Synthesis of 4-Methoxy-2,3,5-trimethylpyridine: a Specific Building Block for Compounds with Gastric-acid Inhibiting Activity

Martin Mittelbach[a,*], Hans-Werner Schmidt[a], Georg Uray[a], Hans Junek[a], Bo Lamm[b], Kjell Ankner[b], Arne Brändström[b] and Roger Simonsson[b]

[a]Institute for Organic Chemistry, Karl-Franzens University, A-8010 Graz, Austria and [b]Ab Hässle, S-431 83 Mölndal, Sweden

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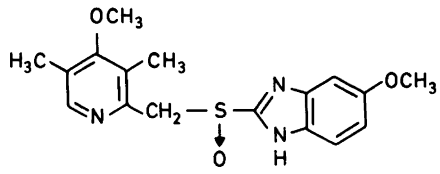
A new synthesis of 4-methoxy-2,3,5-trimethylpyridine (**2**), an important building block for the preparation of gastric-acid inhibiting compounds, is described. Condensation of ethyl 3-amino-2-methyl-2-butenoate (**3**) and diethyl 2-methylmalonate (**4**) gives 4-hydroxy-3,5,6-trimethyl-2(1*H*)-pyridone **5**. Reaction of **5** with phosphoryl chloride affords 2,4-dichloro-3,5,6-trimethylpyridine (**9a**), which, upon hydrogenolysis with palladium on charcoal, gives 2,3,5-trimethylpyridine (**10**). However, selective hydrogenolysis in acidic solution yields 4-chloro-2-3-5-trimethylpyridine (**11**). Substitution of the chlorine in **11** with methoxide ion gives 4-methoxy-2,3,5-trimethylpyridine (**2**), which can be oxidized to the corresponding *N*-oxide (**13**). This constitutes a new and efficient route to compound **2** in an overall yield of 43 %.

In the last ten years research in the field of gastric-acid secretion has resulted in a new class of antisecretory compounds, which share structural similarities.[1–4] 'Omeprazole' (**1**), 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1*H*-benzimidazole, is one representative with excellent acid-secretion inhibiting properties.[5–8] All of these active agents consist of two different heterocyclic parts linked via a sulfide or a sulfoxide group. In each case one of these parts is a pyridine derivative, especially the (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl group, for which 4-methoxy-2,3,5-trimethylpyridine (**2**) is a key intermediate.



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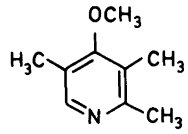

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* To whom correspondence should be addressed

Compound **2** has hitherto not been described but its *N*-oxide (**13**) is known from the patent literature.[9] This preparation starts from 3,5-dimethylpyridine, which is methylated with methyllithium to give 2,3,5-trimethylpyridine. After being oxidized to the corresponding *N*-oxide it can be nitrated selectively to give the 4-nitro derivative. The nitro group is then substituted by methoxide ion to give the 4-methoxy-2,3,5-trimethylpyridine *N*-oxide (**13**). This route has serious disadvantages, especially in large-scale synthesis. The starting material, 3,5-dimethylpyridine, is expensive, the use of methyllithium is not very suitable for industrial application, and, above all, nitropyridines and their *N*-oxides are suspected carcinogens.

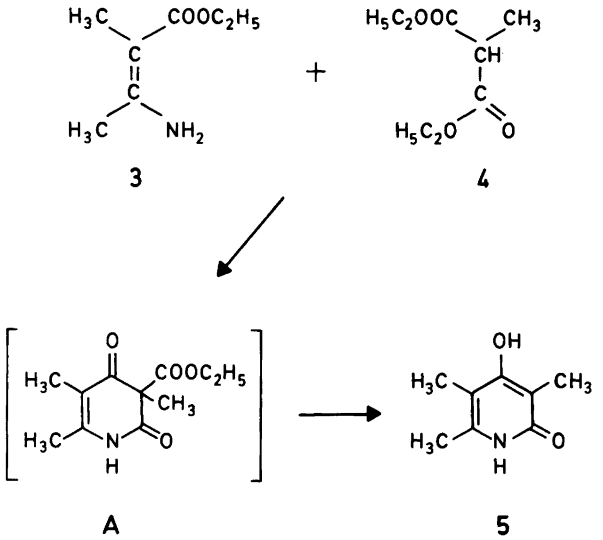
In this paper we present a straightforward route for the synthesis of **2** and its *N*-oxide (**13**) starting from simple open-chain educts.[10]

The condensation of 3-amino-2-butenoates with dialkyl malonates leads to 4-hydroxy-2(1*H*)-pyridones.[11,12]

By analogy, for appropriate substitution of the desired pyridine derivative it was necessary to use 3-amino-2-methyl-2-butenoate (**3**) and diethyl 2-methylmalonate (**4**). The amino ester (**3**) could be easily prepared in quantitative yield by heating 2-methyl-3-oxobutanoate in liquid ammonia. Very low yields of **3** were obtained when aqueous or gaseous ammonia was used as described in the literature.[13] Condensation of **3** with diethyl 2-methylmalonate using one equivalent of sodium ethoxide in ethanol gave the desired 4-hydroxy-3,5,6-trimethyl-2(1*H*)pyridone (**5**) in 76 % yield. The corresponding intermediate **A** could not be isolated, since loss of the ethoxycarbonyl group occurred spontaneously.

Rapid treatment of **5** with phosphorus pentachloride or phosphoryl bromide led to the 4-monohalogenated products (**6**). The position of the halogen atom could be verified by reduction of **6a** to **7**, which upon treatment with phosphoryl chloride gave the monochloropyridine (**8**). The structure of **8** was confirmed by its ^{1}H NMR spectrum, which showed the aromatic proton at 7.19 ppm, rather than at 8.2 ppm for C-2 pyridyl protons. In contrast, treatment of **5** with an excess of phosphoryl chloride or phosphoryl bromide in a sealed tube afforded the corresponding 2,4-dihalogenated derivatives (**9**). Hydrogenolysis of both halogen atoms under slightly basic conditions gave 2,3,5-trimethylpyridine (**10**), one of the known, but not easily available intermediates[14] for the synthesis of omeprazole (**1**). As mentioned above, preparation of **1** via 2,3,5-trimethylpyridine (**10**) leads to the formation of the unwanted 4-nitropyridine derivatives.

Synthesis of the key intermediate **2** without generation of nitro pyridine derivatives could be achieved by selective substitution of the chlorine at position 4 of the dichloro product (**9**) by a methoxide ion. However, none of our experi-



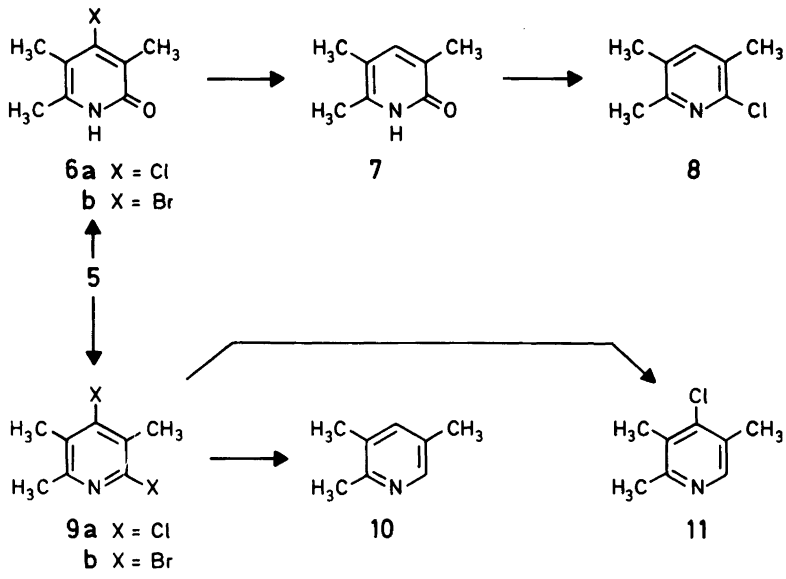
ments with methoxide ion showed sufficient selectivity. Surprisingly, selective catalytic hydrogenolysis of **9** in glacial acetic acid gave predominantely the desired 4-monochloro derivative **11** in addition to the 2-chloro-3,5,6-trimethylpyridine (**8**) and the completely dechlorinated product (**10**). The separation of pure **11** was considered possible in view of the different pK_a values of the starting material and reaction products. At pH 2.1 the starting material ($pK_a = 0.98$) and the side product 2-chloro-3,5,6-trimethylpyridine (**8**) were removed from aqueous solution by extraction with diethyl ether. After the pH had been adjusted to 4.6, **11** was isolated by extraction in 78% yield, leaving the 2,3,5-trimethylpyridine protonated.

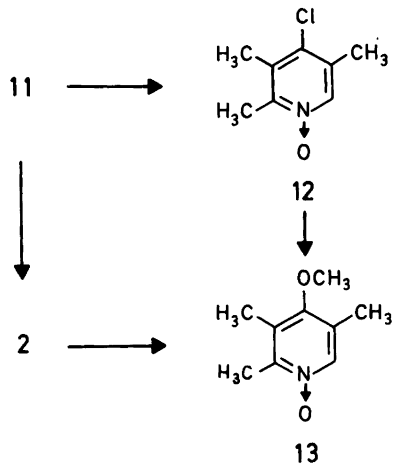
Substitution of the chlorine in **11** by methoxide ion should give the desired 4-methoxy-2,3,5-trimethylpyridine (**2**). Simple heating of **11** with methoxide in methanol gave **2** only in poor yields. Even drastic reaction conditions in a sealed tube did not improve the reaction. However, a recently described method[15] using methanol and freshly powdered KOH in dimethyl sulfoxide gave the methoxy products (**2**) in 77% yield. Oxidation of **2** afforded the corresponding *N*-oxide (**13**), which also could be synthesized from **11** by oxidation to the *N*-oxide (**12**) and further substitution of the chlorine by methoxide ion. Both routes gave the *N*-oxide (**13**) in comparable yields.

Experimental

Ethyl 3-amino-2-methyl-2-butenoate (**3**). A mixture of ethyl 2-methylacetoacetate (1000 g, 6.94 mol) and liquid ammonia (340 g, 20 mol) was stirred in an autoclave and the temperature was gradually increased to 80 °C over 4 h. This temperature was maintained for 14 h, then decreased to 40 °C and the excess ammonia was evaporated. Toluene (1000 ml) was added and the reaction water was separated. After the organic layer had been dried and evaporated, 980 g (99%) of **3** were obtained: m.p. 48–51 °C (lit.,[13] m.p. 52 °C); ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 1.25 (t, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 4.12 (q, 2 H, CH_2).

4-Hydroxy-3,5,6-trimethyl-2(1H)-pyridone (**5**). A solution of diethyl 2-methylmalonate (**4**) (131.0 g, 0.75 mol) in 40 ml toluene was added to a solution of sodium (17.7 g, 0.77 mol) in 260 ml absolute ethanol and the mixture was stirred for 30 min. A solution of **3** (108.0 g, 0.75 mol) in 100 ml toluene was added and the mixture was heated under reflux for 24 h during which time a precipitate was formed. After 500 ml water had been added the mixture was stirred and heated to 40 °C until a two-phase system had formed. The water layer was washed with toluene and neutralized with conc. hydrochloric acid to pH = 7.0. The precipitate thus obtained was filtered, washed





with water and dried to give 87.0 g (76%) colorless crystals: m.p. 260°C (decomp). ^{1}H NMR ([$^2H_6$]Me_2SO; $SiMe_4$): δ 1.91 (s, 6 H, CH_3), 2.12 (s, 3 H, CH_6). Anal. $C_8H_{11}NO_2$: C, H, N.

4-Chloro-3,5,6-trimethyl-2(1H)pyridone (**6a**). A mixture of **5** (6.12 g, 40 mmol) and phosphorus pentachloride (12.48 g, 60 mmol) was heated at 100°C for 1 h. The resulting oil was treated with ethanol and the crystalline residue thus obtained was filtered and recrystallized from ethanol. The yield was 4.5 g (66%) of colorless needles: m.p. 225°C. ^{1}H NMR ([$^2H_6$]Me_2SO; $SiMe_4$): δ 2.05 (s, 6 H, CH_3), 2.21 (s, 3 H, CH_3), 11.50 (broad, 1 H, NH). Anal. $C_8H_{10}ClNO$: C, H, Cl, N.

4-Bromo-3,5,6-trimethyl-2(1H)-pyridone (**6b**). A mixture of **5** (6.12 g, 40 mmol) and phosphoryl bromide (17.2 g, 60 mmol) was heated at 110°C for 1 h. The cooled mixture was poured onto crushed ice, filtered and recrystallized from ethanol. The yield was 8.0 g (93%) of colorless needles: m.p. 227°C. ^{1}H NMR ([$^2H_6$]Me_2SO; $SiMe_4$): δ 2.00 (s, 6 H, CH_3), 2.17 (s, 3 H, CH_3), 11.00 (broad, 1 H, NH). Anal. $C_8H_{10}BrNO$: C, H, Br, N.

3,5,6-Trimethyl-2(1H)-pyridone (**7**). A solution of **6a** (1.71 g, 10 mmol) in 50 ml isopropyl alcohol was treated with palladium chloride (0.2 g) and potassium acetate (2.0 g). The mixture was hydrogenated at 4 bar for 5 h. After the reaction mixture had been filtered, the solvent was distilled off and the residue was treated with water. The solid product was filtered off to give 1.0 g (73%) of **7**: m.p. 169°C. ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.07 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 7.08 (s, 1 H, CH), 13.30 (s, 1 H, NH). Anal. $C_8H_{11}NO$: C, H, N.

2-Chloro-3,5,6-trimethylpyridine (**8**). A mixture of **7** (1.37 g, 10 mmol) and phosphoryl chloride (6.7 g, 44 mmol) was heated in a sealed tube at 150°C for 5 h. The mixture was poured onto crushed ice, whereupon the neutralized solution was extracted with diethyl ether. The evaporated extracts gave 1.0 g (65%) of **8**: m.p. 60°C. ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.23 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 7.19 (s, 1 H, CH). Anal. $C_8H_{10}ClN$: C, H, Cl, N.

2,4-Dichloro-3,5,6-trimethylpyridine (**9a**). A mixture of **5** (76.6 g, 0.50 mol) and phosphoryl chloride (201 g, 1.31 mol) was heated in an autoclave at 150°C for 4 h. The mixture was cooled and poured onto 500 g of crushed ice. The precipitated product was taken up in toluene. After having been washed and dried, the toluene layer was evaporated to give an oil that solidified on being cooled. The yield was 90.3 g (95%) of colorless needles from water–ethanol: m.p. 70°C. ^{1}H NMR ([$^2H_6$]Me_2SO; $SiMe_4$): δ 2.20 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3). Anal. $C_8H_9Cl_2N$: C, H, Cl, N.

2,4-Dibromo-3,5,6-trimethylpyridine (**9b**). A mixture of **5** (6.12 g, 40 mmol) and phosphoryl bromide (14.3 g, 50 mmol) was heated under reflux for 20 min. The mixture was cooled and poured onto crushed ice, and the crystalline product was filtered and recrystallized from ethanol with addition of charcoal. The yield was 4.6 g (42%) of colorless needles: m.p. 70°C. ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.43 (s, 3 H, CH_3), 2.60 (s, 6 H, CH_3). Anal. $C_8H_9Br_2N$: C, H, Br, N.

2,3,5-Trimethylpyridine (**10**). (*a*) A solution of **9a** (19.0 g, 0.10 mol) in 150 ml ethanol was treated with 1 g Pd/C (10%) and 10 ml conc. NH_3. The hydrogenation was performed at 3 bar until the calculated amount of hydrogen had been absorbed (ca. 3 h). The reaction mixture was filtered, the filtrate was evaporated, and the residual oil was distilled under reduced pressure. The yield was 10.0 g (83%): b.p. 63–65°C (12 mm)

[lit.,[14] b.p. 65–68 °C (12 mm)]. Anal. $C_8H_{11}N$: C, H, N.

(*b*) A solution of **9a** (3.8 g, 20 mmol) in 30 ml ethanol was treated with 5 g of zinc powder. After 10 ml of 2 M H_2SO_4 had been added the mixture was heated under reflux for 1 h. The cooled, filtered solution was adjusted with 2 M NaOH to pH 6.0. The precipitated zinc salts were removed by filtration and the filtrate was extracted three times with light petroleum. After the combined extracts had been dried and evaporated, 2.0 g (83 %) of **10** were obtained.

4-Chloro-2,3,5-trimethylpyridine (**11**). A solution of **9a** (19.0 g, 0.10 mol) in 30 ml ethanol was treated with 4 ml conc. H_2SO_4 and 0.5 g Pd/C (10 %). The hydrogenation was performed at 2 bar and 20 °C until one equivalent of hydrogen had been consumed. After filtration of the catalyst and evaporation of the solvent, the residue was diluted with water and the pH was adjusted to 2.1. The aqueous solution was extracted with toluene. The toluene layer contained starting material and 2-chloro-3,5,6-trimethylpyridine, the aqueous layer **11** and 2,3,5-trimethylpyridine. The pH of the water phase was adjusted to 4.6 and **11** was then extracted with toluene (3×30 ml). Evaporation of the solvent gave 12.1 g (78 %) of **11** as colorless oil. ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.30 (s, 6 H, CH_3), 2.50 (s, 3 H, CH_3), 8.25 (s, 1 H, CH). Anal. $C_8H_{10}ClN$: C, H, Cl, N.

4-Methoxy-2,3-5-trimethylpyridine (**2**). A mixture of **11** (15.6 g, 0.1 mol), methanol (9.4 g) and freshly powdered KOH (15.6 g) in 250 ml dimethyl sulfoxide was heated with stirring for 15 h at 60 °C. The cooled mixture was diluted with 700 ml water and extracted 3 times with 50 ml dichloromethane. After the solvent had been dried and evaporated 11.6 g (77 %) of **2** were obtained as a colorless oil. ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.20 (s, 6 H, CH_3), 2.45 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 8.20 (s, 1 H, CH). Anal. $C_9H_{13}NO$: C, H, N.

4-Chloro-2,3,5-trimethylpyridine N-*oxide* (**12**). A solution of **11** (11.3 g, 72.8 mmol) in 50 ml glacial acetic acid was heated to 60 °C and then slowly treated with 10.3 ml 30 % H_2O_2. The temperature was maintained for 4 h and finally increased to 90 °C for 2 h. A small amount of Pd/C was added to destroy excess H_2O_2. The solvent was evaporated, and the residue was made alkaline and extracted with diethyl ether to remove unchanged starting material. The aqueous phase was saturated with NaCl and extracted several times with dichloromethane. The organic layer was dried and evaporated to give 10.1 g (83 %) of **12**: m.p. 148 °C: ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.30 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.55 (s, 3 H, CH_3), 8.20 (s, 1 H, CH). Anal. $C_8H_{10}ClNO$: C, H, Cl, N.

4-Methoxy-2,3,5-trimethylpyridine N-*oxide* (**13**). (*a*) A solution of **12** (0.86 g, 5 mmol) in 8.5 ml 2 M sodium methoxide solution was heated in a closed vessel at 70 °C for 16 h. After the solvent had been evaporated the residue was treated with water and extracted with dichloromethane. From the dried, evaporated extracts were obtained 0.77 g (92 %) of **13** as a waxy solid: m.p. 35 °C. ^{1}H NMR ($CDCl_3$; $SiMe_4$): δ 2.25 (s, 6 H, CH_3), 2.50 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 8.20 (s, 1 H, CH). Anal. $C_9H_{13}NO_2$: C, H, N.

(*b*) A solution of **2** (15.1 g, 0.1 mol) in 50 ml glacial acetic acid and 25 ml 30 % H_2O_2 was stirred at 30 °C for 1 h. The temperature was gradually increased to 70 °C and maintained for 5 h, then increased to 90 °C before the addition of a small amount of Pd/C to destroy the excess H_2O_2. The solvents were evaporated under reduced pressure. Toluene was added and stripped off in order to remove any water from the product. The yield was 15.9 g (95 %) of a partly crystalline product: m.p. 35 °C.

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