NEW EFFICIENT SYNTHESIS OF ETHYL 2,3-CYCLOALKEN-OPYRIDINE-4-CARBOXYLATE

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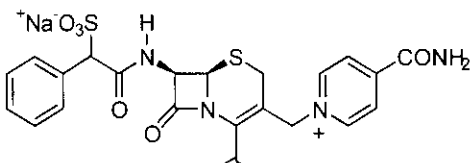
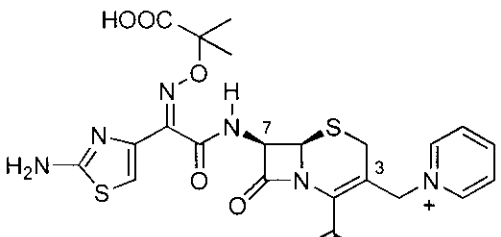
Abstract- Ethyl 2,3-cycloalkenopyridine-4-carboxylates (**6a-c**) from 2-chlorocycloalkanone and ethyl cyanoacetate have been synthesized in 4 steps with overall 68, 68, 25% isolation yield for cyclopenteno (**6a**), cyclohexeno (**6b**) and cycloheptено (**6c**) derivatives, respectively. Pyridine ring is constructed from 1,5-dicarbonyl precursor and nitrogen source. In order to prepare 1,5-dicarbonyl precursor, malonic ester synthesis is used. Alkylation of 2-chlorocycloalkanone (**1a-c**) with ethyl cyanoacetate affords ethyl cyano-(2-oxocycloalkanoyl)acetate (**3a-c**). Second alkylation of **3a-c** with allyl bromide gives ethyl 2-cyano-2-(2-oxocycloalkanoyl)-4-pentenoate (**4a-c**). Ozonolysis of olefins (**4a-c**), and continuously pyridine ring formation with hydroxylamine provides ethyl 2,3-cycloalkenopyridine-4-carboxylate *N*-oxide (**7a-c**). This *N*-oxide is easily reduced with phosphorous trichloride in chloroform. Replacement of hydroxylamine hydrochloride by ammonium formate as a nitrogen source reduced one step in this process, directly forming 2,3-cycloalkenopyridine-4-carboxylate.

INTRODUCTION

Our continuing interest[1] in developing new cephalosporins, which have good activity including against MRSA strains,[2] absorption, and long half-life *in vivo*, has led us to synthesize 2,3-cycloalkenopyridine-4-carboxylic acid derivatives. The derivatives of pyridinecarboxylic acid derivatives have been found in nature as alkaloids,[3] vitamines and enzyme cofactors.[4] Due to their biological activities, they are considered as important compounds. In addition, cycloalkenopyridines and pyridinecarboxylic acid derivatives of cephalosporins such as cefpirome[5] and cefsulodin[6] have a good antibacterial activity and are on the market.

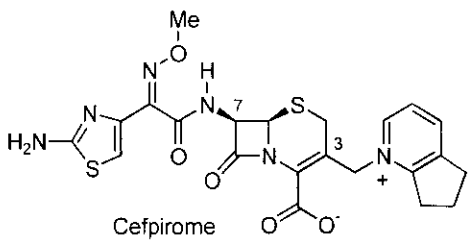


Cefsulodin

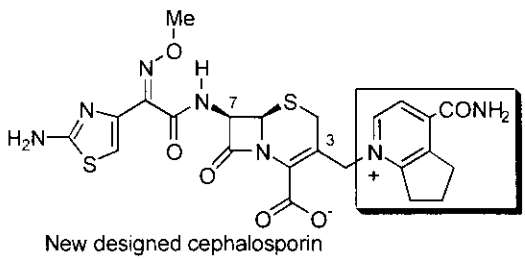


Ceftazidime

One of cephalosporins on the market which has pyridinium salt at the C-3 position is ceftazidime having a good biological activity.[7] The introduction of cyclopenteno group on the C-2 and C-3 positions like cefpirome as well as carbamoyl group on the C-4 of pyridine like cefsulodin was thought to be exhibited better antibacterial activities.



Cefpirome



New designed cephalosporin

The desire of new cephalosporin prompted us to design the efficient synthetic route for ethyl 2,3-cycloalkenopyridine-4-caboxylate. Several reports for the synthesis of alkyl 2,3-cycloalkenopyridine-4-carboxylate have appeared. For example, methyl 2,3-cyclohexenopyridine-4-carboxylate (methyl ester of **6b**) was first synthesized in 5 steps with low yield by Isler *et al.* in 1955.[8] In 1958, Libermann *et al.* reported synthesis of ethyl 2,3-cyclopentenopyridine-4-carboxylate (**6a**) using Isler's method with better yield but only 6.9% overall yield.[9] The exemplified two method involved reduction process of 4-carboalkoxy-6-chloro-2,3-cycloalkenopyridine using Pd/C in final step, which was prepared by the chlorination

of 6-hydroxy-2,3-cycloalkenopyridine-4-carboxylic acid with $POCl_3$. Lowe III *et al.* in 1989 reported synthesis of cyclopenteno compound (**6a**) in 9.5% overall yield with minor modification of dehydroxylation.[10] Herein we report an alternative efficient route to ethyl 2,3- cycloalkenopyridine-4-carboxylate (**6**).

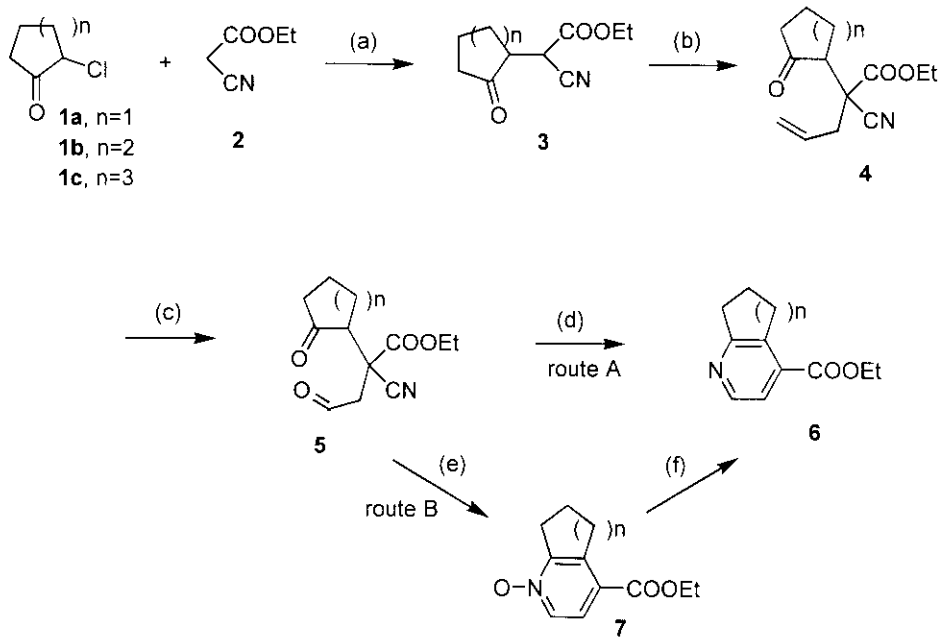
RESULTS AND DISCUSSION

While 2,3-cyclohexenopyridine is obtained through hydrogenation of quinoline, other 2,3-cycloalkenopyridines were not accessible until a synthetic process developed by Beschke.[11] A new synthesis involved a heterocyclic gas-phase reaction of cycloalkanones with alkenones and ammonia. Although the yield of this process is high, (usually 60-90%), there are lots of difficulties for using this process at laboratory. In order to synthesize 2,3-cycloalkenopyridine-4-carboxylate, we developed a new synthetic route using malonic ester synthesis. In our knowledge, there has been no example of the synthesis of a pyridine ring using malonic ester synthesis. We choose the ethyl cyanoacetate instead of malonic ester because of good leaving ability of CN group. This process contains four steps. 1) Monoalkyation of 2-chlorocycloalkanones with ethyl cyanoacetate affords compounds (**3a-c**) in good yields. 2) Allylation of **3a-c** with allyl bromide gives **4a-c**. 3) 1,5-Dicarbonyl compounds (**5a-c**) are obtained by ozonolysis of olefin compounds (**4a-c**). 4) Pyridine ring formation is undergone by the reaction of 1,5-dicarbonyl compounds (**5a-c**) with ammonium formate as nitrogen source. This process provides little different results by the size of rings. Thus, in this report, we discuss the first general common preparation of three different 2,3-cycloalkenopyridine-4-carboxylates, then report the different results of each other.

The starting materials for the synthesis (Scheme 1) are ethyl cyanoacetate and 2-chlorocycloalkanone. The alkylation of 2-chlorocycloalkanone with cyanoacetate in the presence of potassium *t*-butoxide at 0 °C for 3 h provides ethyl cyano-(2-oxocycloalkyl)acetate in 90, 93, 58% yields for cyclopentanone, cyclohexanone and cycloheptanone, respectively. The use of potassium *t*-butoxide gave better results than other weak base such as sodium methoxide or ethoxide. Second alkylation of ethyl cyano-(2-oxocycloalkyl)acetate with allyl bromide was done in the presence of potassium *t*-butoxide in refluxing THF for 3 h, providing **4a-c** in 87, 85, 54% yields, respectively. Allyl compounds (**4a-c**) underwent an ozonolysis reaction in dichloromethane, giving aldehydes (**5a-c**) in higher than 94% yields. The construction of pyridine ring was carried out with hydroxylamine hydrochloride in ethanol. When hydroxylamine hydrochloride was used as a nitrogen source, we obtained *N*-oxide of 2,3-

cycloalkenopyridine-4-carboxylate (**7**) (route B in Scheme 1). This *N*-oxide group was easily removed by the treatment of PCl_3 in refluxing chloroform for 30 min. When we used ammonium formate instead of using hydroxylamine hydrochloride as a nitrogen source, ethyl 2,3-cycloalkenopyridine-4-carboxylate (**6**) was directly obtained, consequently reducing one step in this process (route A in Scheme 1). In case of using ammonium acetate instead of ammonium formate as a nitrogen source, the reaction condition was not easily controlled and the compound (**6**) could not be separated from the reaction mixture.

Scheme 1.



[a]Reagents and Reaction conditions: (a) *t*-BuOK, THF, 0 °C, 3 h, 90% (n=1), 93% (n=2), 58% (n=3); (b) allyl bromide, THF, reflux, 3 h, 87, 85, 54%; (c) O_3, CH_2Cl_2, -78 °C, 20 min, Me_2S, 90, 94, 96%; (d) HCO_2NH_4, MeOH, rt, 45 min, 97, 91, 84%; (e) $NH_2OH{\cdot}HCl$, EtOH, reflux, 30 min, 78, 75, 81%; (f) PCl_3, $CHCl_3$, reflux, 30 min, 91, 84, 98%.

Synthesis of ethyl 2,3-cyclopentenopyridine-4-carboxylate (6a)

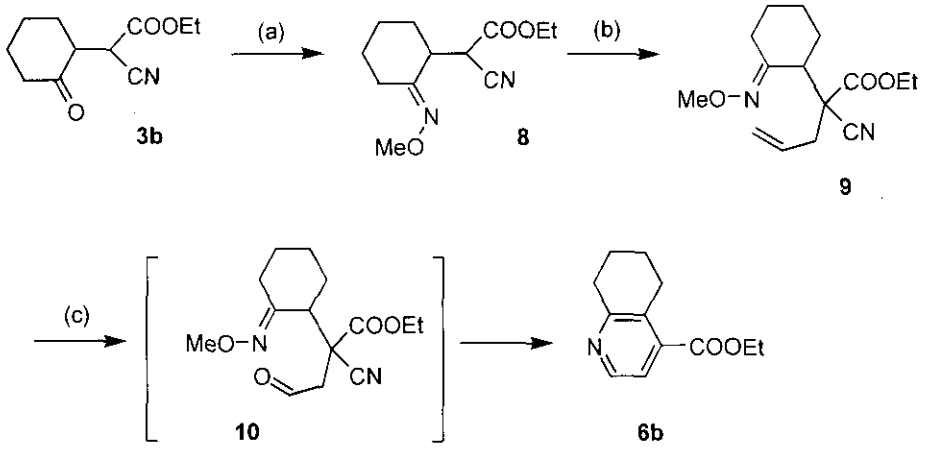
According to the process in Scheme 1, **6a** was synthesized very efficiently with high yields in each steps. First, we used hydroxylamine hydrochloride in pyridine ring formation step, then

N-oxide (**7a**) was formed, and then one more step was required to remove *N*-oxide. Later ammonium formate has been used instead of hydroxylamine hydrochloride provided higher yield with one-step less. The overall isolation yield of four steps was 68%.

Synthesis of ethyl 2,3-cyclohexenopyridine-4-carboxylate (6b)

Compounds (**3a-c**) are diastereomers. In case of **3a**, we could not separate diastereomers each other. A mixture of cyclohexylacetate diastereomers (**3b**) was separated into solid and liquid phase by standing for two weeks at room temperature. The solid product is one of diastereomer in pure form, showing the ^{1}H NMR of the methine proton next to cyano group at δ 3.55 (d, 1H, J = 4.70 Hz). On the other hand, the liquid product contains mixture of two diastereomers in the ratio of 1.5 to 1, showing the ^{1}H NMR of the methine proton next to cyano group at δ 3.93 (d, 1H, J = 6.32 Hz) as well as 3.55 (d, 1H, J = 4.70 Hz). In the beginning of this experiment, due to shortage of experience, transformation from **3b** to **4b** by second alkylation with allyl bromide gave low yield, while transformation from **3a** to **4a** provided high yield, Later, when we have had enough experience, we synthesized **6b** with the same overall yield (68%) as **6a**. Meanwhile we designed another route to synthesize **6b** in the Scheme 2.

Scheme 2.



[a]Reagents and Reaction conditions: (a) $NH_2OMe{\cdot}HCl$, pyridine, MeOH, rt, 1 h, 95%; (b) allyl bromide, THF, reflux, 2 h, 89%; (c) O_3, CH_2Cl_2, -78 °C, 30 min, Me_2S, 52%.

The key modification is the protection of carbonyl group of compound (**3b**) with *O*-methylhydroxylamine. The alkylation of protected ketone (**8**) with allyl bromide underwent well in

89% yield. In addition, the ozonolysis product (**10**) could not be isolated and provided a desired product (**6b**) during the removal of solvent *in vacuo* after workup. Eventually the introduction of methoxylamime hydrochloride to carbonyl group acts as a nitrogen source.

Synthesis of ethyl cycloheptenopyridine-4-carboxylate (6c)

We have obtained the compound (**6c**) with lower overall yield (25%) than **6a-b**. The reported yield for **6c** is obtained from single experiment without optimization.

In summary, the above results emphasize a versatile utility of a new synthetic process of 2,3-cycloalkenopyridine-4-carboxylate.

EXPERIMENTAL

Materials and methods. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Gemini-300 (300 MHz, Varian) and a Bruker 200 spectrometers and are reported in parts per million downfield from internal tetramethylsilane. Solvents and reagents were purchased from the following commercial sources: Aldrich, Kanto, Acros. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Other solvents were used as receive, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed with Merck silica gel F-254 glass-backed plates. Visualization was achieved by phosphomolybdic acid (PMA), $KMnO_4$, or anisaldehyde spray reagents, iodine, or UV illumination. Flash chromatography was performed according to Still[12] using Woelm silica gel (0.040-0.063 mm) or basic alumina. MS spectra were obtained on HP590 GC/MS 5972 MSD and VG70-VSEQ mass spectrometers for low and high resolution spectra, respectively.

Ethyl cyano-(2-oxocyclohexyl)acetate (3b). To the mixture of ethyl cyanoacetate (196 g, 17.35 mmol) and potassium *t*-butoxide (2.03 g, 18.10 mmol) in dry THF (30 mL) was added 2-chlorocyclohexanone (2.00 g, 15.08 mmol) at 0 °C. After stirred for 3 h, the solvent was removed *in vacuo* and water (100 mL) was added to the residue, which was then extracted with ethyl acetate (20 mL x 3). The organic layer was dried over anhydrous $MgSO_4$ and was evaporated under reduced pressure to 2.89 g (93%) of compound (**3b**) as a yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, 3H, J = 7.11 Hz), 1.62-2.58 (m, 8H), 3.04-3.18 (m, 1H, diastereomeric CO-C<u>H</u>-(CN-CH-CO_2Et)), 3.55, 3.93 (dd, 1H, diastereomeric CN-C<u>H</u>-CO_2Et, J = 4.70 Hz, J = 6.32 Hz), 4.29 (q, 2H, J = 7.11 Hz); IR (neat) 2229 (CN), 1745, 1721 (C=O) cm^{-1}; MS: m/z (%) 209 (M^+, 1), 164 (17), 108 (15), 97 (100), 80 (22), 55 (61). HRMS calcd for $C_{11}H_{15}NO_3$ 209.1052,

found 209.1052

Ethyl cyano-(2-oxocyclopentyl)acetate (**3a**). Colorless liquid; yield 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3H, CH_3, *J* = 6.90 Hz), 1.83-2.90 (m, 6H), 3.07-3.14 (m, 1H, diastereomeric CO-C<u>H</u>-(CN-CH-CO_2Et)), 4.03, 4.08 (dd, 1H, diastereomeric CN-C<u>H</u>-CO_2Et, *J* = 3.60 Hz, *J* = 3.60 Hz,), 4.30 (m, 2H, CH_2); IR (neat) 2976, 2235 (CN), 1745 (C=O); MS: m/z (%) 195 (M^+, 21), 150 (23), 122 (49), 94 (43), 67 (100). HRMS calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0891.

Ethyl cyano-(2-oxocycloheptyl)acetate (**3c**). Pale yellowish liquid; yield 58%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28-1.35 (m, 3H, CH_3), 1.40-2.12 (m, 8H), 2.42-2.85 (m, 2H), 3.21-3.37 (m, 1H, diastereomeric CO-C<u>H</u>-(CN-CH-CO_2Et)), 3.73, 4.02 (dd, 1H, diastereomeric CN-C<u>H</u>-CO_2Et , *J* = 6.32, *J* = 7.90 Hz), 4.21-4.32 (m, 2H, CH_2); IR (neat) 2249 (CN), 1756, 1716 (C=O) cm^{-1}. MS: m/z (%) 223 (M^+, 2), 178 (21), 150 (31), 122 (21), 111 (94), 98 (59), 55 (100). HRMS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1208.

Ethyl 2-cyano-2-(2-oxocyclohexyl)-4-pentenoate (**4b**). To the solution of **3b** (1.00 g, 4.78 mmol) in dry THF (20 mL) was added potassium *t*-butoxide (0.64 g, 5.74 mmol) at rt and the mixture was stirred for 3 h. To the mixture was added allyl bromide (0.58 g, 4.78 mmol) by a syringe and then the mixture was refluxed for 3 h at which time no spot corresponding to **3b** was observed on TLC. Water (20 mL) was added to the reaction mixture, and the mixture was extracted with ether (20 mL x 3). The organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by silica gel column chromatography of the residue using a mixture of hexane and ethyl acetate (v/v, 5:1) as an eluent gave **4b** (1.02 g, 85%) as a scarlet oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.05 Hz), 1.60-2.50 (m, 8H), 2.65-2.75 (m, 2H), 2.90-3.10 (m, 1H CH2-CO-C<u>H</u>-), 4.20-4.33(m, 2H, $OC\underline{H}_2CH_3$), 5.14-5.28 (m, 2H, CH=C<u>H</u>$_2$), 5.70-5.90 (m, 1H $CH_2C\underline{H}$=CH_2); IR (neat) 2246 (CN), 1740, 1721 (C=O) cm^{-1}; MS: m/z (%) 249 (M^+, 0.3), 176 (29), 162 (8), 106 (7), 98 (100), 70 (11), 55 (18). HRMS calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1363. *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.28; H, 7.55; N, 5.74.

Ethyl 2-cyano-2-(2-oxocyclopentyl)-4-pentenoate (**4a**). Pale yellowish liquid; yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 6.90 Hz), 1.74-2.89 (m, 8H, (C=O)-C<u>H</u>$_2$-C<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$CH=C<u>H</u>$_2$), 3.16-3.26 (m, 1H, CH_2-CO-C<u>H</u>-), 4.18-4.37 (m, 2H, $OC\underline{H}_2CH_3$), 5.20 (d, 2H, *J* = 12.0 Hz, CH=C<u>H</u>$_2$), 5.67-5.85 (m, 1H, CH_2-C<u>H</u>=CH_2); IR (neat) 2980, 2240 (CN), 1751 (C=O) cm^{-1}; MS: m/z (%) 235 (M^+, 0.6), 162 (13), 106 (6), 84 (100). HRMS calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1209. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.51; H, 7.39; N, 5.78.

Ethyl 2-cyano-2-(2-oxocycloheptyl)-4-pentenoate (**4c**). Pale yellow liquid; yield 54%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.35 (t, 3H, *J* = 7.10 Hz), 1.55-2.70 (m, 10H), 2.70-2.80 (m, 2H), 3.10-3.20 (m, 1H, CH_2-CO-C<u>H</u>), 4.15-4.30 (m, 2H, OC<u>H_2</u>CH_3), 5.10-5.21 (m, 2H, CH=C<u>H_2</u>), 5.65-5.87 (m, 1H, CH_2C<u>H</u>=CH_2); IR (neat) 2937, 2268 (CN), 1756, 1711 (C=O) cm^{-1}; MS: m/z (%) 263 (M^+, 1), 190 (88), 148 (24), 112 (100), 111 (47), 84 (30), 55 (33). HRMS calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1521. *Anal.* Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.70; H, 7.78; N, 5.09.

Ethyl 2,3-cyclohexenopyridine-4-carboxylate *N*-oxide (**7b**). *Via route B in Scheme 1.* The compound (**4b**) (1.01 g, 4.05 mmol) was dissolved in CH_2Cl_2 (20 mL) and the ozone passed for 20 min through the solution of the **4b** at -78 °C. To the reaction solution was added dimethyl sulfide (0.75 g, 12.15 mmol) and the solution was then carefully warmed up to rt in the water bath. After stirring for 2 h, the solution was washed with water (200 mL x 3). The solution was dried over anhydrous $MgSO_4$. Removal of solvent, followed by silica gel column chromatography of the residue using a mixture of hexane and ethyl acetate (v/v, 5:1) as an eluent gave ethyl 2-cyano-2-(2-oxocyclohexyl)-4-oxobutyrate (**5b**) (0.96 g, 94%) as a yellowish liquid : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, 3H, *J* = 6.90 Hz), 1.63-2.90 (m, 10H), 3.01-3.20 (m, 1H CH_2-CO-C<u>H</u>), 4.30 (q, 2H, OC<u>H_2</u>CH_3, *J* = 6.90 Hz), 9.80 (s, 1H, -CHO). HRMS calcd for $C_{13}H_{17}NO_4$ 251.1158, found 251.1157. A mixture of **5b** (0.95 g, 3.78 mmol) and hydroxylamine hydrochloride (0.53 g, 7.56 mmol) in ethanol (20 mL) was refluxed for 3 h, followed by cooling to rt. Removal of solvent *in vacuo* followed by silica gel column chromatography by ether as an eluent gave **7b** (0.63 g, 75 %) as a yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, 3H, *J* = 6.90 Hz), 1.70-1.95 (m, 4H), 2.90-3.15 (m, 4H), 4.36 (q, 2H, *J* = 6.90 Hz), 7.70 (d, 1H, *J* = 6.6 Hz), 8.25 (d, 1H, *J* = 6.6 Hz); IR (neat) 1718 (C=O), 1254 cm^{-1}; MS: m/z (%) 221 (M^+, 40), 176 (100), 158 (38), 130 (52), 117 (18). HRMS calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1053. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.41; H, 7.02; N, 6.51.

Ethyl 2,3-cyclopentenopyridine-4-carboxylate *N*-oxide (**7a**). *Via route B in Scheme 1.* The ozonolysis of ethyl 2-cyano-2-(2-oxocyclopentyl)-4-pentenoate (**4a**) (7.70 g, 32.73 mmol), followed by silica gel column chromatography of the residue using a mixture of hexane and ethyl acetate (v/v, 5:1) as an eluent gave ethyl 2-cyano-2-(2-oxocyclopentyl)-4-oxobutyrate (**5a**) (6.98 g, 90%) as a yellowish oil; ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.40 (t, 3H, *J* = 7.0 Hz), 1.70-2.90 (m, 7H), 3.21 (s, 2H, CH_2CHO), 4.35 (q, 2H, *J* = 7.0 Hz), 9.80 (s, 1H, CHO); IR (neat) 1740 (C=O), 1260 cm^{-1} ; MS: m/z (%) 237 (M^+, 5), 219 (11), 191 (10), 164 (45), 118 (37), 83 (100). HRMS calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.1001. The reaction of **5a** (4.70 g, 19.81 mmol) with

hydroxylamine hydrochloride (2.78 g, 39.62 mmol) in ethanol (100 mL) as described in the preparation of **7b,** followed by silica gel column chromatography by ether as an eluent gave **7a** (3.20 g, 78%) as a brownish solid; mp 99.5 °C ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (t, 3H, *J* = 7.0 Hz), 2.23 (quintet, 2H, *J* = 7.5 Hz), 3.23 (t, 2H, *J* = 7.5 Hz), 3.43 (t, 2H, *J* = 7.5 Hz), 4.44 (q, 2H, *J* = 7.0 Hz), 7.83 (d, 1H, *J* = 6.8 Hz), 8.23 (d, 1H, *J* = 6.8 Hz); IR (KBr) 1273, 1703 cm^{-1}; MS: m/z (%) 207 (M^+, 59), 162 (100), 117 (43), 77 (20), 63 (14). HRMS calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0899. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.55; H, 6.30; N, 6.80.

Ethyl 2,3-cycloheptenopyridine-4-carboxylate *N*-oxide (**7c**). *Via route B in Scheme 1.* The ozonolysis of ethyl 2-cyano-2-(2-oxocycloheptyl)-4-pentenoate (**4c**) (0.30 g, 1.14 mmol), followed by silica gel column chromatography of the residue using a mixture of hexane and ethyl acetate (v/v, 5:1) as an eluent gave ethyl 2-cyano-2-(2-oxocycloheptyl)-4-oxobutyrate (**5c**), (0.15 g, 96%) as a yellowish oil; ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.35 (t, 3H *J* = 7.0 Hz), 1.50-2.70 (m, 12H), 3.10-3.20 (m, 1H), 4.15-4.32 (m, 2H), 9.80 (s, 1H, CHO); MS: m/z (%) 265 (M^+, 0.2), 164 (22), 112 (54), 111 (100), 55 (72). The reaction of **5c** (0.15 g, 0.58 mmol) with hydroxylamine hydrochloride (0,08 g, 1.16 mmol) as described in the preparation of **7b,** followed by silica gel column chromatography by ether as an eluent gave **7c** (0.11 g, 81%) as a yellowish oil; ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.35 (t, 3H *J* = 7.2 Hz), 1.68-1.95 (m, 6H), 3.15-3.25 (m, 2H), 3.40-3.53 (m, 2H), 4.35 (q, 2H, *J* = 7.2 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 8.35 (d, 1H, *J* = 7.8 Hz) ; IR (neat) 1718 (C=O), 1444, 1254 cm^{-1}. HRMS calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1208. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.41; N, 6.12.

Ethyl 2,3-cyclohexenopyridine-4-carboxylate (**6b**). *Via route B in Scheme 1.* The mixture of **7b** (0.16 g, 0.72 mmol) and phosphorus trichloride (0.28 g, 2.16 mmol) in chloroform (20 mL) was refluxed for 30 min. The reaction mixture was washed with aqueous saturated sodium bicarbonate solution until no gas was evolved, and washed with water, and dried over Na_2SO_4. The removal of solvent *in vacuo*, followed by silica gel column chromatography of the residue using a mixture of hexane and ethyl acetate (v/v, 3:1) as an eluent gave **6b** (0.12 g, 84%) as a yellowish oil; ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.60-1.90 (m, 4H), 2.80-3.08 (m, 4H), 4.36 (q, 2H, *J* = 7.1 Hz), 7.39 (d, 1H, *J* = 5.0 Hz), 8.02 (d, 1H, *J* = 5.0 Hz) ; IR (neat) 1282, 1163 cm^{-1}; MS: m/z (%) 205 (M^+,42), 176 (100), 159 (63), 130 (48), 117 (23). HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1103. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.19; H, 7.29; N, 6.80.

Ethyl 2,3-cyclopentenopyridine-4-carboxylate (**6a**). *Via route B in Scheme 1.* The treatment

of **7a** (0.92 g, 4.45 mmol) with PCl_3 (1.73 g, 13.35 mmol) as described in the preparation of **6b,** followed by silica gel column chromatography using a mixture of hexane and ethyl acetate (v/v, 3:1) as an eluent gave **6a** (0.84 g, 99%) as a yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, 3H, *J* = 7.0 Hz), 2.15 (quintet, 2H, *J* = 7.8 Hz), 3.23 (t, 2H, *J* = 7.8 Hz), 3.35 (t, 2H, *J* = 7.8 Hz), 4.50 (q, 2H, *J* = 7.0 Hz), 7.73 (d, 1H, *J* = 5.2 Hz), 8.67 (d, 1H, *J* = 5.2 Hz); IR (neat) 1724, 1277, 1144 cm^{-1} ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 164.4, 143.3, 141.3, 137.1, 122.2, 82.1, 82.7, 31.7, 22.7, 14.2 ; MS: m/z (%) 191 (M^+, 46), 162 (100), 145 (13), 117 (43), 91 (17), 63 (13). HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0946. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.21; H, 7.01; N, 7.30.

Ethyl 2,3-cycloheptenopyridine-4-carboxylate (**6c**). *Via route B in Scheme 1.* The treatment of **7c** (0.05 g, 0.20 mmol) with PCl_3 (0.08 g, 0.60 mmol) as described in the preparation of **6b,** followed by silica gel column chromatography using a mixture of hexane and ethyl acetate (v/v, 3:1) as an eluent gave **6c** (0.04 g, 98%) as a yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1,35 (t, 3H, *J* = 7.1 Hz), 1.62-1.92 (m, 6H), 2.90-3.00 (m, 2H), 3.10-3.20 (m, 2H), 4.40 (q, 2H, *J* = 7.1 Hz), 7.30 (d, 1H, *J* = 5.2 Hz), 8.34 (d,1H, *J* = 5.2 Hz); IR (neat) 1728 (C=O) 1286, 1130 cm^{-1}; MS: m/z (%) 219 (M^+, 44), 190 (81), 173 (100), 144 (30), 117 (18). HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1259. *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71. 19; H, 7.99; N, 6.45.

Ethyl 2,3-cyclopentenopyridine-4-carboxylate (**6a**). *Via route A in Scheme 1.* To a ethyl 2-cyano-2-(2-oxocyclohexyl)-4-oxobutyrate (**5a)** (35.0 g, 0.147 mol) in a absolute MeOH (300 mL) was added ammonium formate (32.57 g, 0.516 mol; 3.5 eq. to **5a**) at rt and the mixture was stirred for 45 min maintaining below 20 °C. Removal of solvent under reduced pressure was followed by addition of CH_2Cl_2 (200 mL) and water (100 mL), and the organic layer then was separated. The organic layer was washed with 3% $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and condensed to give **6a** (27.18 g, 97%), which was not in need of futher purification.

Ethyl 2,3-cyclohexenopyridine-4-carboxylate (**6b**). *Via route A in Scheme 1.* From the reaction of ethyl 2-cyano-2-(2-oxocyclohexyl)-4-oxobutyrate (**5b**) with ammonium formate as described in the preparation of **6a**, there was obtained **6b** in 91% yield from the silica gel column chromatography using a mixture of hexane and ethyl acetate (v/v, 3:1) as an eluent.

Ethyl 2,3-cycloheptenopyridine-4-carboxylate (**6c**). *Via route A in Scheme 1.* From the reaction of ethyl 2-cyano-2-(2-oxocycloheptyl)-4-oxobutyrate (**5c**) with ammonium formate, there was obtained **6c** in 84% yield from the silica gel column chromatography using a mixture of

hexane and ethyl acetate (v/v, 3:1) as an eluent.

Ethyl 2-cyano-2-(2-methoxyiminocyclohexyl)acetate (**8**). To the mixed solution of methoxylamine hydrochloride (5.12 g, 61.33 mmol) and pyridine (6.67 g, 84.33 mmol) in methanol (80 mL) was added dropwise the solution of **3b** (8.01 g, 38.33 mmol) in methanol (20 mL) at rt. The mixture was stirred for 1 h at which time no spot corresponding to **3b** was observed on TLC. Water (150 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (80 mL x 3). The organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent gave **8** (8.64 g, 95%) as a yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, 3H, J = 7.2 Hz) 1.40-2.12 (m, 8H), 2.78-3.00 (m, 1H), 3.50, 4.10 (dd, 1H, diasteromeric H, J = 4.70 Hz, J = 6.30 Hz, CN-C<u>H</u>-CO_2Et), 3.80 (s, 3H), 4.30 (q, 2H, J = 7.2 Hz); IR (neat) 2249, 1746 (C=O), 1457, 1247 cm^{-1}; MS: m/z (%), 238 (M^+, 9), 193 (14), 165 (100), 161 (15), 133 (15), 94 (14), 79. *Anal.* Calcd for $C_{12}H_{17}N_2O_3$: C, 60.74; H, 7.22; N, 11.80. Found: C, 60.51; H, 7.59; N, 11.94.

Ethyl 2-cyano-2-(2-methoxyiminocyclohexyl)-4-pentenoate (**9**). To the solution of **8** (3.00 g, 12.60 mmol) in dried THF (30 mL) was added potassium *t*-butoxide (1.70 g, 15.12 mmol) at rt and the mixture was stirred for 4 h. Allyl bromide (1.68 g, 13.86 mmol) was added to the reaction mixture and the mixture was refluxed for 2 h. The reaction mixture was poured into water (100 mL) and was extracted with ether (50 mL x 3). The organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent, followed by silica gel column chromatography of the residue using a mixture of hexane and ethyl acetate (v/v, 5:1) as an eluent gave **9** (3.14 g, 89%) as a yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J = 7.2 Hz) 1.40-2.85 (m, 10H), 3.02-3.32 (m, 1H), 3.91(s, 3H, OCH_3), 4.20-4.39 (m, 2H, OC<u>H</u>$_2$$CH_3$), 5.15-5.25 (m, 2H, CH=C<u>H</u>$_2$), 5.72-5.95 (m, 1H, C<u>H</u>=CH_2); IR (neat) 2259 (CN), 1746 (C=O), 1457, 1232 cm^{-1}; MS: m/z (%) 278 (M^+, 0.4), 205 (46), 127 (100), 96 (18). *Anal.* Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.52; H, 7.99; N, 10.22.

Ethyl 2,3-cyclohexenopyridine-4-carboxylate (**6b**). *Via Scheme 2.* The ozone gas was flowed through the solution of **9** (3.00 g, 10.78 mmol) in dichloromethane (30 mL) for 30 min at -78 °C. To the reaction mixture was added dimethyl sulfide (2.01 g, 32.34 mmol) and the reaction mixture was warmed up to rt. The reaction mixture was washed with water (30 mL x 5), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel column (1.5 x 3 cm). Elution with a mixture of ethyl acetate and hexane(v/v, 1:3) and removal of solvent gave a **6b** (1.16 g, 52%) as a yellowish liquid. During the evaporation of solvent, aldehyde compound (**10**) underwent pyridine ring formation provided

a compound (**6b**).

ACKNOWLEDGMENTS

This work was supported by a grant from MOST and KIST and supported by Korean Ministry of Education through Research Fund (No. BSRI-96-3443).

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Received, 17th February, 1998