Organic Process Research & Development **2004**, *8,* 781−787

Synthesis of the Intermediate of Gemifloxacin by the Chemoselective Hydrogenation of 4-Cyano-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine. Part 1. Screening of Metal Catalysts

Hyun Kuk Noh,[†] Jae Sung Lee,[†] Yeongdae Kim,[‡] Gyohyun Hwang,[‡] Jay Hyok Chang,[§] Hyunik Shin,[§] Do Hyun Nam,[§] and Kyung Hee Lee*[,†]

Department of Chemical Engineering and School of Environmental Engineering, Pohang University of Science and Technology (POSTECH), San 31 Hyoja-dong, Pohang 790-784, Korea; Corporate R&D, LG Chemical Ltd., 104-1, Moonji-dong, Yusong-gu, Daejon, 305-380, Korea; and Chemical Development Division, LG Life Sciences, Ltd./R&D, 104-1, Moonji-dong, Yusong-gu, Daejon 305-380, Korea

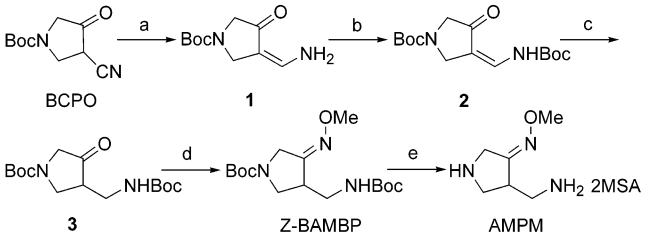
Abstract:

A novel synthetic route was devised for 4-aminomethyl-3-*Z*-methoxyiminopyrrolidine methanesulfonate (AMPM), the key intermediate of gemifloxacin, based on chemoselective hydrogenation of the cyano group in 4-cyano-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (CMBP) with minimum reduction of the methyloxime group employing (*t*-Boc)$_2$O (BOC) as in situ protecting agent. Over Raney nickel or cobalt catalysts, without in situ BOC protection of amine, the side reaction to 4-aminomethyl-3-amino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (AABP) was extensive by simultaneous hydrogenation of the methyloxime and cyano groups in CMBP, resulting in over-reduction of the desired intermediate, 4-aminomethyl-3-*Z*-methoxyimino 1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP) all the way to AABP. When in situ BOC protection was performed, the selectivity to the desired 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-BAMBP) rose to as high as 91% over Raney cobalt by suppressing the over-reduction of *Z*-AMBP to AABP. On the basis of these observations, a CMBP hydrogenation process over Raney cobalt was proposed. Among noble metal catalysts, only Pd was found to show a high activity. Over Pd catalyst, 4-cyano-3-amino-1-(*N*-*tert*-butoxycarbonyl)-3,4-pyrroline (CABP) was found to be a major byproduct, while the formation of AABP or 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-(*N*-*tert*-butoxycarbonyl)amino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (BABABP) was greatly suppressed. The byproduct CABP formed by hydrogenolysis of the methyl group in the methyloxime group in CMBP could be recycled to the original substrate, 1-(*N*-*tert*-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO) by an acid-catalyzed hydrolysis.

1. Introduction

4-Aminomethyl-3-*Z*-methoxyiminopyrrolidine (AMP) and its methanesulfonate salt (AMPM) are key intermediates in synthesizing gemifloxacin. Gemifloxacin (Factive) is a novel quinolone antibacterial drug developed by the LG Life Science Co. and approved by the U.S. Food and Drug Administration (FDA) in 2003. The drug possesses extremely potent antimicrobial activity against Gram-positive organisms and shows an excellent in vivo and in vitro efficacy and pharmacokinetic profile.[1−5]

Scheme 1. **Current process for the synthesis of 4-aminomethyl-3-*Z*-methoxyiminopyrrolidine methanesulfonate (AMPM)[a]**



[a] Conditions: reagent: (a) Raney Ni, H_2, IPA−H_2O, 40 °C; (b) (*t*-Boc)$_2$O, KOH, DME−H_2O, 0 °C; (c) Pd/C, H_2, THF−H_2O, room temperature; (d) $MeONH_2$·HCl, NaOAc, EtOH−THF, 40 °C; (e) methanesulfonic acid, MeOH, 0 °C.[6,7]

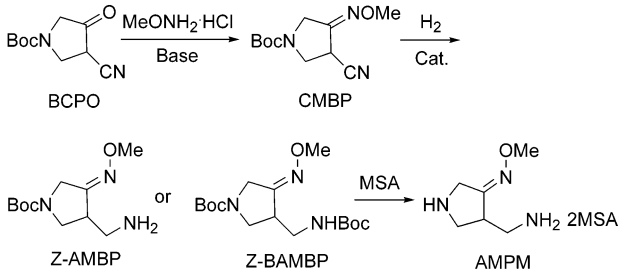
At present, AMPM is manufactured by a five-step process starting from 1-(*N*-*tert*-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO) (Scheme 1).[6,7] Hydrogenation of BCPO over Raney nickel catalyst yields mainly 1-(*N*-*tert*-butoxycarbonyl)-4-aminomethylene-pyrrolidine-3-one (**1**) by selective hydrogenation of the cyano group with subsequent double bond migration. Consequently, the enamine group should be protected (and activated) by (*t*-Boc)$_2$O (BOC) in a strong alkali medium to give 1-(*N*-*tert*-butoxycarbonyl)-4-(*N*-*tert*-butoxycarbonyl)aminomethylene-pyrrolidine-3-one (**2**) for subsequent hydrogenation of the double bond over Pd/C. The final product, AMPM, can be produced without difficulty by introducing the methyloxime group on the ketone group in 1-(*N*-*tert*-butoxycarbonyl)-4-(*N*-*tert*-butoxycarbonyl)ami-

* To whom correspondence should be addressed. Telephone: 82-54-279-2263. Fax: 82-54-279-5528. E-mail: kyunglee@postech.ac.kr.
[†] Pohang University of Science and Technology (POSTECH).
[‡] LG Chemical Ltd..
[§] LG Life Sciences, Ltd./R&D.

(1) Oh, J. I.; Paek, K. S.; Ahn, M. J.; Kim, M. Y.; Hong, C. Y.; Kim, I. C.; Kwak, J. H. *Antimicrob. Agents Chemother.* **1996**, *40*, 1564.
(2) Hong, C. Y.; Kim, Y. K.; Chang, J. H.; Kim, S. H.; Choi, H.; Nam, D. H.; Kim, Y. Z.; Kwak, J. H. *J. Med. Chem.* **1997**, *40*, 3584.
(3) Hong, C. Y.; Kim, Y. K.; Kim, S. H.; Chang, J. H.; Choi, H.; Nam, D. H.; Kim, A. R.; Lee, J. H.; Park, K. S. U.S. Patent 5,633,262, 1998.
(4) Hong, C. Y.; Kim, Y. K.; Kim, S. H.; Chang, J. H.; Choi, H.; Nam, D. H.; Kim, A. R.; Lee, J. H.; Park, K. S. U.S. Patent 5,869,670, 1999.
(5) Hong, C. Y. *Farmaco* **2001**, *56*, 41.
(6) Moon, K. Y.; Kim, W. S.; Lee, T. H.; Chang, J. H. U.S. Patent 6,307,059, 1999.
(7) Grinter, T. J.; Howie, S. WO 0117961, 2000.

10.1021/op049913u CCC: $27.50
Published on Web 09/03/2004

Scheme 2. **Novel process for synthesizing 4-aminomethyl-3-*Z*-methoxyiminopyrrolidine methanesulphonate (AMPM)**



nomethylpyrrolidine-3-one (**3**) and subsequent deprotection with MSA.

Many attempts have been made for the direct chemoselective full hydrogenation of the cyano group in BCPO to the aminomethyl group without much success thus far. The reason for the only partial hydrogenation of the cyano group in BCPO is not clear yet, but it may be due to the highly stable six-membered ring structure of 1-(*N*-*tert*-butoxycarbonyl)-4-aminomethylene-pyrrolidine-3-one by intramolecular hydrogen bonding between the hydrogen atom in the aminomethylene group and the oxygen atom in the ketone group. This partial hydrogenation is the major reason for the requirement of two hydrogenation steps and BOC protection step for transformation of the cyano group to the aminomethyl group.

If we could reduce the number of these reaction steps, the overall AMPM process would become greatly simplified, resulting in an improved efficiency and a reduced production cost. In search for this type of improved process for AMPM manufacture, we have invented a novel process which comprises only one hydrogenation step (Scheme 2). In this new process, the methyloxime group is introduced first, yielding 4-cyano-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)-pyrrolidine (CMBP), and this compound is subjected to hydrogenation and subsequent deprotection with MSA to complete a three-step process including a single hydrogenation step.

There exists, however, a great challenge in this new process that the methyloxime group in CMBP is also apt to be hydrogenated over ordinary hydrogenation catalysts as well as the cyano group, and it is therefore expected that the chemoselectivity toward 4-aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP) or 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-BAMBP) may be low.[8]

Actually hydrogenation of oximes and *O*-alkyloximes proceeds in a very similar way to that of nitriles.[9,10] Like nitrile hydrogenation, amines are produced in the hydrogenation of oximes and *O*-alkyloximes mainly via imine intermediate which is formed by hydrogenolysis of the *N*−O bond. The imine intermediate is responsible for various side reactions; higher amines may be formed by coupling between the produced amine and the imine in the same way as in the nitrile hydrogenation. In the presence of water, hydrolysis of imines may lead to formation of carbonyl compounds which can be reduced further to alcohols.[8,9,11−12] Additionally, hydroxylamines and *O*-alkylhydroxylamines can be produced in the hydrogenation of oximes and *O*-alkyloximes especially over platinum catalyst.

Thus, we can expect that countless side products may be generated in CMBP hydrogenation and that achieving a high chemoselectivity toward *Z*-AMBP or *Z*-BAMBP would be a great challenge. There has been almost no research on the chemoselective hydrogenation of the cyano group in a α-methoxyiminonitrile compound keeping methyloxime intact. This contribution deals with heterogeneous catalytic chemoselective hydrogenation of CMBP in liquid phase with BOC as an in situ protecting agent of amine that can be applied to the manufacture of 4-aminomethyl-3-*Z*-methoxyiminopyrrolidine methanesulfonate (AMPM), the novel pharmaceutical intermediate especially for gemifloxacin.

Table 1. **Operating conditions of HPLC**

column	symmetry C18, 5.0 um, 4.6 mm × 150 mm
mobile phase	A: acetonitrile (HPLC grade, Baker)
	B: water (0.1% trifluoroacetic acid)
total flow rate	1.0 mL/min
detection (UV)	197 nm
column temperature	ambient

Table 2. **Gradient elution composition of HPLC (A: acetonitrile, B: water (0.1% trifluoroacetic acid))**

time	% A	% B
0	20	80
3	50	50
5	50	50
11	70	30
13	100	0
19	100	0
21	20	80
24	20	80

2. Experimental Section

2.1. Analytical Methods. The reaction mixtures were analyzed in the course of the reaction with HPLC (Waters 1525) with a UV detector (Waters 2487). The operating conditions and gradient elution composition of HPLC are shown in Tables 1 and 2. Reaction products such as 4-aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP), 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-BAMBP), 4-cyano-3-amino-1-(*N*-*tert*-butoxycarbonyl)-3,4-pyrroline (CABP), 4-aminomethyl-3-amino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (AABP), and 4-(*N*-*tert*-butoxycarbonyl)aminomethyl-3-(*N*-*tert*-butoxycarbonyl)amino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (BABABP) were identified by HPLC and LC−MS (Finnegan LCQ(067-MS-05))

(8) Bellefon, C.; Fouilloux, P. *Catal. Rev. Sci. Eng.* **1994**, *36*, 459.
(9) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons: New York, 2002.
(10) Rylander, P. N. *Hydrogenation Methods*; Academic Press Inc.: New York, 1985.
(11) Odo, K.; Ichikawa, E.; Shirai, K.; Sugino, K. *J. Org. Chem.* **1957**, *22*, 1715.
(12) Albert, H.; Taguchi, H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1629.

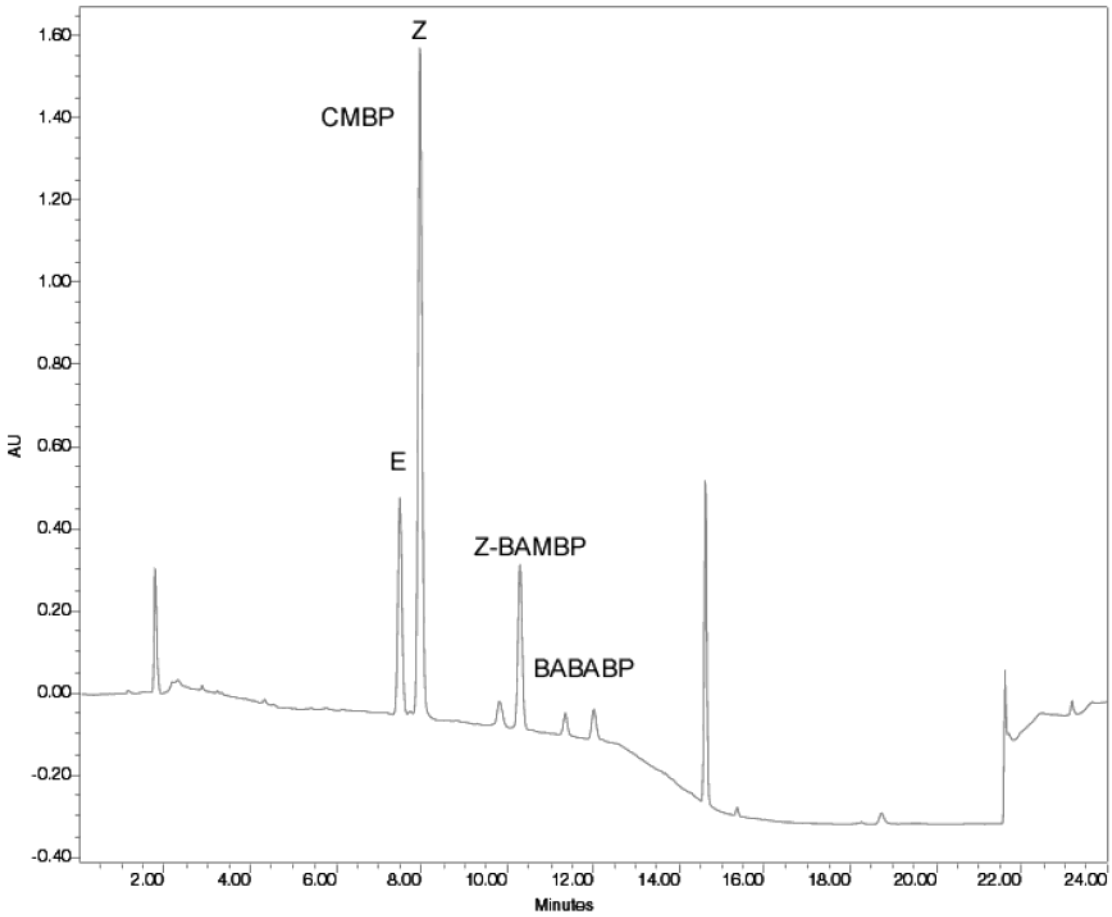


Figure 1. **A sample chromatogram in CMBP hydrogenation with in situ BOC protection.**

Table 3. **List of the relative HPLC retention times for the compounds in the report**

compound	retention time [min]
CMBP	*E*-isomer: 7.5, *Z*-isomer: 8.1
AABP	1.21
BABABP	11.3
Z-AMBP	3.01
Z-BAMBP	10.5
CABP	5.4
BCPO	4.37−6.33 (broad)
BOC	12.2

by comparison with the standard samples obtained from the LG Life Science Co. Because *Z*-isomer is the desired product, the selectivity to *Z*-AMBP or *Z*-BAMBP was calculated on the basis of the amount of *Z*-isomers.[13] A list of the relative HPLC retention times for the compounds in the report is shown in Table 3 and a sample chromatogram included in Figure 1.

2.2. Preparation of 4-Cyano-3-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (CMBP). CMBP, the substrate for chemoselective hydrogenation, was prepared as follows: 5.25 g of 1-(*N*-*tert*-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO) received from the LG Life Science Co. was dissolved in 50 mL of MeOH (Baker) and 1.2 equiv of pyridine (99%, Aldrich) was introduced thereto as a base. Without bases, both reaction rate and CMBP yield were found to be lower than in the presence of base. Subsequently 1.2 equiv of $MeONH_2$·HCl (98%, Aldrich) was added, and the mixture was agitated at ambient temperature for about 5 h to obtain CMBP by introducing the methyloxime group.

After completion of the reaction, 25 mL of water was added to the solution, and MeOH was removed in vacuo. The 25 mL of CH_2Cl_2 (Baker) was poured into the obtained solution, and the layers were separated. The organic layer was thoroughly washed, first with saturated $NaHCO_3$ (2 × 25 mL) and then with saturated NaCl solution (2 × 25 mL) thoroughly, and CH_2Cl_2 was removed by vacuum distillation to obtain yellowish, oily CMBP with 95% yield. From HPLC analysis, the product was found to consist of *E*- and *Z*-isomers with a 1:4 ratio.

Spectral data for CMBP: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (2H, s), 3.99 (0.8H, s), 3.96 (2.2H, s), 4.15−3.95 (1H, hidden proton), 3.86 (1H, broad t, J = 7.2 Hz), 3.71 (1H, dd, J = 7.2, J_2 11.2 Hz), 1.5 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.6, 116.1, 81.2, 63.0, 47.6, 45.2, 31.6, 28.3; IR 2249.8, 1694.3 cm^{-1}.

2.3. Liquid-Phase Hydrogenation of CMBP To Prepare 4-Aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-AMBP) and 4-(*N*-*tert*-Butoxycarbonyl)aminomethyl-3-*Z*-methoxyimino-1-(*N*-*tert*-butoxycarbonyl)pyrrolidine (*Z*-BAMBP). Raney-type

(13) Over both Raney metal and Pd catalysts, the hydrogenation rates of *Z*- and *E*-CMBP were actually same.

Table 4. **Liquid-phase CMBP hydrogenation over Raney-type catalyst system: without in situ BOC protection of amine produced[a]**

catalyst	time [h]	conversion of CMBP [%]	selectivity to *Z*-AMBP [%]
Raney Ni	1	31	27
	7	98	17
Raney Ni (Mo)[b]	1	29	38
	7	95	20
Raney Co	1	2	87
	7	13	76
Raney Co[c]	1	11	79
	7	68	58
Raney Co (Ni, Cr)[d]	1	9	83
	7	56	58
Raney Cu	1	0	–
	7	0	–

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; IPA 30 mL; H_2O 20 mL; Raney metal 50 mol % of CMBP; H_2 500 psi; $T = 313$ K. [b] Mo (2.5 wt %)-doped Raney nickel; 20 mol % of CMBP. [c] Raney cobalt of 300 mol % of CMBP. [d] Ni-, Cr-doped Raney cobalt (Co: 94.8 wt %, Ni: 2.9 wt %, Cr: 2.3 wt %).

catalysts that are immersed in water were purchased from Grace Co. and utilized as received unless otherwise stated. The composition of Ni- and Cr-doped Raney cobalt analyzed by ICP was 94.8 wt % Co, 2.9 wt % Ni, and 2.3 wt % Cr. Noble metal catalysts such as Pd, Pt, Ru, and Rh on supports and their precursors were purchased from Aldrich. Most of the Pd catalysts were used as received, but if necessary, they were utilized after reduction in H_2 stream at 473 K for 1−2 h. Supported Pt, Ru, and Rh catalysts were activated in H_2 stream at 573 K for 3 h before CMBP hydrogenation.

The liquid-phase hydrogenation of CMBP was conducted in a 100-mL Hastelloy-C autoclave reactor (Autoclave Engineers). Typically CMBP, a solvent, a catalyst, and an additive, e.g., (*t*-Boc)$_2$O (99%, Aldrich) were introduced in the reaction vessel. Typical solvent was 30 mL of isopropyl alcohol (IPA) and 20 mL of water. After the purge of the reactor with hydrogen twice, the reactor was pressurized to 60−500 psi with H_2. The reaction was conducted typically at 283−323 K with agitation at 1000 rpm to minimize the external mass transfer limitation.

Spectral data for *Z*-AMBP: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (2H, broad, s), 3.89 (3H, s), 3.87 (1H, broad, s), 3.77 (1H, broad, m), 3.36 (1H, broad, s), 2.89 (2H, broad, s), 1.49 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 151.0, 76.6, 58.7, 45.1, 44.5, 42.9, 40.8, 25.0; IR 1694.5 cm $^{-1}$.

Spectral data for *Z*-BAMBP: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (1H, broad, N<u>H</u>CO$_2$-*t*-Bu, s), 4.08 (2H, s), 3.81 (3H, s), 3.75 (1H, broad t, $J = 8.0$ Hz), 3.50 (1H, broad, s), 3.41 (1H, broad, s), 3.28 (1H, broad, s), 3.00 (1H, broad t, $J = 8$ Hz), 1.40 (18H, s); IR 1709.3, 1687.6 cm^{-1}.

3. Results and Discussion

3.1. Raney-Type Catalyst System. *3.1.1. Hydrogenation Without in Situ BOC Protection.* In Table 4, the results of hydrogenation with Raney-type catalysts are presented with no in situ protection of amine with BOC. When Raney nickel was employed as the catalyst, the CMBP conversion was very high, while the selectivity toward *Z*-AMBP was very poor. The major byproduct was 4-aminomethyl-3-amino-1-(*N-tert*-butoxycarbonyl)pyrrolidine (AABP) which was formed by complete reduction of the methyloxime group as well as the cyano group. The 2.5 wt % Mo-promoted Raney nickel increased the reaction rate greatly, and thus the catalyst loading was reduced to 20 mol % to obtain the data in Table 4. However, the selectivity to *Z*-AMBP was almost invariant.

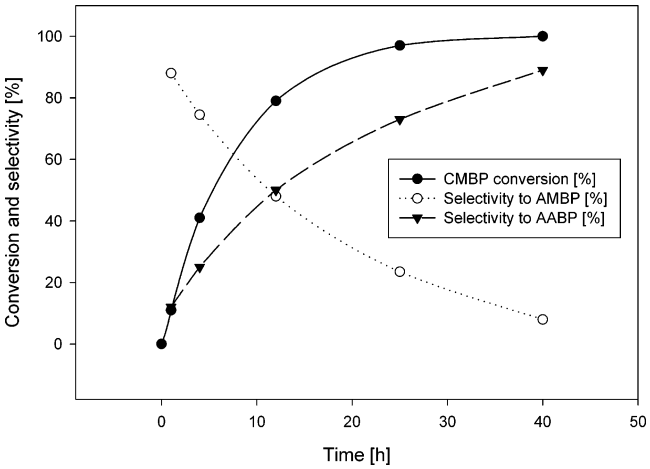


Figure 2. **CMBP hydrogenation without in situ BOC protection. Reaction conditions: $T = 313$ K, H_2 500 psi, IPA 30 mL, H_2O 20 mL, CMBP 0.5 mmol, Raney Cobalt (doped with Ni, Cr) 0.03 g.**

Among Raney-type catalysts, Raney cobalt showed the highest selectivity toward *Z*-AMBP, although the hydrogenation rate was very slow. When Raney cobalt catalysts were employed, AABP was also observed as the major byproduct as over Raney nickel. Doping Raney cobalt with Ni and Cr gave a dramatic increase in activity in comparison with undoped Raney cobalt, while the high selectivity to *Z*-AMBP was maintained almost the same. Raney Cu showed no activity at all in the hydrogenation of CMBP.

Representative time vs conversion and selectivity curves in CMBP hydrogenation over Raney Co (Ni, Cr) catalyst are shown in Figure 2. The drop of the selectivity to *Z*-AMBP with time was accompanied by the increase in the proportion of AABP. The reduction continued even after 100% conversion of CMBP, and the proportion of *Z*-AMBP decreased while that of AABP increased. These observations indicate that the formed *Z*-AMBP is further reduced by hydrogenation of the methyloxime group in *Z*-AMBP to the amine group.

On the basis of these observations, a hydrogenation pathway of CMBP without in situ BOC protection may be proposed as shown in Scheme 3. In this case, the pathway from CMBP to AABP via *Z*-AMBP is dominant. The reaction pathway could be more complex than this in a real situation, because there may exist various side reactions due to active species such as imine. However, other side products were found in negligible amounts, with the exception of the compounds specified in Scheme 3. Thus, AABP is expected to be formed via this serial-parallel hydrogenation pathway.

3.1.2. Effect of in Situ BOC Protection. To suppress the over-hydrogenation of *Z*-AMBP, CMBP hydrogenation with in situ protection of amine with BOC was carried out as shown in Table 5. In this case, the desired product was 4-(*N-tert*-butoxycarbonyl)aminomethyl-3-*Z*-methoxyimino-

Scheme 3. **CMBP hydrogenation pathway with no in situ protection over Raney cobalt catalyst**

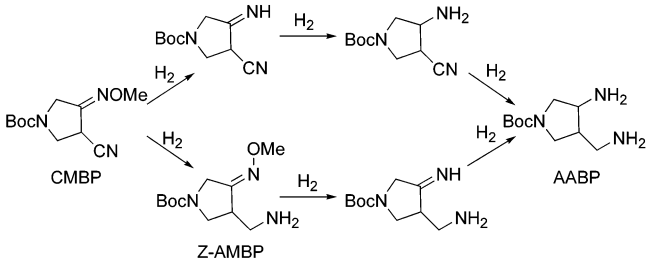


Table 5. **Liquid-phase CMBP hydrogenation over Raney-type catalyst system with in situ BOC protection[a]**

catalyst	conversion of CMBP [%]	selectivity [%]	
		Z-BAMBP	BABABP
Raney Ni	85	26	70
Raney Ni (Mo)[b]	81	32	63
Raney Co[c]	51	83	13
Raney Co (Ni, Cr)	40	86	10
Raney Co (Ni, Cr)[d]	34	87	10
Raney Co[c,e]	18	83	12
Raney Co (Ni, Cr)[e]	15	91	4
Raney Co (Ni, Cr)[f]	27	89	7
Raney Co (Ni, Cr)[g]	42	85	10

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; IPA 30 mL; H_2O 20 mL; BOC 4 equiv of CMBP; Raney metal 50 mol % of CMBP; H_2 500 psi; $T = 298$ K; time = 7 h. [b] 20 mol % of CMBP. [c] Raney cobalt 300 mol % of CMBP. [d] BOC 100 equiv. [e] IPA 40 mL + H_2O 10 mL. [f] $T = 278$ K. [g] $P = 1000$ psi.

1-(*N-tert*-butoxycarbonyl)pyrrolidine (*Z*-BAMBP), and the major byproduct was 4-(*N-tert*-butoxycarbonyl)aminomethyl-3-(*N-tert*-butoxycarbonyl)amino 1-(*N-tert*-butoxycarbonyl)-pyrrolidine (BABABP). When Mo-promoted Raney nickel was employed as a catalyst, the *Z*-BAMBP selectivity was 32% with in situ BOC protection. Note that the *Z*-AMBP selectivity was 20% at 7 h without the protection as shown in Table 4. When Ni-, Cr-promoted Raney cobalt catalyst was employed with in situ BOC protection, the selectivity toward *Z*-BAMBP increased greatly to as high as 91% with the much lower content of BABABP although CMBP conversion was reduced somewhat relative to the case with no in situ BOC protection.

The representative time vs conversion and selectivity curves over Ni-, Cr-doped Raney Co catalyst with in situ BOC protection are shown in Figure 3. It is evident that decrement of the selectivity of *Z*-BAMBP is much slower than that in Figure 2. Thus, *Z*-BAMBP is transformed into BABABP in a much lower rate with the in situ BOC protection than that without the protection. However, even though the amount of BOC was increased as high as 100 equiv relative to that of CMBP, the selectivity toward BABABP was almost invariant, indicating that 4 equiv of BOC was enough for the protection of *Z*-AMBP from further hydrogenation. From these observations, we can understand that in situ protection of the amine group in *Z*-AMBP with BOC hinders the serial hydrogenation of *Z*-AMBP to AABP and that adsorption of *Z*-AMBP via its amine group on the catalytic surface is responsible for the serial reaction. A plausible hydrogenation pathway of CMBP with in situ BOC

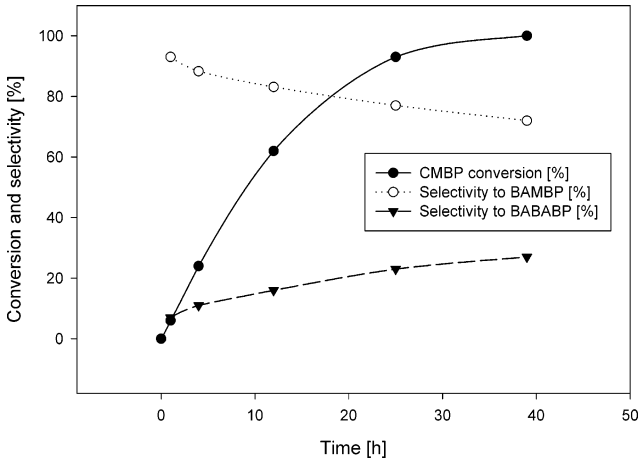
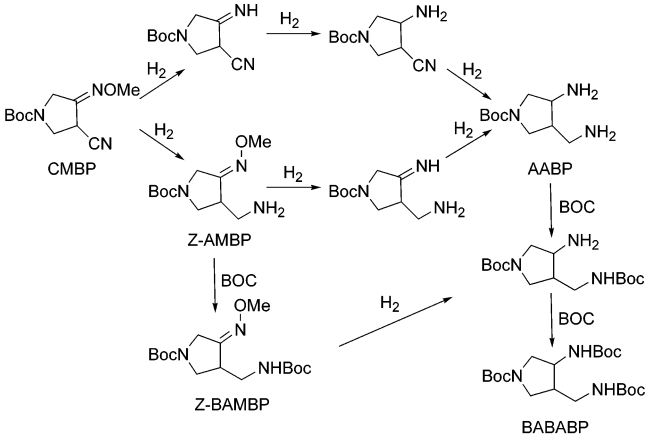


Figure 3. **CMBP hydrogenation with in situ BOC protection. Reaction conditions: $T = 298$ K, H_2 500 psi, IPA 30 mL, H_2O 20 mL, BOC 4 equiv of CMBP, CMBP 0.5 mmol, Raney Cobalt (doped with Ni, Cr) 0.03 g.**

Scheme 4. **CMBP hydrogenation pathway with in situ BOC protection over Raney cobalt catalyst**



protection is proposed on the basis of these observations in Scheme 4. In this scheme, the reaction pathway from CMBP to *Z*-BAMBP via *Z*-AMBP is dominant, and hydrogenation of *Z*-BAMBP to BABABP is negligible.

A certain amount of water was found to be essential for high rates in CMBP hydrogenation. The data in Table 5 were obtained with 30 mL of IPA and 20 mL of H_2O as solvent. As the volume of water was reduced to 10 mL with 40 mL of IPA, the rate decreased abruptly (seventh entry). It is known that carbonyl compound may be formed via hydrolysis of imine intermediate in nitrile or oxime hydrogenation in the presence of water. However, a few hydrolysis products were found, and the selectivity to *Z*-BAMBP was almost invariant with an increase in the amount of water. Therefore, the addition of a proper amount of water was found to be beneficial in view of the reaction rate with no significant side reaction caused by it. To achieve still higher selectivity to *Z*-BAMBP, reaction temperature (eighth entry), pressure (ninth entry), and organic solvents (not shown) were varied, but they gave no marked effects on the selectivity.

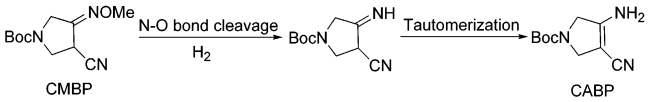
3.2. Pd Catalyst System. Liquid-phase CMBP hydrogenation over Pd catalysts was carried out using BOC as the in situ protecting agent (Table 6). The side reaction to 4-(*N-tert*-butoxycarbonyl)aminomethyl-3-(*N-tert*-butoxycarbonyl)-

Table 6. **Liquid-phase CMBP hydrogenation over Pd catalyst; screening test with various supported Pd catalysts with in situ BOC protection[a]**

		selectivity [%]		
catalyst	conversion of CMBP [%]	*Z*-BAMBP (or Z-AMBP)	CABP	BABABP (or AABP)
5% Pd/C	72	74	20	2
1% Pd/C	83	71	21	3
1% Pd/C[b]	78	61	22	9
1% Pd/C[c]	57	75	22	1
1% Pd/C[d]	85	70	23	3
5% Pd/Al_2O_3	67	73	23	2
1% Pd/C[e]	26	78	19	1

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; IPA 30 mL; H_2O 20 mL; BOC 4 equiv of CMBP; Pd 5 mol % of CMBP; H_2 500 psi; T = 298 K; Time = 7 h. [b] No BOC. [c] T = 278 K. [d] H_2 1000 psi. [e] IPA 45 mL, water 5 mL.

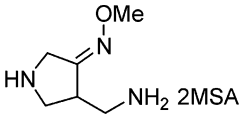
Scheme 5. **Proposed reaction pathway to CABP in hydrogenation of CMBP over Pd catalyst**



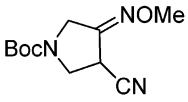
amino-1-(*N-tert*-butoxycarbonyl)pyrrolidine (BABABP) was suppressed to a great extent over Pd catalysts compared with Raney metal catalysts. However, over Pd catalysts, a new byproduct became the major byproduct that did not appear in CMBP hydrogenation over Raney nickel and Raney cobalt systems. This new byproduct was found highly stable and was not hydrogenated further over Pd catalyst. The new byproduct has been identified as 4-cyano-3-amino-1-(*N-tert*-butoxycarbonyl)-3,4-pyrroline (CABP), which is formed by hydrogenation of the methyloxime group in CMBP. The byproduct was converted to the initial starting substrate, 1-(*N-tert*-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO) when acid was added. The plausible reaction pathway of CMBP to CABP over Pd catalyst was proposed as in Scheme 5. First the N−O bond in CMBP is hydrogenolyzed, and the resulting imine intermediate is tautomerized to the enamine structure of CABP.

The transformation of CABP to BCPO in the presence of acid is considered to be owing to hydrolysis of CABP. Thus, it is known that imines are liable to be converted to ketones or aldehydes by hydrolysis in the presence of water,[9,11−13] and the acid added may take part in the hydrolysis reaction as catalyst to change CABP to its imine structure. The stability of CABP may probably come from a six-membered ring hydrogen-bonding structure like the one in 1-(*N-tert*-butoxycarbonyl)-4-aminomethylene-pyrrolidine-3-one(**1**).

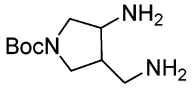
Scheme 6. **Glossary**



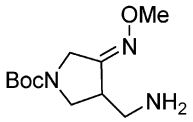
: 4-aminomethyl-3-Z-methoxyiminopyrrolidine methanesulfonate (AMPM)



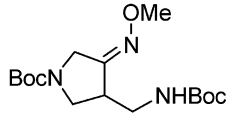
: 4-cyano-3-methoxyimino-1-(N-t-butoxycarbonyl)-pyrrolidine (CMBP)



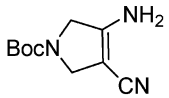
:4-aminomethyl-3-amino-1-(N-t-butoxycarbonyl)-pyrrolidine (AABP)



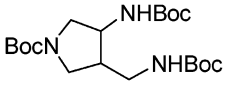
:4-aminomethyl-3-Z-methoxyimino 1-(N-t-butoxycarbonyl)-pyrrolidine (Z-AMBP)



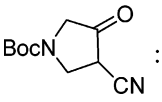
:4-(N-t-butoxycarbonyl)-aminomethyl-3-Z-methoxyimino-1-(N-t-butoxycarbonyl)-pyrrolidine(Z- BAMBP)



: 4-cyano-3-amino-1-(N-t-butoxycarbonyl)-(3,4)-pyrroline (CABP)



:4-(N-t-butoxycarbonyl)-aminomethyl-3-(N-t-butoxycarbonyl)-amino-1-(N-t-butoxycarbonyl)- pyrrolidine (BABABP)



:1-(N-t-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO)

Table 7. **Liquid-phase CMBP hydrogenation over noble metal catalyst systems[a]**

catalyst	conversion of CMBP [%]	selectivity to *Z*-BAMBP [%]
1 wt % Pt/C	21	72
PtO_2	28	69
5 wt % Ru/Al_2O_3	18	73
5 wt % Ru/C	20	75
5 wt % Rh/Al_2O_3	35	60

[a] The following reaction conditions were used unless otherwise stated. CMBP 0.5 mmol; IPA 30 mL; H_2O 20 mL; BOC 4 equiv of CMBP; metallic species 5 mol % of CMBP; H_2 500 psi; T = 298 K; time = 24 h.

Similar to the Raney metal catalytic system, a certain amount of water was also found essential for an acceptable reaction rate over Pd catalyst system in CMBP hydrogenation, and the selectivity to *Z*-BAMBP was not affected by water added. Reduction in water content of solvent decreased the reaction rate significantly (seventh entry of Table 6). In anhydrous conditions, the reaction did not proceed significantly.

At 100% conversion of CMBP, the selectivity to *Z*-BAMBP over 1% Pd/C was about 65% with in situ BOC protection. Various attempts were made to increase the selectivity by suppressing side reaction to CABP such as a change of reaction temperature, pressure, and organic solvents, but they were of no avail. However, Pd catalyst systems gave good *Z*-BAMBP yields with a higher reaction rate than Raney cobalt catalysts. Furthermore, considering CABP could be recycled back to BCPO, the advantage of Pd catalyst systems becomes even greater.

3.3. Other Noble Metal Catalysts. Pt, Ru, and Rh catalysts were tried as catalysts for CMBP hydrogenation. However, the reaction rate was poor with a low selectivity to *Z*-BAMBP (Table 7), and they did not show better results than Pd. It was remarkable that CABP was also found as the main side product over these catalysts as it was in the Pd catalytic system, suggesting these noble metals behave in a similar way in the hydrogenation of CMBP.

4. Conclusions

Over Raney nickel or cobalt catalysts, without in situ BOC protection of initially formed amine, the side reaction to AABP by hydrogenation of the methyloxime group as well as the cyano group in CMBP was extensive, together with serial hydrogenation of *Z*-AMBP to AABP. When in situ BOC protection was performed, the selectivity to *Z*-BAMBP rose as high as 91% over Raney cobalt by suppressing the over-reduction of *Z*-AMBP to AABP. Among noble metal catalysts, Pd showed reasonable activity and selectivity. CABP was found to be a major byproduct over Pd catalyst, while the formation of AABP or BABABP was substantially reduced. CABP appeared to be formed by hydrogenolysis of the methyl group in the methyloxime group in CMBP and could be recycled to the original substrate, 1-(*N*-*tert*-butoxycarbonyl)-4-cyano-pyrrolidine-3-one (BCPO) by an acid-catalyzed hydrolysis.

Acknowledgment

We are grateful for the financial support provided by the Brain Korea 21 project of the Ministry of Education in 2003, Korea, and by the LG life Science Co., Korea.

Received for review April 28, 2004.

OP049913U