Cobalt-catalyzed carbonylation of phenylacetaldehyde to N-acetyl-beta-phenylalanine

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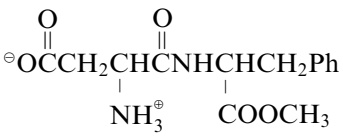
N-acetyl-beta-phenylalanine has been produced by the reaction of phenylacetaldehyde, acetamide and CO/H_2 in the presence of cobalt carbonyl catalyst. N-acetyl-beta-phenylalanine yields of 72–82 mol% and cobalt recoveries of 98% had been achieved under the conditions of 2000 psi of 3 : 1 CO/H_2 and 80°C in a batch process. The presence of a suitable ligand, 1,2-bis(diphenylphosphino)ethane, was essential for maintaining cobalt in homogeneous solution. The feasibility of using a continuous phase reactor with a dual feed stream system was demonstrated. N-acetyl-beta-phenylalanine is proposed to be the precursor to L-phenylalanine, the key intermediate for aspartame sweetener.

Keywords: cobalt carbonyl, homogeneous, carbonylation, phenylalanine, aspartame, 1,2-bis(diphenylphosphino)ethane, amidocarbonylation

1. Introduction

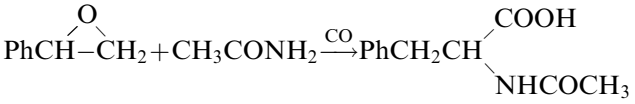
Recently, the progress in hydroformylation and carbonylation has been reviewed [1]. Amidocarbonylation is one of the promising technology advances for industrial applications [2–8]. The reaction was first discovered by Wakamatsu in 1971[2], and became a versatile carbonylation technology for making industrial products such as surfactants and specialty aminoacids, including L-phenylalanine [6–8].

L-phenylalanine is a key intermediate for aspartame sweetener, a methyl ester of the L-phenylalanine-L-aspartic acid dipeptide :



Currently, L-phenylalanine is produced commercially from the fermentation of tyrosine which is isolated from hydrolysis of natural proteins [9]. Chemical synthetic methods [10] under study included asymmetric hydrogenation of benzaldehyde and glycine derivatives and derivations from cinnamic acid, benzyl chloride and ethyl benzylacetoacetate intermediates. Normally, chemical processes produce both D- and L-forms of aminoacids. Through the racemization and recycling of the D-form, L-phenylalanine is isolated.

Conventionally, the Strecker reaction involving cyanide and ammonia feedstocks is used to prepare the alpha aminoacid [11]. The amidocarbonylation is a more environmentally benign process. In 1985, Ojima reported an in situ rearrangement and carbonylation of styrene oxide to phenylalanine precursor [5]. Presumably, the mild Lewis acid promoted rearrangement of styrene oxide to phenylacetaldehyde and subsequently cobalt catalyzed amidocarbonylation, as described in reaction (1):



(1)

In 1991, we reported a catalyst system of cobalt carbonyl and a diphosphine ligand for a number of applications for the amidocarbonylation of detergent range alpha-olefins, formaldehyde and phenylacetaldehyde [6]. However, those processes were performed in batch reactors to understand the scope of versatility. In order to gauge the commercial feasibility, a continuous phase reaction with duel feed stream system has been developed.

2. Experimental

2.1. Batch reaction

Dicobalt octacarbonyl and 1,2-bis(diphenylphosphino)ethane (DIPHOS) catalyst. A 183 cm^3 glass-lined autoclave was charged with dicobalt octacarbonyl (0.68 g, 2.0 mmol), 1,2-bis(diphenylphosphino)ethane (0.20 g, 0.5 mmol), phenylacetaldehyde (6.0 g, 50 mmol), acetamide (3.0 g, 51 mmol) and ethyl acetate (15 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 (totally ca. 3 : 1 ratio of CO to H_2). The system

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was heated to 80°C and held for 4 h. During the process, the pressure went up to 2175 psi and then dropped to 2100 psi, indicating 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 a high vacuum to remove solvent and then analyzed by H-NMR. The H-NMR spectrum showed δ 2.0 (s, 3H, –COC<u>H</u>$_3$), δ 3.05 (m, 2H, –C<u>H</u>$_2$–Ph), δ 4.5 (m, 1 H, CO–C<u>H</u>–N) and δ 8.23 (d, 1H, –N<u>H</u>–CO). N-acetyl-beta-phenylalanine 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%.

Dicobalt octacarbonyl and diphenyl sulfoxide catalyst. The above experimental procedures were repeated, except using $Co_2(CO)_8$ (0.68 g, 2.0 mmol), diphenyl sulfoxide (0.20 g), phenylacetaldehyde (6.0 g, 50 mmol), acetamide (3.0 g, 51 mmol) and ethyl acetate (15 g). The initial pressure was 1000 psi of CO/H_2 at 1 : 1, plus 1000 psi of pure CO, resulting in 2000 psi total pressure of CO/H_2 at 3 : 1 molar ratio. The operating conditions were 80°C and 4 h. The resulting product solution was a homogeneous dark brown solution. The analysis of H-NMR indicated the desired product was the major product. The cobalt in the product solution was ca. 7940 ppm with an estimation of cobalt recovery at 80%.

Dicobalt octacarbonyl catalyst (without ligand). The above experimental procedures were repeated, except using $Co_2(CO)_8$ (0.68 g, 2.0 mmol), phenylacetaldehyde (6.0 g, 50 mmol), acetamide (3.0 g, 51 mmol) and ethyl acetate (15 g). The reaction conditions were CO/H_2 at 3 : 1, 2300 psi, 80°C and 4 h. The resulting product solution was analyzed to be ca. 82% yield based on phenylacetaldehyde charged. However, the cobalt analysis showed only 4170 ppm in product solution (ca. 46% cobalt recovery in solution, based on the theoretical 9100 ppm).

Dicobalt octacarbonyl catalyst (at higher temperature). The same experimental procedures were employed, except using 120°C reaction temperature instead of 80°C. The mixtures of $Co_2(CO)_8$ (0.68 g, 2.0 mmol), phenylacetaldehyde (6.0 g, 50 mmol), acetamide (3.0 g, 51 mmol) and ethyl acetate (15 g) were subjected to reaction conditions of 2000 psi of CO/H_2 at 3 : 1 molar ratio, 120°C and 2 h. The resulting product solution was analyzed by H-NMR to be ca. 55 mol% N-acetyl-beta-phenylalanine based on phenylacetaldehyde charged.

2.2. Continuous phase reaction

The carbonylation of phenylacetaldehyde was investigated in continuous unit equipment using a stirred tank, 300 ml capacity reactor, equipped with duel pump system for feeding two separate lines of starting materials. One feedtank contained the catalyst solution of $Co_2(CO)_8$ (34.2 g, 0.1 mol), DIPHOS (10 g, 0.025 mol), EtOAc solvent (900 g) and starting material of $PhCH_2CHO$ (600 g, 5 mol) in a homogeneous solution. Another feed stream was made up of acetamide solution by dissolving CH_3CONH_2 (400 g, 6.8 mmol) in EtOAc (800 g) and co-solvent CH_3OH (80 g). Methanol co-solvent was required to maintain the homogeneous solution. Summary data for a series of eight runs over a spectrum of conditions are given in table 1. Product solutions were generally analyzed by NMR to determine the concentration of desired amidoacid using the integration of the characteristic δ 4.5 (m, 1H, CO–C<u>H</u>–N) chemical shift.

3. Results and discussion

The reaction for producing N-acetyl-beta-phenylalanine is described in reaction (2):

$$PhCH_2CHO + CH_3CONH_2 \xrightarrow{CO} PhCH_2CH\begin{matrix}\diagup COOH \\ \diagdown NHCOCH_3\end{matrix} \qquad (2)$$

Table 1
Phenylacetaldehyde carbonylation to N-acetyl-phenylalanine

Run	Temp. (°C)	Feed rate (cm^3/h)		Gas rate (ℓ/h)	Hold time (h)	Yield [c] (%)	Feed in (g)	Recovered (g)
		stream 1 [a]	stream 2 [b]					
1	80	20	20	20	4.5	25	152	141
2	80	20	10	20	6.0	53	86	73
3	80	10	5	10	12.0	37	57	62
4	100	20	10	10	6.0	27	114	114
5	120	20	10	10	6.0	0	–	–
6	100	20	20	10	4.5	12	152	164
7	100	20	20	5	4.5	trace	133	130
8	80	20	10	5	6.0	trace	114	119

[a] Stream 1 (catalyst solution): $PhCH_2CHO$ (600 g, 5 mol); EtOAc (900 g); $Co_2(CO)_8$ (34.2 g, 0.1 mol); DIPHOS (10 g, 0.025 mol).
[b] Stream 2 (acetamide solution): CH_3CONH_2 (400 g, 6.8 mmol); EtOAc (800 g); CH_3OH (80 g).
[c] Determined by H-NMR based on the total charge of phenylacetaldehyde.

The reaction parameters were screened in batch process [6–8]. It was found that under the conditions of 80°C reaction temperature, 2300 psi pressure of CO/H_2 at 3 : 1 molar ratio, with $Co_2(CO)_8$ catalyst, the mixture of phenylacetaldehyde and acetamide was converted into N-acetyl-beta-phenylalanine at ca. 82% yield. In contrast, the same reaction but at 120°C afforded the desired product at lower selectivity. Presumably the side reactions occurred at higher reaction temperature. Without ligand, the cobalt recovery in the product solution was only 46% based on the charged. The catalyst recovery was improved while using DIPHOS as ligand at 1 to 4 P/Co ratio. Similar results but lower reaction rate were obtained when P/Co ratio ranged between 1/4 and 1. The 98% cobalt recovery and a reasonable yield (72%) of N-acetyl-beta-phenylalanine were obtained. It appeared that DIPHOS was a more stable complexing ligand with cobalt carbonyl than diphenyl sulfoxide, based on the results of cobalt recovery. When diphenyl sulfoxide was used as the ligand, the cobalt recovery was 80% [6].

In the batch process, all reactants including acetamide and dicobalt octacarbonyl solids were directly charged into the reactor. The mixture became a homogeneous solution and the catalyst was formed in situ. In order to operate the reaction in a commercial fashion, it requires the pumping of the feedstock into a continuous phase autoclave against syngas pressure under steady state conditions. During the solvent screening, it was realized that acetamide was not readily dissolved in ethyl acetate. Furthermore, acetamide reacted with dicobalt octacarbonyl/ethyl acetate solution to form a precipitated adduct at room temperature. To overcome these problems, a dual liquid feed stream system was designed to facilitate two stable feed solutions. In the catalyst solution (feed stream 1), it contained dicobalt octacarbonyl and phenylacetaldehyde in ethyl acetate. The acetamide, in a separated stream (feed stream 2), was in a solution of ethyl acetate with a minimum amount of methanol co-solvent. Methanol was required to keep acetamide in ethyl acetate solution. As the result, both feed stream solutions were considered stable at room temperature.

Several important reaction features are identified below:

(1) In the batch process, over 80% yields at 80°C reaction temperature and a much lower yield at 120°C were observed.

(2) DIPHOS appeared to be a good ligand in complexing with cobalt carbonyl to form a stable catalyst. A 98% of cobalt recovery in the homogeneous solution was achieved.

(3) The reaction can be carried out in a continuous phase reactor. Feeding two separated streams of homogeneous catalyst and acetamide solutions had been demonstrated.

(4) Under the steady state, a 50% yield to N-acetyl-beta-phenylalanine at 80°C was observed. At higher temperature, the reaction was less selective and produced significant amount of undesired byproducts.

4. Conclusion

The amidocarbonylation technology for making aspartame intermediate, N-acetyl-beta-phenylalanine, from phenylacetaldehyde, acetamide and carbon monoxide/hydrogen has been developed. It was essential to select the optimal reaction temperature and suitable ligand in order to achieve high product yield and catalyst recovery. The feasibility of using a continuous phase operation with a duel feed stream system was demonstrated.

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