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Syngas reactions

XIV *. Amidocarbonylation as a route to α-amidocarboxylic acids **

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Abstract

The amidocarbonylation of olefin and aldehyde substrates has been applied to the synthesis of a variety of amidocarboxylic acids, including surface active agents (e.g. C_{14}–C_{16} *N*-acyl-α-amino acids), specialty surfactants (such as the sarcosinates), intermediates for sweeteners (e.g. aspartame), food additives (e.g. glutamic acid), and certain chelating agents. Homogeneous cobalt and rhodium-based catalysts, modified, for example, with sulfoxide and bidentate phosphine ligands, have been tailored to the synthesis of each individual class of product. Process studies, including examinations of reaction rate, product selectivity, as well as catalyst stability, have been undertaken for *N*-acetylglycine and amido acid surfactant syntheses.

Introduction

Amidocarbonylation, particularly the synthesis of *N*-acyl-α-amino acids from either aldehyde or olefin feedstocks, plus carbon monoxide and amide, has been examined by a number of researchers [1–4]; both cobalt [1,2] and mixed-metal [3] homogeneous catalyst systems have been developed. The products find application in diverse areas, including enhanced oil recovery [5], liquid detergents [6] and gas scrubbing agents [7]. Ojima has further extended the scope of amidocarbonylation technology to substrates such as trifluoropropene (TFP), oxiranes, and allyl alcohols [4,8,9].

Currently, most amino acids are obtained from natural sources and/or fermentation. Amidocarbonylation can be considered as a viable alternative to the conventional Strecker reaction, which utilizes toxic hydrogen cyanide and ammonia to make α-amino acids from aldehydes. Since 1983, we have been interested in amidocarbonylation technology for two reasons: (a) it is an extension of our

* For Part XIII see ref. 11.
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synthesis gas research to produce specialty chemicals [10,11] and (b) amidocarbonylation is a unique technique for constructing two functionalities in a single step.

Herein, we report the use of amidocarbonylation technology for the syntheses of a wide range of amido acids, including surface active agents (C_{14}–C_{16} amido acids), specialty surfactants (sarcosinates), intermediates for aspartame sweeteners (β-phenylalanine and *N*-acetylglycine), food additives (sodium monoglutamate) and chelating agents (iminoacetic acid and polyamidoacids).

Results and discussion

Aldehyde amidocarbonylation

1. N-*Acetylglycine.* *N*-Acetylglycine, the simplest amino acid, was first synthesized in this work in 63% yield from paraformaldehyde, carbon monoxide and acetamide (eq. 1) using dicobalt octacarbonyl in ethyl acetate as the catalyst precursor. Cobalt catalyst recovery in solution, however, was < 10%. The effect of various added Group VB and VIB ligands upon the glycine yield, and upon cobalt catalyst recovery, was therefore also studied. Data are summarized in Table 1 and a typical preparation (Entry 2 in Table 1) is given in the Experimental Section [12]. The addition of diphenylsulfoxide or succinonitrile increased the *N*-acetylglycine yield to 78%, while cobalt recovery improved dramatically to 85%. The use of tri-n-butylphosphine, on the other hand, allowed reaction to proceed at lower pressures. Chelating agents, such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), adversely affected both the cobalt recovery and production of desired glycine derivative.

$$(CH_2O)_x + CH_3CONH_2 \xrightarrow[Co_2(CO)_8]{CO/H_2} \underset{\text{(I)}}{CH_2(COOH)(NHCOCH_3)} + \underset{\text{(II)}}{CH_2(NHCOCH_3)_2} \quad (1)$$

2. L-*Phenylalanine.* L-Phenylalanine is a key intermediate in the preparation of the sweetener, aspartame—a methyl ester of the L-phenylalanine/L-aspartic acid dipeptide [13]. Currently L-phenylalanine is produced by tyrosine fermentation [13], but other synthetic routes have been proposed, such as the oxidative carbonylation

Table 1

N-Acetylglycine synthesis

Ligand	Conditions [a]				Molar ratio [b]		Yield of I [b] (%)	Co recovery (%)
	CO/H_2	Pressure (psi)	Temp. (°C)	Time (h)	(I)	(II)		
None	3:1	2900	120	2	80	20	63	<10
Ph_2SO	3:1	2900	120	2	94	6	68	81
Succinonitrile	3:1	2900	120	2	100	0	78	80
TMEDA	3:1	2900	120	2	0	100	0	–
n-Bu_3P	8:1	800	110	5	85	15	70	80
None	8:1	800	110	5	–	–	0	–

[a] Reactor charge: paraformaldehyde, 2.0 g; acetamide, 5.9 g; $Co_2(CO)_8$, 0.34 g, EtOAc, 15–20 g. [b] Designations as per eq. 1.

of styrene to form cinnamate ester and subsequent enzymatic amination [14], as well as the amidocarbonylation of styrene oxide [15].

In this work, amidocarbonylation of phenylacetaldehyde (which can be generated from styrene oxide), using a dicobalt octacarbonyl-DIPHOS (4:1 molar ratio) catalyst precursor, afforded *N*-acetyl-β-phenylalanine (eq. 2) in 72% yield with > 98% cobalt recovery [16]. Typical operating conditions are as follows: CO/H_2, 3:1; 2200 psi, 80 °C, 4 h; a typical preparative procedure is provided in the Experimental Section.

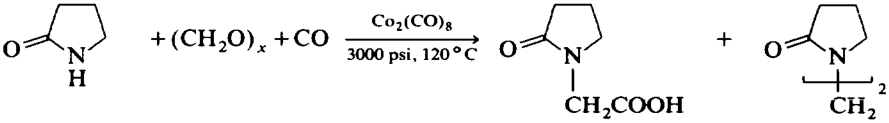
$$PhCH_2CHO + CH_3CONH_2 \xrightarrow{CO/H_2} PhCH_2CH\begin{cases} COOH \\ NHCOCH_3 \end{cases} \qquad (2)$$

3. Alkyl sarcosinates. Sarcosinate specialty surfactants are traditionally made by treatment of the corresponding amino acid with an acyl chloride. The use of a secondary amide for amidocarbonylation has been reported to give poor yields of amido acid since the corresponding oxazolone intermediate cannot be formed [2,17–19]. We have found, however, that the amidocarbonylation of *N*-methylamide gives excellent yields of *N*-acyl sarcosinates (eq. 3) when conducted in the presence of dicobalt octacarbonyl at 120 °C with $CO/H_2 = 3$. Sarcosinate selectivity is typically 95%, at 92% *N*-methylamide conversion (see Experimental Section).

$$C_{11}H_{23}C(=O)OH + CH_3NH_2 \longrightarrow C_{11}H_{23}C(=O)NH(CH_3) \xrightarrow[CO/H_2]{(CH_2O)_x} C_{11}H_{23}C(=O)N(CH_3)CH_2COOH \qquad (3)$$

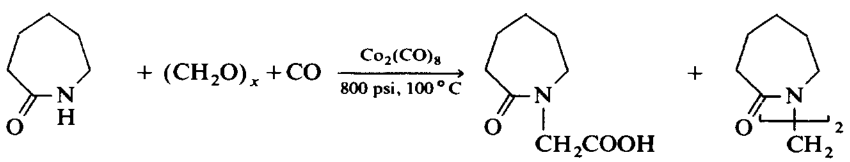
This simple synthesis, which avoids the use of chloride, allows the introduction of both the carboxylic acid and the secondary amide moieties in a single step [20].

4. Other amido acids. Other amido acids may be prepared via formaldehyde amidocarbonylation in the presence of various *N*-substituted acyclic amides (see Experimental Section) as well as cyclic amides, including γ-butyrolactam and ϵ-caprolactam [21]. Dicobalt octacarbonyl is again the catalyst precursor, and conditions are moderate. *N*-(2-Pyrrolidone)-2-acetic acid and *N*-(ϵ-caprolactam)-2-acetic acid are two of the desired products (eqs. 4 and 5).



(4)

(3:2)



(5)

(1:2)

Olefin amidocarbonylation

1. Monoolefins. In 1981, Stern patented a procedure for making *N*-acetylamino acids from monoolefins, acetamide and synthesis gas in the presence of dicobalt octacarbonyl [3], where hydroformylation and amidocarbonylation occur in a single step. The product mix was typically a 11.5 : 1 ratio of linear to branched amido acids (in contrast to the 2.4 : 1 ratio for the corresponding two-step route, 1-dodecene the starting olefin). Ojima reported predominantly branched-chain amido acid products (94% regioselectivity) with TFP and $Rh_6(CO)_{16}$ cocatalyst [4,9]. Similar products find applications in cosmetics [22].

Our results demonstrate that starting with C_{12} α-olefin, amido acids with up to 95% linearity can be prepared using the $Co_2(CO)_8$–$HRh(CO)(PPh_3)_3$ couple (see Table 2). The advantages of this bimetallic system are excellent reproducibility, high yield, and high linearity of the desired amino acid product (eq. 6), as well as the need for only moderate syngas pressures. The process to make C_{16} amido acid from 1-tetradecene has been optimized [23,24], and a recrystallization procedure designed to purify the amido acid product while recovering the cobalt/rhodium catalyst has been developed [24]. A typical procedure for synthesizing these C_{16} amido acids is outlined in the Experimental Section.

$$RCH{=}CH_2 + CH_3CONH_2 + CO/H_2 \longrightarrow RCH_2CH_2CH\begin{matrix}\diagup\ COOH \\ \diagdown\ NHCOCH_3\end{matrix} \qquad (6)$$

In a second development, we have demonstrated that using homogeneous cobalt catalysis alone, but with the addition of certain bidentate phosphines, it is possible to achieve reaction 6 at lower pressures (see Table 3) [23]. For example, combinations of dicobalt octacarbonyl with 1,3-bis(diphenylphosphino)propane afforded good activity for 1-dodecene amidocarbonylation at 800 psi syngas pressure (see Experimental Section).

A variety of other terminal, internal and vinylic C_3–C_{18} olefins may also be amidocarbonylated in good yields by these procedures. Typical results are summarized in Table 4 and a typical preparation starting from cyclohexene is given in the Experimental Section. Applications for these iminoacetic acid derivatives would be as surface active or chelating agents.

Table 2

C_{16} amido acid synthesis—Co/Rh catalysis

Catalyst/cocatalyst	Conditions	$RCH_2CH_2CH\begin{matrix}\diagup\ COOH \\ \diagdown\ NHCOCH_3\end{matrix}$	
		Yield (%)	Linearity (%)
$Co_2(CO)_8$	1900 psi, 100–110 °C	70	92
$Co_2(CO)_8$–$Rh_6(CO)_{16}$ (35 : 1)	2000 psi, 100 °C	70	75
$Co_2(CO)_8$–$HRh(CO)(PPh_3)_3$ (40 : 1)	2000 psi, 100 °C	89	95
$Co_2(CO)_8$–$HRh(CO)(PPh_3)_3$ (40 : 1)	800 psi, 100 °C	55	–

Table 3

C_{14} amido acid synthesis—effect of P-ligands

Ligand	Temp. (°C)	Olefin conversion (%)	Cobalt recovery (%)
None	130	68	81
$Ph_2P(CH_2)PPh_2$	130	40	80
$Ph_2P(CH_2)_2PPh_2$	130	80	–
$Ph_2P(CH_2)_3PPh_2$	130	95	85
$Ph_2P(CH_2)_4PPh_2$	130	60	–
$Ph_2P(CH_2)_6PPh_2$	130	75	100
n-Bu_3P	130	60	–
$Ph_2P(CH_2)_3PPh_2$	150	95	80
None	150	0	–

Reactor charge: $Co_2(CO)_8$, 2.0 mmol; C_{12} olefin, 100 mmol; acetamide, 100 mmol *p*-dioxane, 30 g, P-ligand, 1.0 mmol. Operating conditions: CO/H_2, 1:1; 800 psi; 4 h.

Table 4

Amidocarbonylation of various monoolefins

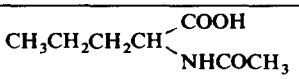
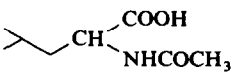
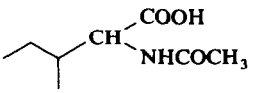
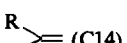
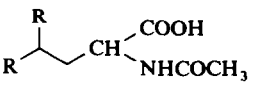
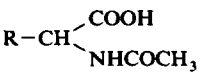
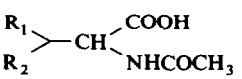
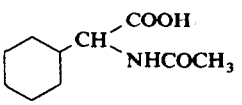
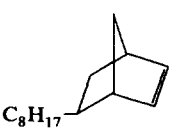
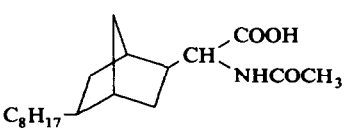
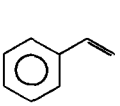
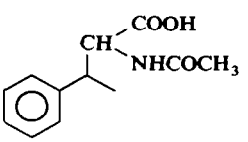
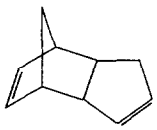
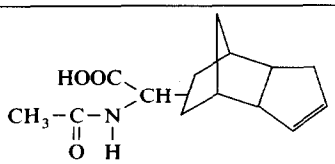
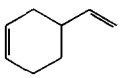
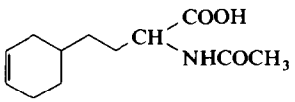
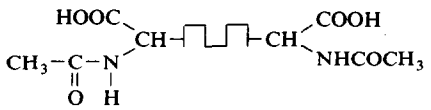
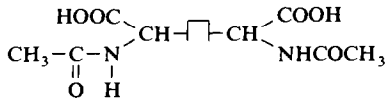
Starting olefin	Major product	Yield; m.p.
		70%
		84%; 128–135°C
		34%; 130–135°C
		66%; 93–98°C
1-$C_{10}^{=}$ to $C_{14}^{=}$		91%; ca. 95°C
7-C_{14}^{-} or 9-C_{18}^{-}		85%; liquid
		85%; 180–186°C
		80–90%
		75%

Table 5

The amidocarbonylation of various diolefins

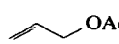
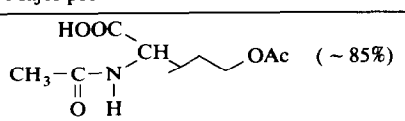
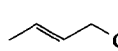
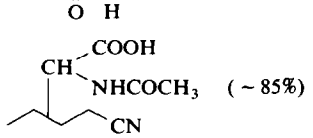
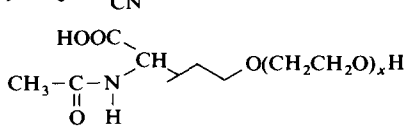
Starting materials	Products	Yield
		78%
		–
		45%
		47%

2. Diolefins. Certain *N*-acyl-α-amino acids have also been prepared from diolefins, such as dicyclopentadiene, 4-vinyl-1-cyclohexene, 1,3-butadiene and 1,7-octadiene (see Table 5). Monoamido acids are the predominant products when starting with unsymmetrical dienes such as dicyclopentadiene and 4-vinyl-1-cyclohexene; diamido acids were produced with symmetric dienes. A number of these polyamido acids have potential as chelating agents.

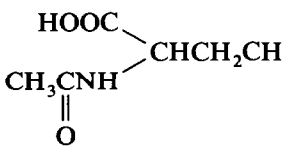
3. Functionalized olefins. When amidocarbonylation was extended to functionalized olefins, a number of interesting amidoacids were obtained. *N*-Acetyl-glutamic acid ester, a precursor for monosodium glutamate, can be synthesized from acrylate ester, acetamide and synthesis gas in 85% yield (eq. 7) [25]. This *in situ* hydroformy-

Table 6

The amidocarbonylation of functionalized olefins

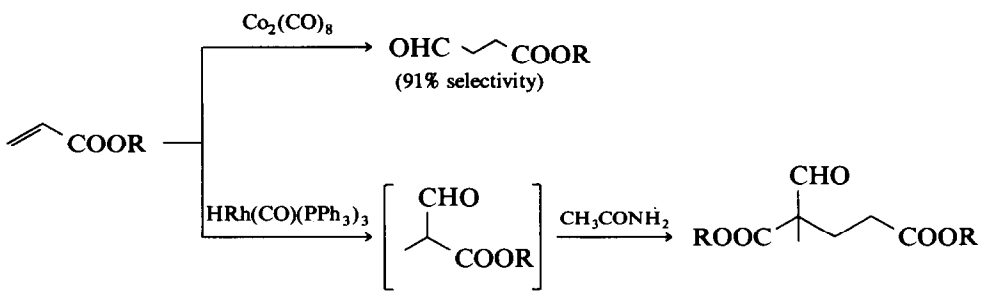
Starting olefins	Major products	Application
	 (~ 85%)	Polyamide-ester
	 (~ 85%)	Polyamide
		Surfactant

lation/amidocarbonylation route afforded the linear amino acid as the major product (see Experimental Section). By comparison, rhodium-catalyzed hydroformylation of acrylate afforded dimethyl 2-formyl-2-methylglutarate at 75% selectivity and 60% conversion. This product was derived from hydroformylation of acrylate at the α-position and subsequent Michael addition to a second equivalent of acrylate (eq. 8) [26].



(7)

(85% yield)



(8)

The reactions of allyl acetate, 2-pentenenitrile and allyl alcohol ethoxylate afforded the corresponding amido acids in good yield. These structures are cited in Table 6 and a typical preparation is given in the Experimental Section. The products could find applications as surfactants or in polyamidepolyesters.

Conclusions

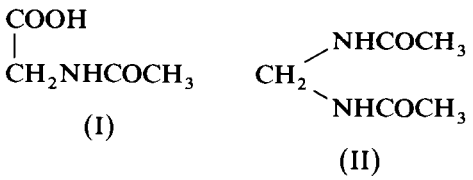
The development of new, improved amidocarbonylation technology, including both (a) the homogeneous cobalt–diphenyl sulfoxide and succinonitrile couples for enhanced catalyst recovery and increased yield of desired product during aldehyde amidocarbonylation, and (b) the use of the $Co_2(CO)_8$–$HRh(CO)(PPh_3)_3$ and $Co_2(CO)_8$–$Ph_2P(CH_2)_3PPh_2$ catalysts for olefin hydroformylation/amidocarbonylation, greatly extends the scope of this chemistry. In particular, both *N*-acetylglycine and *N*-acetyl-β-phenylalanine, potential intermediates in aspartame synthesis, have been selectively generated in one step, while the preparation of a number of potential specialty surfactants and chelating agents has been demonstrated. Interestingly, glutamic acid has been generated from acrylic acid in one step. Some of the more significant advantages of this new amidocarbonylation technology include: (1) scope, the ability to make a broad spectrum of amino acid products; (2) less

hazardous reagents than for the Strecker process; (3) inexpensive feedstocks, generating specialty chemicals from commercially available aldehydes/olefins; and (4) the opportunity to prepare specialty chemicals using synthesis gas as a basic building block. It is in these respects that the amidocarbonylation reaction is a remarkably versatile, and useful, developing technology.

Experimental section

Typical preparation of N-*acetylglycine*

A 183 ml capacity rocking autoclave, equipped with a glass-liner, was charged with dicobalt octacarbonyl (0.34 g, 1.0 mmol), phenylsulfoxide (0.202 g, 1.0 mmol), paraformaldehyde (2.0 g, 66 mmol), acetamide (5.9 g, 100 mmol) and ethyl acetate (15 g). The reactor was sealed and flushed with the mixture of CO/H_2 (1 : 1 molar ratio). The system was pressured with CO/H_2 (1 : 1) to 1200 psi and then pressured with pure CO to 2300 psi, resulting in a ca. 3 : 1 molar ratio of CO to H_2. The autoclave was heated to 120 °C and held at this temperature for ~ 2 h. The maximum pressure of the reactor was 2900 psi during the run. After the designated reaction time, the system was cooled to room temperature and the excess gas was vented. The resulting product materials were filtered and both the solid (6.5 g) and liquid (17.9 g, brown color) fractions recovered. The ^{1}H-NMR analyses showed the solid portion comprised two products, *N*-acetylglycine (I) and bisamidal (II).



(I)

(II)

The molar ratio of *N*-acetylglycine (I) and bisamidal (II) in the product solid was 17.6 : 1.0. The yield of *N*-acetylglycine (I), basis paraformaldehyde charged, was 68 mol %. The yield of bisamidal (II) was 4%. The relative selectivity for I and II was 94 mol% versus 6 mol%.

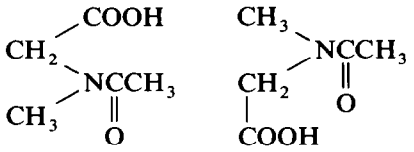
The liquid product fraction was found to contain 5250 ppm soluble cobalt. This represents a ca. 81% recovery of cobalt in solution basis $Co_2(CO)_8$ charged.

It is of note that no significant amounts of compounds I and II could be found in the liquid product fraction. This synthesis procedure therefore allows for a relatively easy separation of solid *N*-acetylglycine product I from the soluble cobalt-containing catalyst fraction.

Typical preparation of N-*methyl*-N-*acetylglycine*

A glass-lined reactor equipped with rocking device was charged with dicobalt octacarbonyl (0.34 g, 1 mmol), paraformaldehyde (2.0 g, 0.066 mol), *N*-methylacetamide (6.0 g, 0.082 mol) and ethyl acetate (15.0 g). The reactor was sealed and flushed with synthesis gas ($CO + H_2$). The system was pressured with a CO/H_2 mixture (1 : 1 molar ratio) to 1200 psi, then with CO to 2400 psi (resulting in a 1 : 4 ratio of H_2/CO). The mixture was heated to 120 °C and 3000 psi of pressure was recorded during this process. After two hours reaction time, the system was allowed to cool to room temperature, and excess gas was vented. The resulting product

mixture comprised 8.0 g of solid and 15.5 g of liquid. ^{1}H-NMR spectroscopy of the solid material showed the presence of *N*-methylacetamide (1 part by mole) and two isomeric forms (*syn*/*anti*) of *N*-methyl-*N*-acetylglycine (III), 4.6 parts; IV, 10.2 parts).

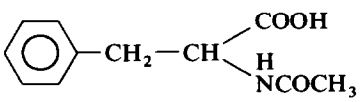


(III) (IV)

The ^{1}H-NMR spectrum of III showed δ 2.2 (s, 3H, $-COCH_3$), δ 3.2 (s, 3H, $N-CH_3$) and δ 4.2 (s, 2H, $CO-CH_2-N$). The ^{1}H-NMR spectrum of IV showed δ 2.1 (s, 3H, $-COCH_3$), δ 3.0 (s, 3H, $N-CH_3$) and δ 4.3 (s, 2H, $CO-CH_2-N$). The total yield of *N*-methyl-*N*-acetylglycine was estimated to be ca. 73%, basis paraformaldehyde charged. Cobalt analysis of the liquid product was 6380 ppm (86% recovery).

Typical preparation of N-*acetyl-β-phenylalanine*

A glass-lined autoclave was charged with dicobalt octacarbonyl (0.68 g, 2.0 mmol), 1,2-bis(diphenylphosphino)ethane (0.20 g), phenylacetaldehyde (6.0 g), acetamide (3.0 g) and ethyl acetate (15.0 g). The reactor was purged with CO/H_2 mixture (1 : 1 molar ratio) to 1000 psi and with pure CO to a final pressure of 2000 psi (resulting in a ca. 3 : 1 ratio of CO to H_2). The system was heated to 80 °C and held at that temperature for four hours. During this process, the pressure went up to 2175 psi and then dropped to 2100 psi, indicating considerable gas consumption. After the reactor was cooled to room temperature, a deep-brown homogeneous solution (ca. 25.9 g) was recovered. A portion of product solution was subjected to high vacuum in order to remove solvent and then analyzed. *N*-Acetylphenylalanine (V) was obtained at ca. 72 mol% yield based on phenylacetaldehyde charged. The cobalt analysis showed 9950 ppm cobalt in product solution; estimated cobalt recovery in solution was > 98%:



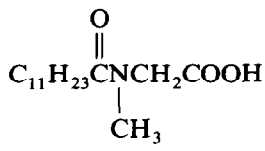
(V)

The ^{1}H-NMR spectrum of V showed δ 2.0 (s, 3H, $-COCH_3$), δ 3.05 (m, 2H, $-CH_2-Ph$), δ 4.5 (m, 1H, $CO-CH-N$), δ 8.25 (d, 1H, $-NH-CO$).

Typical preparation of N-*acyl sarcosinate*

A 300 ml magnedrive autoclave was charged with 100 g of lauric acid and 10 g of methylamine and then heated at 230 °C for three hours. The recovered solid product was analyzed to be a mixture of *N*-methyl lauramide and lauric acid in ca. 4.0 to 3.0 ratio. A sample of this crude product mixture (14.0 g) was recharged to the reactor with paraformaldehyde (1.0 g), dicobalt octacarbonyl (0.34 g, 1 mmol) and EtOAc (10.0 g). The reaction conditions were 3000 psi of CO/H_2 (3 : 1), 120 °C

and the reaction time two hours. The recovered solution (25.6 g) was analyzed by ^{1}H-NMR spectroscopy and showed ca. 92% conversion of *N*-methyl lauramide and 95% selectivity to sarcosinate (VI).



(VI)

The ^{1}H-NMR of structure VI showed δ 0.9 (s, 3H, $-CH_3$), δ 1.05–1.85 (s, 18H, $-CH_2-$), δ 2.35 (t, 2H, $-CH_2CO$), δ 3.2 (s, 3H, $-NCH_3$), δ 4.2 (m, 2H, CO–CH–N).

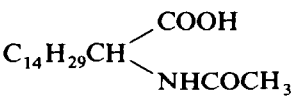
Typical preparation of C_{16} amido acid—Rh / Co catalysis

To a glass-lined pressure reactor was charged $HRh(CO)(PPh_3)_3$ (0.046 g), $Co_2(CO)_8$ (0.34 g), acetamide (3.0 g), 1-tetradecene (9.8 g) and ethyl acetate (10.0 g). The reactor was sealed and pressured with CO/H_2 (1 : 1 molar ratio), then amidocarbonylation allowed to proceed at the conditions of 2000 psi, 100 °C for four hours. After amidocarbonylation, upon cooling to room temperature, the recovered materials (25.4 g) included some crystalline solid, and following filtration, the crude C_{16} amido acid (13.8 g) was obtained. The yield of this compound was estimated to be ca. 89%. The crude product contained some rhodium and cobalt catalyst.

A portion of C_{16} amido acid crude product (21 g, grey solid, contaminated with 253 ppm Co and < 1 ppm Rh) was dissolved in hot ethanol (ca. 50 °C). The hot solution was filtered to remove trace amounts of insoluble material and the filtrate cooled to room temperature. A crystalline solid appeared (ca. 12 g), this was filtered off and the liquid filtrate was decanted into 100 cm^3 of deionized water. A white solid was collected and dried to afford 9.0 g of desired C_{16} amido acid product with contamination of 43 ppm Co and < 1 ppm Rh.

Typical preparation of C_{16} amido acid—Co catalysis

A 300 ml stirred autoclave was charged with $Co_2(CO)_8$ (0.68 g, 2 mmol), bis-1,2(diphenylphosphino)ethane (0.21 g, 0.50 mmol), 1-tetradecene (9.8 g, 0.05 *M*), acetamide (2.9 g, 0.05 *M*) and *p*-dioxane (20 g). The system was purged with a mixture of CO/H_2 (1 : 1 molar ratio) and pressured to 100 psi. At 130 °C, the pressure was raised to 800 psi and maintained at this pressure by incremental addition of the CO/H_2 mixture. After four hours, the reaction was terminated and the reaction mixture was analyzed by ^{1}H-NMR spectroscopy, it showed the presence of *N*-acetylamino acid (VII) at ca. 85% selectivity, based on converted 1-tetradecene. A cobalt analysis of the product solution indicated ca. 95% cobalt recovery.



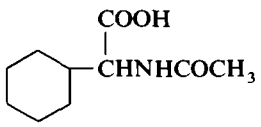
(VII)

The ^{1}H-NMR spectrum of VII showed δ 0.86 (t, 3H, $-CH_3$), δ 1.0–1.8 (s, 26H, $-CH_2-$), δ 1.95 (s, 3H, $-CO-CH_3$), δ 4.25 (m, 1H, CO–CH–N), δ 8.1 (d, 1H, –NH–CO).

Typical amidocarbonylation of cyclohexene

Experimental procedures identical to the above were employed, except the reactants were $HRh(CO)(PPh_3)_3$ (0.046 g), $Co_2(CO)_8$ (0.34 g), acetamide (3.0 g), cyclohexene (4.1 g, 50 mmol) and ethyl acetate (10.0 g); the reaction conditions were $CO/H_2 = 1:1$ and 120 °C for four hours.

The resulting product mixture (19.2 g) was filtered and the solid material (8.5 g) was analyzed by ^{1}H-NMR spectroscopy showing structure VIII.

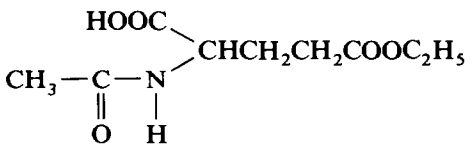


(VIII)

The melting point of compound VIII was 180–186 °C and the yield was 85%.

Typical preparation of N*-acetylglutamic acid ester*

A glass-lined reactor was charged with dicobalt octacarbonyl (5.1 g, 15 mmol), acetamide (53 g, 898 mmol), ethyl acrylate (75 g, 750 mmol), and *p*-dioxane (150 g). The reactor was purged of air and pressured with CO/H_2 (1 : 1 ratio) to 500 psi. The system was heated to 130–153 °C, then pressured with additional CO/H_2 to 2000 psi. During two hours reaction time, 2000 psi of pressure was maintained by frequently adding increments of CO/H_2 gas. After cooling to room temperature, a homogeneous, light-brown solution (314.3 g) was recovered. An aliquot of the product mixture was added to 10% Na_2CO_3 and then solid K_2CO_3 added to adjust the pH to 10. The solution was extracted twice with methyl acetate to remove the by-products. The acidity of the aqueous solution was then adjusted with 85% phosphoric acid until the pH was 2 and again extracted with ether and methyl acetate to afford 126 g of compound IX. The structure (IX) was confirmed by ^{1}H-NMR and IR.



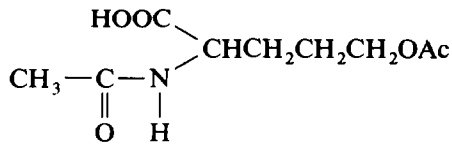
(IX)

The ^{1}H-NMR spectrum of IX methyl ester showed δ 1.7 (m, 2H, $-CH_2-$), δ 1.9 (s, 3H, $-CH_3$), δ 2.5 (m, 2H, $-CH_2CO$), δ 3.75 (s, 3H, $-OCH_3$), δ 4.28 (m, 1H, $-CH<$), δ 8.1 (d, 1H, –NH–CO).

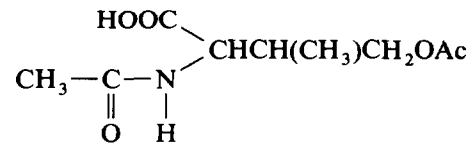
Typical amidocarbonylation of allyl acetate

A glass-lined reactor was charged with $Co_2(CO)_8$ (6.8 g, 20 mmol), acetamide (60 g), allyl acetate (100 g) and *p*-dioxane (100 g). The reactor was flushed with CO/H_2 (1 : 1) and pressured to 500 psi, then heated to 130 °C. At this temperature, the

pressure was raised slowly to 2000 psi, and maintained for two hours. The product mixture (310 g, deep brown solution) was extracted with aqueous ethyl acetate solution, the remaining solvent removed by evaporation and the residual dried to afford ca. 87 g pure products (ca. 43%). ^{1}H-NMR confirmed structures X and XI as follows:



(X)



(XI)

The ^{1}H-NMR spectrum of XI showed δ 0.92 (d, 3H, $-CH_3$) δ 1.9 (bm, 1H, $-CH-CH-CH_3$), δ 4.07 (m, 2H, $-CH_2OC-$), δ 4.27 (m, 1H, CO–CH–N), δ 8.17 (d, 1H, –NH–CO).

Acknowledgment

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