SYNTHESIS OF 2-HYDROXYMETHYL-3,5-DIMETHYL-4-METHOXYPYRIDINE : A KEY INTERMEDIATE FOR OMEPRAZOLE

Shan-Yen Chou* and Shyh-Fong Chen

Development Center For Biotechnology, 102, Lane 169, Kang Ning St., Hsichih, Taipei Hsien, Taiwan, R.O.C.

Abstract- A synthesis of 2-hydroxymethyl-3,5-dimethyl-4-methoxypyridine, a key intermediate for the preparation of gastric acid inhibiting compound omeprazole, is described. The procedure consists of preparation of pyrone, pyridone and pyridine derivatives sequentially.

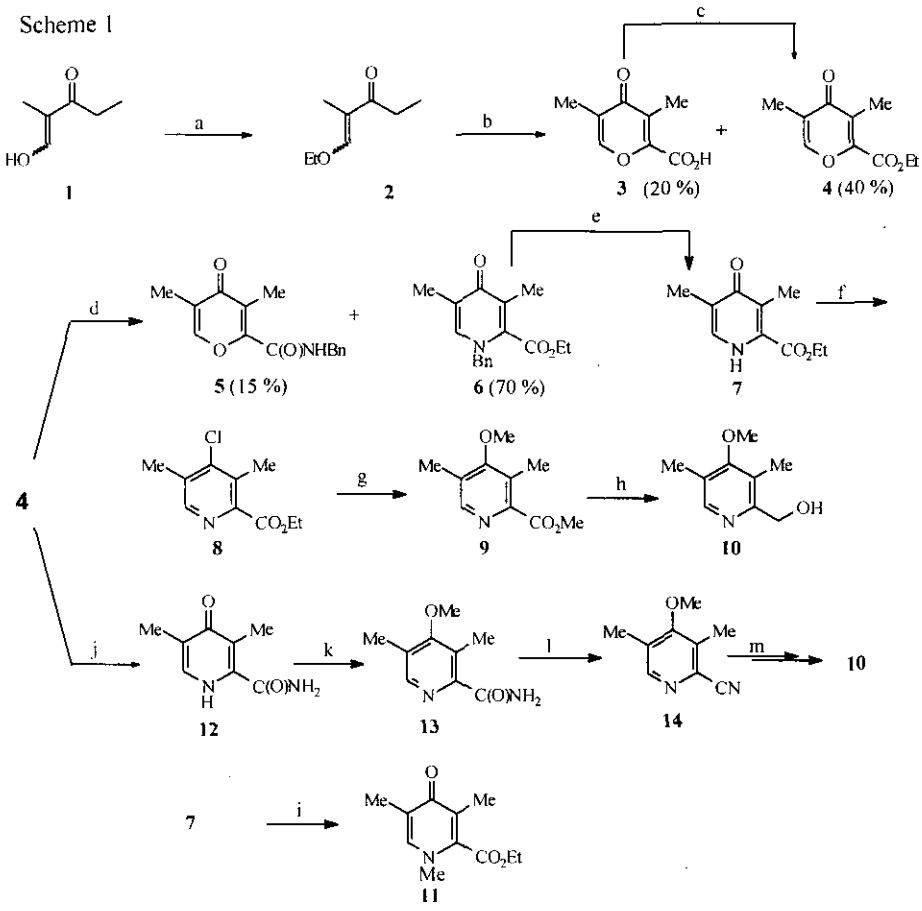
In recent years research in the field of gastric acid secretion has resulted in the discovery of a new class of antisecretory compounds.[1-4] Omeprazole (brand name : Prilosec), prepared by coupling of 2-chloromethyl-3,5-dimethyl-4-methoxypyridine and 5-methoxy-2-mercaptobenzimidazole, followed by oxidation,[5,6] is a representative with highly specific inhibiting action on the gastric proton pump, $(H^+ + K^+)$-ATPase. The pyridine part was easily prepared from 2-hydroxymethyl-3,5-dimethyl-4-methoxypyridine (**10**) by chlorination [1) $SOCl_2$, 2) neutralization with 10% K_2CO_3]. Two syntheses of **10** using either 2,3,5-trimethylpyridine or 3,5-dimethylpyridine as starting material had appeared.[5-8] One of the most interesting conversions is the acylation of a substituted pyridine *N*-oxide to form a substituted 2-acetoxypyridine.[9-11]

Dedicated to Professor **Sheng-Hsu Zee** at National Tsing Hua University on the occassion of his 68 birthday.

Recently, a more practical synthesis of omeprazole using easily crystallized pyridino-thioether-benzimidazole acetamide as an intermediate was disclosed.[12]

In this article we report two alternative routes for a synthesis of **10**, starting from open chain educt (**1**) and employing pyrone (**4**) as a common intermediate (Scheme 1)

Scheme 1



a. EtBr, K_2CO_3, acetone, 84 %; b. NaOEt, $(CO_2Et)_2$, EtOH; c. EtOH, H_2SO_4, 92 %; d. $BnNH_2$, *p*-TSA, toluene; e. H_2 / 10% Pd-C, HOAc, 81%; f. $POCl_3$, 88% crude; g. MeONa, MeOH, 80 % crude; h. $LiAlH_4$, THF, 0℃, 50 %; i. NaH, MeI, DMF, 65 %; j. NH_3, EtOH, autoclave, 91%; k. Me_2SO_4, K_2CO_3, acetone, 90%; l. $(CF_3CO)_2O$, CH_2Cl_2, pyridine, 91%; m. see references 7 and 8.

Alkylation of 1-hydroxy-2-methylpent-1-en-3-one (**1**)[13] with 290 mol % of ethyl bromide in refluxing acetone gave *O*-alkylated product (**2**) in 84% yield. Acylation followed by concomitant ring-closure of **2**

using diethyl oxalate gave a mixture of **3** (20%) and **4** (40%). Compound (**3**) is a saponification product of **4**, formed by the residual water present in commercial ethanol (0.2% max). Pyrone (**3**) can be converted to **4** by esterification. Ammonolysis of **4** with benzylamine in refluxing toluene led to the γ-pyridone derivative (**6**) (70%) and a side product (**5**) (15%), which were separated by flash column chromatography. Hydrogenolysis of **6** in acetic acid under hydrogen at 55 psi gave **7** (81%), which, upon chlorination with phosphoryl chloride, afforded **8** in 88% crude yield. Methoxylation with concomitant alcoholysis of crude **8** in refluxing methanol in the presence of sodium methoxide yielded **9** in 80% crude yield, which was converted to **10** by $LiAlH_4$ reduction in 50% yield. Attempt to prepare **9** from **7** by the usual methylation method (Me_2SO_4 / acetone, K_2CO_3) failed. Alkylation of **7** with MeI using NaH in DMF gave an undesirable *N*-methylation product (**11**). Compound (**10**) was also synthesized from pyrone (**4**) by an alternative route. Heating of **4** with ethanolic ammonia in an autoclave gave pyridone amide (**12**) in 91% yield. In contrast to compound (**7**), methylation of **12** by the standard method (Me_2SO_4 / acetone, K_2CO_3) led to the desired *O*-methylated product (**13**) in 90% yield. Treatment of **13** with trifluoroacetic anhydride and pyridine in dichloromethane afforded 4-methoxy-3,5-dimethylpyridine-2-carbonitrile (**14**) in 91% yield. Compound (**14**) can be transformed to **10** by a known method,[7,8] thus this pathway is a formal synthesis of **10**.

In conclusion, the two approaches for the preparation of omeprazole key intermediate (**10**) have been accomplished. The starting open-chain educt is easily available. In addition, the suspected carcinogens, the said nitropyridines and their *N*-oxides, can be avoided.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 577 spectrophotometers, Nmr spectra were recorded on a Bruker-AC 200 (200 MHz) spectrometer, $CDCl_3$ and DMSO-d_6 were used as solvents, and TMS was added as an internal standard. Elemental analysis were determined by a Perkin-Elmer 2400. Mass spectra and high-resolution mass spectra were measured on JEOL-JMS-D100 and JEOL-JMSD-HX100

instruments respectively. Catalytic hydrogenations were carried out on a Parr 3911 reactor. Melting pointswere measured in open capillary tubes using Buchi immersion apparatus, and are uncorrected. Separations by flash chromatography were performed on silica gel (230-400 mesh). All reagents were of commercial quality and were used as received.

1-Ethoxy-2-methylpent-1-en-3-one (**2**). To a solution of 1-hydroxy-2-methylpent-1-en-3-one (**1**) (76 g, 0.67 mol) in acetone (1500 ml) was added ethyl bromide (209 g, 1.92 mol) and anhydrous potassium carbonate (115 g, 0.83 mol). The mixture was refluxed for 34 h. After the solvent had been evaporated the residue was treated with water and extracted twice with ether. The extracts were washed with 10% potassium carbonate and dried over anhydrous magnesium sulfate. Evaporation of the ether under reduced pressure followed by vacuum distillation gave **2** (80.3 g, 84 % yield) as a yellow oil. bp 62°C (0.82 mm). Ir (film) ν_{max} : 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ:7.33 (s, 1H), 4.08 (q, J=7.2 Hz, 2H), 2.56 (q, J=7.4 Hz, 2H), 1.73 (s, 3H), 1.36 (t, J=7.2 Hz, 3H). 1.13 (t, J=7.4 Hz, 3H). Anal. Calcd for $C_8H_4O_2$: C, 67.57; H, 9.92. Found : C, 67.25; H, 9.87.

3,5-Dimethyl-4-oxo-4*H*-pyran-2-carboxylic acid (**3**) and **3,5-Dimethyl-4-oxo-4*H*-pyran-2-carboxylic acid ethyl ester** (**4**). To a refluxing ethanolic sodium ethoxide solution (50 ml, 31.3 mmol, 0.626 M) was added a mixture of compound (**2**) (4.05 g, 0.028 mol) and diethyl oxalate (4.1 g, 0.028 mol) over 0.5 h. After another 0.5 h the solvent was evaporated and the residue was poured into ice-water. The mixture was extracted with dichloromethane (100 ml x 2) and washed with water. The organic layer was dried over sodium sulfate and removal of the solvent gave crude product, which was chromatographed on silica gel using 1 : 4 ethyl acetate / hexane as eluent to give **4** as a white powder (2.2 g, 40%). mp 81-83°C (1:4 ethyl acetate/hexane). Ir ($CHCl_3$) ν_{max} : 1725, 1640 , 1620 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ:7.73 (s, 1H), 4.42 (q, J=7.2 Hz, 2H), 2.31 (s, 3H), 1.96 (s, 3H). 1.42 (t, J=7.2 Hz, 3H). Ms (13 eV) m/z (%) : 196.1 (M^+, 45), 167.1 (100). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found : C, 61.18; H, 6.12. The aqueous solution and washings were combined and acidified

with conc. HCl at 0°C. The resulting preciptate was filtered and dried in vacuo to give **3** as a white powder (0.94 g, 20%). mp 185-187°C (3:1 ethyl acetate/benzene). Ir ($CHCl_3$) ν_{max} : 3400 cm^{-1} (br). ^{1}H-Nmr (DMSO-d_6) δ:8.19 (s, 1H), 2.15 (s, 3H), 1.83 (s, 3H). Ms (13 eV) m/z (%) : 168.0 (M^+, 100), 124.1 (20), 95.0 (20). Anal.Calcd for $C_8H_8O_4$: C, 57.15; H, 4.80. Found : C, 57.10; H, 4.75.

Esterification of 3. To a solution of compound (**3**) (3 g, 17.85 mmol) in abs ethanol (30 ml) was added sulfuric acid (0.5 g). The mixture was refluxed for 5 h and then the solvent was evaporated. The residue was partitioned between chloroform and 10% potassium carbonate aqueous solution. The separated chloroform layer was washed with water, dried over sodium sulfate and evaporated to give **4** (3.2 g, 92%).

3,5-Dimethyl-4-oxo-4*H*-pyran-2-carboxylic acid benzylamide (5) and **1-Benzyl-3,5-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid ethyl ester (6)**. A solution of compound (**4**) (5.0 g, 25.5 mmol), benzylamine (2.92 g, 27.3 mmol) and *p*-toluenesulfonic acid monohydrate (0.25 g) in toluene (48 ml) was azeotropically refluxed for 9 h. The resulting solution was washed with 10 % K_2CO_3, dried over sodium sulfate and the solvent was evaporated. The residue was purified on silica gel column chromatography using 1 : 2 ethyl acetate / hexane as eluent to give pyrone (**5**) and pyridone (**6**). Pyrone (**5**) (0.86 g, 15%). mp 143-145°C (3:1 ethyl acetate/hexane). Ir ($CHCl_3$) ν_{max} : 1640 , 1620 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ:7.61 (s, 1H), 7.20-7.40 (m, 5H), 4.59 (d, J=6.0 Hz, 2H), 2.41 (s, 3H), 1.94 (s, 3H). Ms (13 eV) m/z (%) : 257.1 (M^+, 100), 166.0 (25), 124.0 (20), 106.1 (40), 91.1(55). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found : C, 69.98; H, 5.72, N, 5.32. Pyridone (**6**) (5.1 g, 70 %), yellow oil. Ir (film) ν_{max} : 1640, 1610 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ:7.31-7.40 (m, 3H), 7.26 (s, 1H),7.08-7.12 (m, 2H), 4.98 (s, 2H), 4.17 (q, J=7.1 Hz, 2H), 2.02 (s, 3H), 2.00 (s, 3H). 1.20 (t, J=7.1 Hz, 3H). Ms (13 eV) m/z (%) : 285.1 (M^+, 60), 271.1 (100), 256.0 (55), 212.0(20), 180.0 (25). HR-EIms : Found : 285.1332 (M^+), Calcd for $C_{17}H_{19}NO_3$: 285.1365.

3,5-Dimethyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid ethyl ester (7). To a solution of pyridone

(**6**) (5.1 g, 17.89 mmol) in acetic acid (100 ml), was added 10 % Pd-C (1 g), and the reaction mixture was hydrogenated (55 psi) at room temperature for 12 h. The mixture was then filtered through Celite and the filtrate was evaporated. The residue was thoroughly washed with 10 % potassium carbonate, water and dried in vacuo and recrystallized from benzene to give **7** as a white powder (2.8 g, 81 %). mp 124-126°C. Ir ($CHCl_3$) ν_{max} : 3040, 1730, 1630 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 7.52 (br s, 1H), 7.34 (s, 1H), 4.45 (q, J=7.2 Hz, 2H), 2.40 (s, 3H), 2.07 (s, 3H). Ms (13 eV) m/z (%) : 195.0 (M^+, 100), 165.9 (40), 148.9 (50), 122.9 (80), 121.0(100). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found : C, 61.48; H, 6.63; N, 7.09.

4-Chloro-3,5-dimethylpyridine-2-carboxylic acid ethyl ester (**8**). A mixture of pyridone (**7**) (6.3 g, 32.3 mmol) and phosphoryl chloride (21.8 g, 0.14 mol) was heated at 120°C for 1 h and concentrated in vacuo. The residue oil was cooled and poured into ice-water (100 ml) and extracted with dichloromethane (50 ml x 3). The combined extracts was washed successively with water, saturated sodium bicarbonate aqueous solution, brine, and then dried over sodium sulfate. Removal of the solvent in vacuo gave the residue, which was filtered through a short pad of silica gel using 1 : 5 ethyl acetate / hexane as eluent. Evaporation of the solvent gave **8** (6.1 g, 88% crude yield) as a yellow oil. The crude **8** is pure enough to use in the next step without purification. Ir (film) ν_{max} : 1730 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ:8.36 (s, 1H), 4.45 (q, J=7.0 Hz, 2H), 2.58 (s, 3H), 2.41 (s, 3H). 1.43 (t, J=7.0 Hz, 3H). Ms (13 eV) m/z (%) : 214.1 (M^++1, 100), 183.09(20), 168.0 (20), 141.0 (65).

4-Methoxy-3,5-dimethylpyridine-2-carboxylic acid methyl ester (**9**). A solution of crude compound (**8**) (3.4 g, 15.92 mmol) in methanolic sodium methoxide solution (28 ml, 1.86 M, 52.08 mmol) was heated under reflux for 5 h. After the solvent was evaporated, water was added and it was extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated. The residue was purified on silica gel column chromatography using 1 : 5 ethyl acetate /hexane as eluent to give **9** (2.5 g, 80 % crude) as an oil. Ir (film) : ν_{max} : 1725 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ:8.35 (s, 1H), 3.96 (s, 3H), 3.79 (s,

3H), 2.49 (s, 3H). 2.32 (s, 3H). Ms (13 eV) m/z (%) : 196.1 (M^++1, 100), 163.0(20), 137.1 (40), 107.1 (20).

2-Hydroxymethyl-3,5-dimethyl-4-methoxypyridine (10). Lithium aluminum hydride (0.94 g, 25.4 mmol) was dissolved in 100 ml of abs THF and added in a dropwise manner to a stirred solution of **9** (2.5 g, 12.82 mmol) in 20 ml of THF at 0°C. The mixture was stirred at 0℃ for 22 h. Excess $LiAlH_4$ was destroyed with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, and evaporated in vacuum. The resulting product was purified by silica gel column chromatography using 1 : 1 ethyl acetate / hexane as eluent to give **10** (1.1 g, 50 %). It showed same analytic data as those of an authentic sample.[5,6]

1,3,5-Trimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid ethyl ester (11). To a stirred suspenion of sodium hydride (0.12 g, 3 mmol, 60 % dispersion in oil) in DMF (20 ml) was added pyridone (**7**) (0.39 g, 2 mmol) at 0°C. After the mixture was allowed to warm to room temperature and then stirred for 10 min, methyl iodide (0.32 g, 2.24 mmol) was added and then stired for 12 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic extracts was washed with water and brine and then dried over sodium sulfate. The crude product was purified by column chromatograph on silica gel using 1 : 2 ethyl acetate / hexane as eluent to give **11** (0.27 g, 65 % yield) as a brown oil. Ir (film) ν_{max} : 1740, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ:7.22 (s, 1H), 4.46 (q, J=7.2 Hz, 2H), 3.60 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.42 (t, J=7.2 Hz, 3H).

3,5-Dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid amide (12). A solution of pyrone (**4**) (10.2 g, 52.0 mmol) in saturated ethanolic ammonia (180 ml) was heated at 120℃ in an autoclave for 48 h. The mixture was cooled and filtered to give **12** (6.2 g) as a white powder. The filtrate was evaporated, and the residue was triturated with small amount of cold methanol to give **12** (1.7 g) as the second crop. The combined crop of **12** is 7.9 g (91 % yield). mp > 300°C (trituation with MeOH). Ir (KBr) ν_{max} : 1635 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ:8.02 (br s, 1H), 7.85 (br s, 1H), 7.59 (s, 1H), 2.01 (s, 3H). 1.91 (s, 3H). Ms (13 eV)

m/z (%) :166.1(M^+,100), 149.1(50), 121.0(70). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found : C, 57.62; H, 6.03; N, 16.72.

4-Methoxy-3,5-dimethylpyridine-2-carboxylic acid amide (13). A mixture of **12** (1.6 g, 9.6 mmol), dimethyl sulfate (1.2 g, 9.52 mmol), and anhydrous potassium carbonate (4.1 g, 29.7 mmol) in acetone (50 ml) was heated under reflux for 15 h. It was then filtered and washed with acetone. The filtrate was evaporated, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate and evaporated on vacuum. The residue was purified on silica gel column chromatography using 1:2 ethyl acetate/hexane as eluent to give **13** (1.55 g, 90 %). mp : 127-129°C (1:2 ethyl acetate/hexane). Ir ($CHCl_3$) ν_{max} : 1650 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ:8.20 (s, 1H), 7.83 (br s, 1H), 5.56 (br s, 1H), 3.78 (s, 3H), 2.64 (s, 3H), 2.31 (s, 3H). Ms (13 eV) m/z (%) : 180.1 (M^+, 100), 163.1 (100), 135.1 (75), 105.1 (60). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found : C, 59.87; H, 6.56; N, 15.32.

4-Methoxy-3,5-dimethylpyridine-2-carbonitrile (14). To a suspension of amide (**13**) (0.8 g, 4.44 mmol) in dry dichloromethane (20 ml) was successively added pyridine (0.71 g, 8.99 mol) and trifluoroacetic anhydride (1.12 g, 5.33 mmol). The internal temperature was maintained at < 30°C. The mixture was stirred at room temperature overnight. It was washed with water, dried and evaporated on vacuum. The residue was purified on silica gel column chromatography using 1:5 ethyl acetate/hexane as eluent to give **14** (0.65 g, 91 % yield) as a white solid. mp : 58-60°C (1:5 ethyl acetate/hexane), identical in all respects with the material prepared by the known strategy. [7,8]

ACKNOWLEDGEMENTS

We would like to thank the Ministry of Economic Affairs, R.O.C. for their financial support. Analytical support by Dr. Yuh-Shan Chung's group of Development Cencer for Biotechnology is greatly appreciated.

REFERENCES AND NOTES

1. P. Lindberg, A. Brändström, and B. Wallmark, *Trends Pharmacol. Sci.*, 1987, **8**, 399.
2. J. Sih and M. Cho, *Eur. Pat. Appl.*, 1986, 176,308 (*Chem. Abstr.*, 1986, **105**, 60604).
3. M. Roesner, A. Herling, and M. Bickel, *Ger. Offen.* 1986, 3,509,333 (*Chem. Abstr.*, 1986, **106**, 5044).
4. S. Nakagawa, F. Nakano, K. Mastuyama, and H. Takeshita, *Eur. Pat. Appl.*, 1986, 194,458 (*Chem. Abstr.*, 1986, **105**, 226353).
5. U. K. Junggran and S. E. Sjostrand, *Eur. Pat. Appl.*, 1979, 5,129 (*Chem. Abstr.*, 1980, **92**, 198396).
6. U. K. Junggran and S. E. Sjostrand, *U. S. Patent,* 1981, 4,255,431 (*Chem. Abstr.*, 1980, **92**, 198396).
7. B. Karl, *Ger. Offen.* 1990, 3,840,372 (*Chem. Abstr.*, 1990 , **113**, 191167).
8. B. Karl, *Eur. Pat. Appl.*, 1990, 369,208 (*Chem. Abstr.*, 1990, **113**, 191166).
9. For a general discussion, see: A. R. Katrizky and J. M. Lagowski, "*Chemistry of the Heterocyclic N-Oxide*", Academic Press, New York, 1971, pp. 352-365.
10. A. Mckillop and M. K. Bhagrath, *Heterocycles,* 1985, **23**, 1697 and references cited therein.
11. For a recent modification using trifluoroacetic anhydride as a convenient acylating agent, see: C. Fontenas, E. Bejun, H. A. Haddou, and G. G. A. Balavoine, *Synth. Commum.*, 1995, **25**, 629.
12. C. Slemon and B. Macel, *U. S. Patent,* 1994, 5,374,730 (*Chem. Abstr.*, 1995, **122**, 133189).
13. D. C. Myles and M. H. Bigham, *Organic Syntheses,* 1991, **70**, 231.

Received, 14th August, 1996