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Toward Transition Metal-Catalyzed Carbonylation of Methanol without HI as Copromoter: Catalytic Exocyclic Carbonylation of Cycloimino Esters

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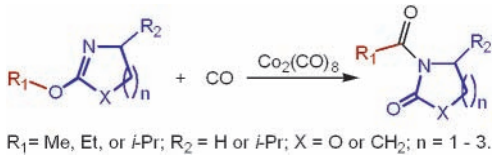
ABSTRACT



R_1= Me, Et, or *i*-Pr; R_2 = H or *i*-Pr; X = O or CH_2; n = 1 - 3.

Initial studies of a rare exocyclic C–O bond carbonylation are reported. Under the catalysis of $Co_2(CO)_8$ in the absence of HI as the copromoter, cycloimino esters are carbonylated to afford *N*-acyllactams in high yields under relatively mild conditions (100–160 °C and 200–1000 psi). The reaction is interesting because it opens up the possibility of carbonylation of alcohols in the absence of HI.

Catalytic carbonylation of carbon−heteroatom bonds is a challenging chemical transformation that has tremendous industrial significance.[1] Most examples of this type of reaction have involved the ring-expanding or ring-opening carbonylation of heterocycles with considerable ring strains.[2−8] However, the most significant commercial success is the Rh-catalyzed carbonylation of methanol for the production of acetic acid and its derivatives, introduced by Monsanto in the early 1970s. A number of variations and improvements of Monsanto's process have been made since then,[9] including the latest BP Chemicals's Ir-catalyzed Cavita process.[9e] All

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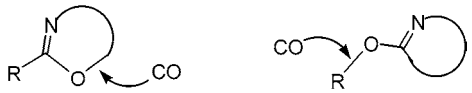
of these processes require HI as the co-promoter because the substrate that directly reacts with the metal catalysts is methyl iodide generated via the equilibrium of methanol and HI with methyl iodide and water. There are considerable advantages if the process can be realized in the absence of HI because the corrosiveness of HI imposes stringent materials requirements for plant construction.[9] This practical problem posts an interesting fundamental challenge as to how to carbonylate a C−O bond in the absence of an added thermodynamic driving force such as ring strain.

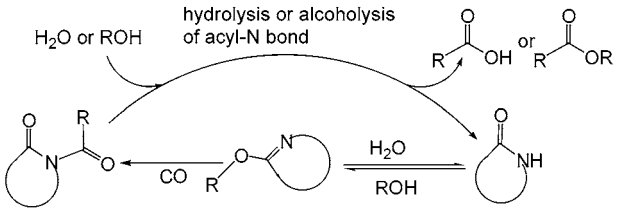
We have recently shown that oxazolines can be carbonylated under relatively mild conditions.[10] Given the fact that there is only a low degree of ring strain present in five-membered rings, it is interesting to explore whether the carbonylation could occur for exocyclic C−O bonds in the cycloimino ester-type structures (Scheme 1). If the exocyclic

Scheme 1. Carbonylation of Endocyclic and Exocyclic C−O Bonds



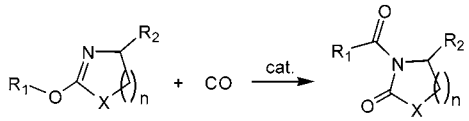
carbonylation were indeed successful, it would then be possible to couple it with the hydrolysis or alcoholysis of the *N*-acyl group of the *N*-acyllactam (exocyclic carbonylation product, vide infra) and the condensation-hydrolysis equilibrium between the lactam and the cycloimino ester to form a reasonable alternative process for the production of carboxylic acids and their derivatives from the corresponding alcohol (Scheme 2). We wish to communicate our preliminary results on the catalytic carbonylation of the exocyclic C−O bond in the cycloimino ester-type structure.

Scheme 2. A Possible HI-Free Process for Production of Carboxylic Acids and Derivatives from Alcohols



A number of potential substrates for the exocyclic carbonylation were scouted using $Co_2(CO)_8$ as the catalyst under a set of constant reaction conditions (1000 psi of CO, 100 °C, and 48 h of reaction time). Under these conditions, 2-methoxypyridine and 3-methoxylpyridine did not undergo carbonylation and were recovered nearly quantitatively. On the other hand, carbonylation of *O*-methyl-ϵ-caprolactim, or 1-aza-2-methoxy-1-cycloheptene, proceeded smoothly and produced *N*-acetyl-ϵ-caprolactam in 96% yield with the company of 4% ϵ-caprolactam (Table 1, entry 1). The

Table 1. Exocyclic Carbonylation of Cycloimino Esters[a]



entry	R_1	R_2	X	n	*T* (°C)	pressure (psi)	yield (%)
1	Me	H	CH_2	3	100	1000	96[f]
2	Et	H	CH_2	3	100	1000	85[f]
3	^{i}Pr	H	CH_2	3	100	1000	33[f]
4	Me	H	CH_2	1	100	1000	96[f]
5	Me	H	CH_2	2	100	1000	97[f]
6	Et	H	O	1	100	1000	50[e]
7	Et	^{i}Pr	O	1	100	1000	70[e]
8	Me	H	CH_2	3	100	200	95[f]
9[b]	Me	H	CH_2	3	160	1000	98[f]
10[c]	Me	H	CH_2	3	100	1000	99[f]
11[b,c]	Me	H	CH_2	3	100	1000	55[e]
12[c,d]	Me	H	CH_2	3	100	1000	7[e]

[a] Reaction conditions unless otherwise specified: 5 mol % $Co_2(CO)_8$, $[Co_2(CO)_8]$ = 0.19 M, 25 mL of dimethoxyethane, reaction time = 48 h. [b] Reaction time = 24 h. [c] 1 mol % $Co_2(CO)_8$. [d] Reaction time = 6 h. [e] Yield estimated by ^{1}H NMR. [f] Yield estimated by GC−MS.

product of formal CO insertion into the methyl−O bond of the substrate was not detectable by ^{1}H NMR. This reaction pattern is general. *O*-Ethyl-ϵ-caprolactim and *O*-isopropyl-ϵ-caprolactim were converted to *N*-propio- and *N*-isobutyro-ϵ-caprolactam, respectively, in successively lower yields (entries 2 and 3). The ring size of the substrates did not substantially affect the carbonylation. High conversions of *O*-methyl-δ-valerolactim and *O*-methyl-γ-butyrolactim to the corresponding *N*-acetyllactam were observed (entries 4 and 5), again with the company of a few percent of the corresponding lactam. Interestingly, in the case of 2-ethoxyl-2-oxazoline where both an endocyclic C−O bond and an exocyclic C−O bond are present (entry 6), the exocyclic carbonylation product 3-propio-2-oxazolidone was produced in 50% yield accompanied by unidentified polymeric byproducts with no detectable amount of the endocyclic carbonylation product, 2-ethoxy-4,5-dihydro-1,3-oxazin-6-ones. An isopropyl group at the C(4) position geminal to the nitrogen completely suppressed the formation of the polymer byproduct and improved the yield of the exocyclic carbonylation product to 70% (entry 7).

The reaction conditions of the carbonylation are rather flexible. Using the commercially available *O*-methyl-ϵ-caprolactim as a prototypical example, we were able to carry out the carbonylation over a relatively wide range of temperatures and pressures (100−160 °C and 200−1000 psi) without compromising the yield (entries 8 and 9). At lower catalyst loadings, the yield of the carbonylation product was actually slightly improved (entries 10 vs 1), while the lactam byproduct diminished. An induction period appears to be involved for the carbonylation. For example, at 1% mol

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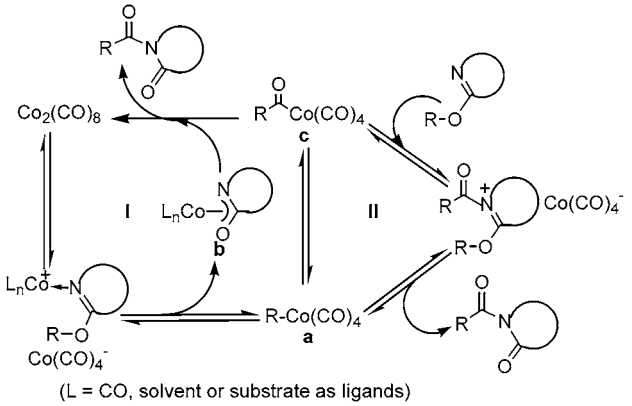
catalyst loading, the conversion of substrate was only 7% in 6 h, 55% in 24 h, but reached completion in 48 h (entries 10−12).

Our original working hypothesis for the mechanism of the exocyclic carbonylation was that the catalytic cycle starts with the ionization of $Co_2(CO)_8$ assisted by the coordination of the substrate to the Lewis acidic cobalt cation followed by the nucleophilic attack of $Co(CO)_4^-$ at the *O*-alkyl group of the coordinated substrate, resulting in two separate intermediates **a** and **b** (catalytic cycle **I**, Scheme 3). CO then

Scheme 3. Two Possible Mechanisms for Exocyclic Carbonylation of Cycloimino Esters



(L = CO, solvent or substrate as ligands)

inserts into the R−Co bond of **a** to afford the acyl−Co species **c**, which is subsequently intermolecularly attacked by the cobalt amidate **b** to give the product and to regenerate $Co_2(CO)_8$. However, we realized during our study that this mechanism does not easily reconcile with some of the facts that we observed. These include the coproduction of the lactam,[11] the diminution of the lactam byproduct at lower catalyst loadings, and the existence of an induction period for the catalysis. We thus suggest an alternative mechanism. In this mechanism, the steps in catalytic cycle **I** that result in the intermediates **a** and **b** are only the initiation steps, which are slow and cause the observed induction period. After the initiation and subsequent CO insertion, the *O*-alkyllactim substrate, as opposed to the amidate **b**, attacks the acyl−Co bond of the intermediate **c** (catalytic cycle **II** in Scheme 3). The resulting $Co(CO)_4^-$ then attacks the *O*-alkyl to release the product and regenerate **a**. The cobalt amidate **b**, which is left out of the catalytic cycle and the amount of which is proportional to the catalyst loading, is likely prone to hydrolysis and, thus, is a reasonable source for the lactam. Although a thorough mechanistic study has not been done at this early stage, we have tested catalytic cycle **II** with a simple experiment. The premises of the experiment are that if catalytic cycle **II** was operative, we should be able to directly enter the catalytic cycle using the equilibrium mixture of $BnCo(CO)_4$ and $BnCOCo(CO)_4$ and that a substantial amount of *N*-phenylacetyllactam should be produced. Indeed, at 50 mol % loading of $BnCo(CO)_4$ and $BnCOCo(CO)_4$, *O*-methyl-ϵ-caprolactim was quantitatively converted to *N*-acetyl-ϵ-caprolactam and *N*-phenylacetyl-ϵ-caprolactam in roughly a 1:1 ratio according to the ^{1}H NMR integration.

In summary, we have reported that the exocyclic C−O bond in cycloimino esters can be readily activated and carbonylated. The reaction offers an opportunity of an alternative process for the production of carboxylic acids from alcohols without the cocatalysis of HI. In this process, an organic amide would replace HI to form the desirable equilibrium that generates the direct reactant for the carbonylation. We are currently investigating this possibility in our laboratory.

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Supporting Information Available: Experimental procedure for carbonylation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) It is unlikely that the lactam byproducts are a result of hydrolysis of *N*-acyllactams during the workup because the *N*-acyllactam hydrolysis does not occur at room temperature. Hydrolysis of *N*-acyllactams after prolonged reflux in a mixture of THF and water afforded selectively acetic acid and the corresponding lactam.