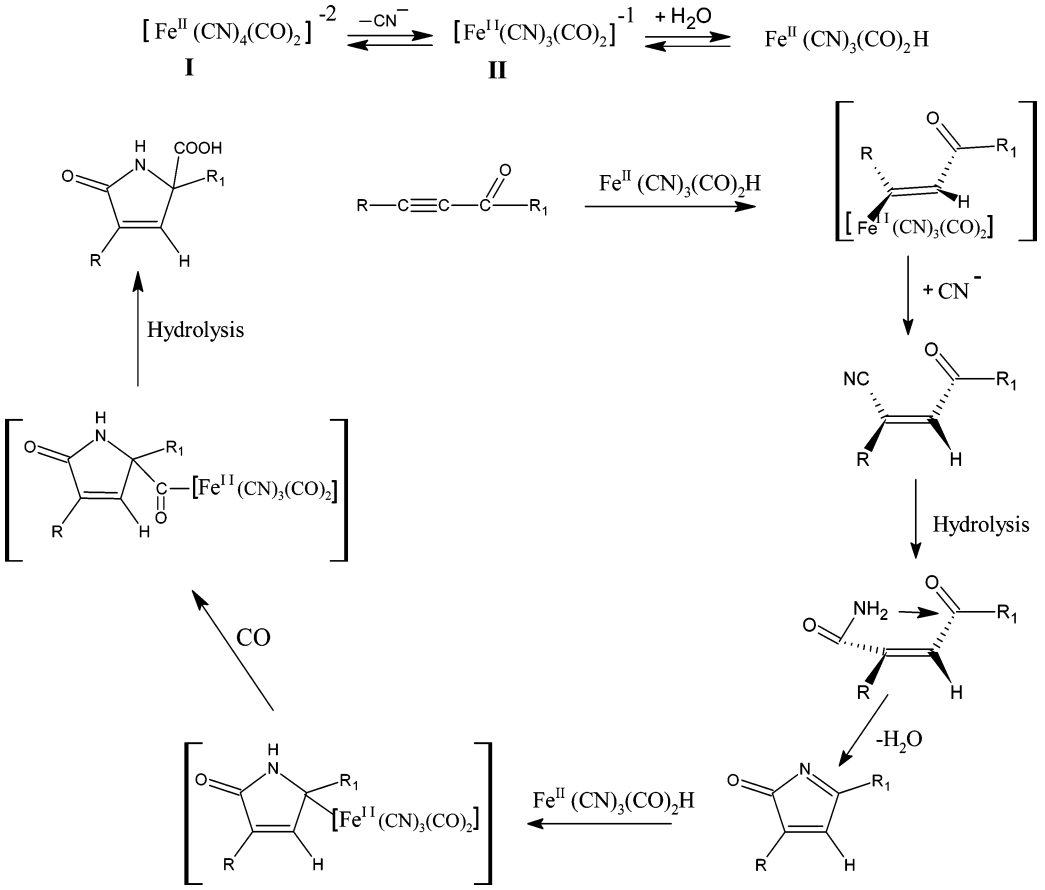
(21) A CIF file has been deposited as Supporting Information.

Scheme 2. Plausible Pathway of the Cycloyclocarbonylation Formation Using the $[Fe^{II}(CN)_6]^{4-}/H_2O/CN^-/CO$ System



ipso), 139.22 (*C*=CH), 145.9 (C=*C*H), 173.51 (O*C*N), 176.61 (*C*OOH).

3-Phenyl-5-carboxy-5-ethyl-3-pyrrolin-2-one (4). The product was obtained as described in the general procedure in 82.0% yield as a white solid (mp 115 °C). Mass spectrum (*m/z*): 231. IR (selected, cm^{-1}): 3371 (s, NH), 3227 (br, OH), 1707 (vs, CO amide), 1718 (vs, CO, carboxy). ^1H NMR (300 MHz, $(CD_3)_2CO$; *δ,* ppm): 0.93 (t, 3H, J = 7 Hz, CH_3CH$_2$), 1.87 (q, 2H, J = 7 Hz, CH$_3$CH_2), 6.90 (s, 1H, C=C*H*), 7.45−7.90 (m, 5H, C$_6H_5$), 7.62 (bs, 1H, NH). 10.45 (s 1H, O*H*). ^{13}C NMR (75 MHz, $(CD_3)_2CO$; *δ,* ppm): 8.62 (*C*H$_3$CH$_2$), 32.00 (CH$_3$*C*H$_2$), 70.30 (N*C*COOH), 128.21, 129.1, 129.22 (C$_6$H$_5$), 138.25 (C ipso), 140.35 (*C*=CH), 144.68 (C=*C*H), 174.55 (O*C*N). 176.41(*C*OOH).

3-Phenyl-5-carboxy-5-propyl-3-pyrrolin-2-one (5). The product was obtained as described in the general procedure in 80.5% yield as a white solid (mp 107 °C). Mass spectrum (*m/z*): 245. IR (selected, cm^{-1}): 3357 (br, NH), 3235 (br, OH), 1708 (vs, CO amide), 1725 (vs, CO carboxy). ^1H NMR (300 MHz, $(CD_3)_2CO$; *δ,* ppm): 0.95 (t, 3H, J = 7 Hz, CH_3CH$_2$), 1.51 (sext, 2H, J = 7 Hz, CH$_3$CH_2CH$_2$), 1.90 (t, 2H, J = 7 Hz, CH$_3$CH$_2$CH_2), 6.95 (s, 1H, C=C*H*), 7.35−7.80 (m, 5H, C$_6H_5$), 7.76 (bs, 1H, NH), 10.45 (s, 1H, O*H*). ^{13}C NMR (75 MHz, $(CD_3)_2CO$; *δ,* ppm): 14.5 (*C*H$_3$CH$_2$), 17.9 (CH$_3$*C*H$_2$), 41.3 (CH$_3$-CH$_2$*C*H$_2$), 70.40 (N*C*COOH), 128.1, 128.9, 129.2 (C$_6$H$_5$), 136.6 (C ipso), 135.1 (*C*=CH), 145.0 (C=*C*H), 171.2 (*C*O amide), 175.11 (*C*OOH).

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Supporting Information Available: Crystallographic data as a CIF file for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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