An Improved Synthesis of Butyl 4-[(4-Amino-5-chloro-2-methoxybenzoyl)amino]-1-piperidineacetate (AU-224)

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A new and facile route for the synthesis of the novel gastrointestinal prokinetic butyl 4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-1-piperidineacetate (1b), which exhibited potent gastro- and colon-prokinetic activities by oral administration without significant side effects, was established. The key intermediate, butyl 4-amino-1-piperidineacetate (16), was prepared from commercially available 4-amino-1-benzylpiperidine (2) in a high yield with four steps. Compound 1b was prepared by condensation of commercially available 4-amino-5-choloro-2-methoxybenzoic acid (7) with 16 in 84% yield. This improved synthetic route was appropriate for large-scale synthesis of 1b.

Key words large-scale synthesis; gastroprokinetic activity; colon-prokinetic activity; butyl 4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-1-piperidineacetate

We recently reported the synthesis and gastrointestinal prokinetic activity of novel benzamide derivatives with amphoteric side chains.[1)] Among them, 4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-1-piperidineacetic acid (**1a**) exhibited the most excellent gastro- and colon-prokinetic activities by intravenous administration to conscious dogs without significant dopamine D_2 receptor antagonist activity. However, **1a** showed only weak gastrointestinal prokinetic activity after oral administration due to its low lipophilicity. After the evaluation of several ester prodrugs of **1a**, the butyl ester (**1b**) was consequently selected as a promising gastrointestinal prokinetic agent without significant side effects.

As described previously,[1)] compound **1b** was prepared by esterification of **1a** with butyl bromide in a large amount of *N*,*N*-dimethylformamide (DMF). The key intermediate **6** was obtained in four steps and an overall yield of 48% from commercially available 4-amino-1-benzylpiperidine (**2**). A compound **1a** was prepared in four steps and an overall yield of 40% from commercially available 4-amino-5-chloro-2-methoxybenzoic acid (**7**) as shown in Chart 2.

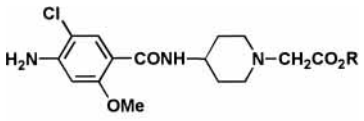
Although the previous route was quite adequate for the synthesis with a wide variety of 4-[(4-amino-5-chloro-2-methoxybenzoyl)amino]-1-piperidinealkanecarboxylic acids or the assorted ester prodrugs of **1a**, the overall yield (14%) of **1b** from **2** was not sufficient and a number of steps (9 steps) were required. We have therefore developed a new and facile synthetic route for a high overall yield with only short steps. In this paper, we describe a new and efficient route for the synthesis of **1b**.

In a new synthetic route, the key intermediate, butyl 4-amino-1-piperidineacetate (**16**), was prepared as shown in Chart 3. The amino group of **2** was protected with di-*tert*-butyl dicarbonate (Boc_2O) in acetonitrile (CH_3CN) to give compound **11**[2)] in 90% yield. Debenzylation of **11** with Pearlman's catalyst[3)] and cyclohexene in ethyl alcohol (EtOH) afforded a secondary amine (**12**)[2)] in 92% yield. Alkylation of **12** with butyl chloroacetate (**14**),[4)] which was derived from chloroacetyl chloride (**13**) and butyl alcohol (*n*-BuOH) in 92% yield, was accomplished using triethylamine (Et_3N) as a base in DMF to give compound **15** in 93% yield. Since the usage of potassium carbonate (K_2CO_3) as a base in this step produced a great deal of the byproduct, butyl 4-*tert*-butoxycarbonylamino-1-piperidinecarboxylate, we changed the base from K_2CO_3 to Et_3N. Next, the deprotection with hydrogen chloride–isopropyl alcohol solution of **15** followed by the removal of acid using Et_3N gave a primary amine (**16**) quantitatively. Compound **7** was converted into the activated ester with ethyl chlorocarbonate ($ClCO_2Et$) in anhydrous tetrahydrofuran (THF) and then amidated with **16** to give the desired ester (**1b**) in good (84%) yield.

In conclusion, we have established an efficient route for the synthesis of **1b**, a novel promising gastro- and colon-prokinetic agent. The new route shortened the total steps of the synthesis of **1b** and consequently improved significantly the total yield (14%→65%) from the starting material **2**. Furthermore, this route was found to be applicable to the large-scale synthesis of **1b**. Pre-clinical studies on **1b** (AU-224) are now in progress.

Experimental

All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Spectral data were obtained using the following apparatus: ^{1}H-NMR spectra with JEOL LA-300 (300 MHz) and JEOL A-500 (500 MHz) spectrometers; mass spectra (MS) with a JEOL JMS-DX 300 mass spectrometer; IR spectra with a Hitachi 270-30 spectrometer. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed using Yanagimoto MT-5 or MT-6 elemental analysis apparatus. TLC was conducted on a 0.25 mm pre-coated silica gel plate ($60F_{254}$, Merck), and spots were detected by inspection under short (254 nm) wavelength UV light, or by the colors developed with iodine. Organic extracts were dried over anhydrous Na_2SO_4.



1a: R = H

1b: R = *n*-Bu

Chart 1

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A Previous Route for Synthesis of **1b**

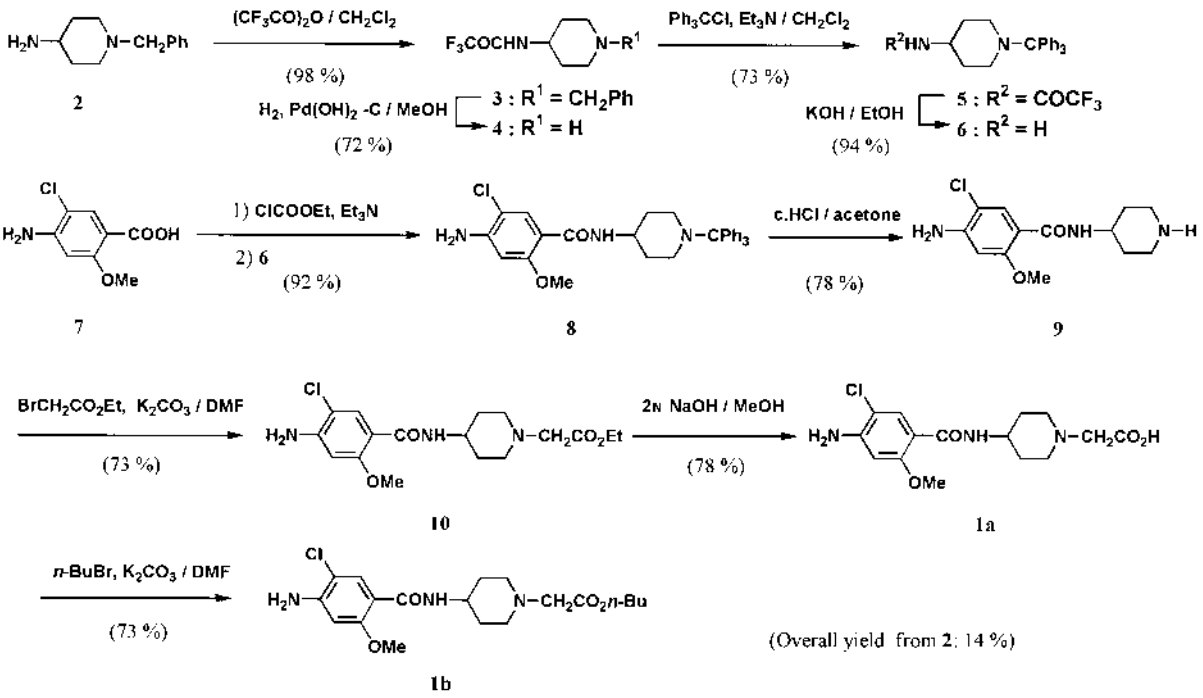

Chart 2

A New Route for Synthesis of **1b**

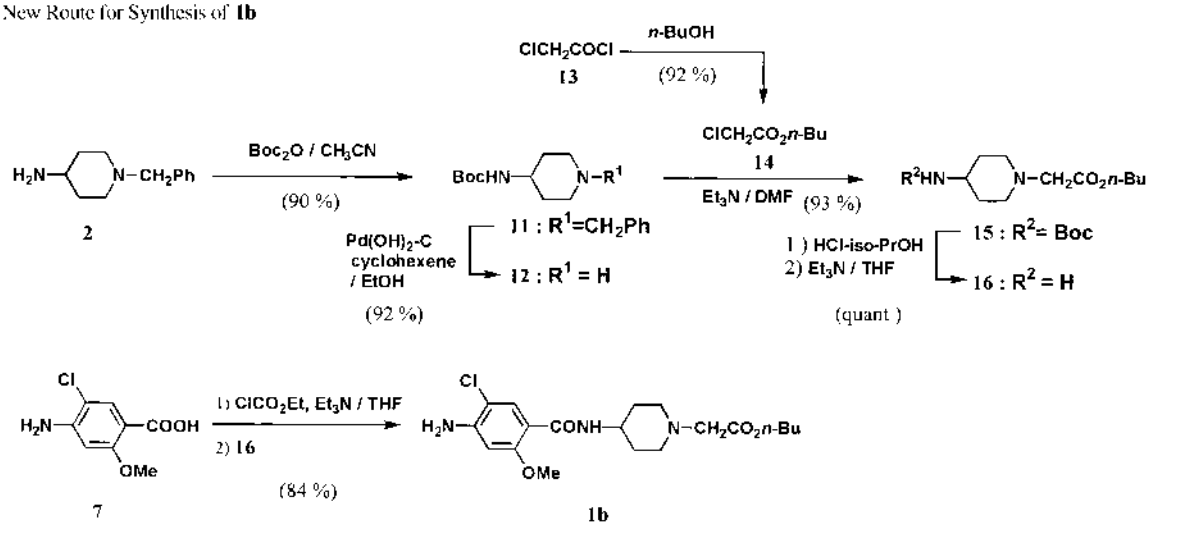

Chart 3

The solvent was evaporated under reduced pressure.

***N*-(1-Benzyl-4-piperidyl)-*tert*-butoxycarbamate (11)** A solution of Boc_2O (1150 g, 5.27 mol) in CH_3CN (2.0 l) was added to a solution of 4-amino-1-benzylpiperidine (1002 g, 5.27 mol) in CH_3CN (8.0 l) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and the resultant crystal was filtered and washed with CH_3CN to give 1383 g of **11** (90%) as a colorless crystal, mp 122—123 °C (lit.[2a]: mp 135—138 °C, lit.[2b]: mp 123 °C). IR ν (KBr) cm^{-1}: 3368, 1686. ^{1}H-NMR ($CDCl_3$): 1.30—1.50 (3H, m), 1.43 (9H, s), 1.85—1.95 (2H, m), 2.00—2.15 (2H, m), 2.75—2.85 (2H, m), 3.49 (2H, s), 3.49 (1H, br s), 4.42 (1H, br s), 7.20—7.35 (5H, m).

***N*-(4-piperidyl)-*tert*-butoxycarbamate (12)** A mixture of **11** (1381 g, 4.76 mol), 20% Pd $(OH)_2$–C (41.4 g) and cyclohexene (481 ml, 4.75 mol) in EtOH (11 l) was refluxed for 3.5 h. The catalyst was removed by filtration and the filtrate was concentrated. The resultant residue was filtered and washed with diisopropyl ether (iso-Pr_2O) to give 873 g of **12** (92%) as a colorless crystal, mp 163—164 °C (lit.[2a]: mp 153—155 °C, lit.[2b]: mp 163 °C). IR ν (KBr) cm^{-1}: 3388, 1694. ^{1}H-NMR ($CDCl_3$): 1.20—1.35 (3H, m), 1.43 (9H, s), 1.90—2.00 (2H, m), 2.60—2.70 (2H, m), 3.00—3.10 (2H, m), 3.50 (1H, br s), 4.47 (1H, br s).

Butyl Chloroacetate (14) Chloroacetyl chloride (3000 g, 26.6 mol) was added to *n*-BuOH (2.55 l, 27.9 mol) under ice-cooling, and the mixture was left for 0 d in a sealed tube. Water and iso-Pr_2O (9.0 l) were added to the mixture and the organic layer was separated. The organic layer was washed with saturated NaCl and dried. The solvent was evaporated and the residue was distilled under reduced pressure and nitrogen atmosphere to give 3675 g of **14** (92%) as colorless liquid, bp_{100} 100—115 °C (lit.[4a]: bp_{20} 81 °C, lit.[4b]: bp 172—174 °C). IR ν (liq.) cm^{-1}: 1760. ^{1}H-NMR ($CDCl_3$): 0.95 (3H, t, J=7 Hz), 1.40 (2H, sext, J=7 Hz), 1.65 (2H, quint, J=7 Hz), 4.06 (2H, s), 4.20 (2H, t, J=7 Hz).

Butyl 4-*tert*-Butoxycarbonylamino-1-piperidineacetate (15) A solution of **14** (0.79 g, 5.25 mmol) in DMF (4 ml) was added to a suspension of

12 (1.00 g, 4.99 mmol) and Et_3N (0.72 ml, 5.25 mol) in DMF (6 ml) at 50 °C and the mixture was stirred at 50 °C for 1 h. Water was poured into the reaction mixture and the resultant crystal was collected and washed successively with water and heptane to give 1.46 g (93%) of **15** as a colorless crystal, mp 115.5—116.5 °C. *Anal*. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.90; H, 9.60; N, 8.88. IR ν (KBr) cm^{-1}: 3384, 1730, 1698. ^{1}H-NMR ($CDCl_3$): 0.93 (3H, t, J=7.5 Hz), 1.37 (2H, sext, J=7.5 Hz), 1.40—1.60 (3H, m), 1.44 (9H, s), 1.62 (2H, quint, J=7.5 Hz), 1.90—1.95 (2H, m), 2.20—2.30 (2H, m), 2.85—2.90 (2H, m), 3.20 (2H, s), 3.47 (1H, br s), 4.12 (2H, t, J=7.5 Hz), 4.43 (1H, br s).

Butyl 4-Amino-1-piperidineacetate (16) A mixture of **15** (1.35 g, 4.29 mmol) in 36% hydrogen chloride–isopropyl alcohol solution (6 ml) was stirred for 15 min at room temperature. The solvent was evaporated and a solution of Et_3N (1.3 ml, 9.48 mmol) in THF (5 ml) was added to the residue. The resultant precipitate was filtered off. The filtrate was concentrated to give 0.94 g (quantitatively) of **16** as colorless liquid. MS *m/z*: 214 (M^+). IR ν (liq.) cm^{-1}: 2960, 2940, 1746. ^{1}H-NMR ($CDCl_3$): 0.93 (3H, t, J=7.5 Hz), 1.37 (2H, sext, J=7.5 Hz), 1.45—1.55 (2H, m), 1.55—1.65 (2H, m), 1.86 (2H, d, J=12 Hz), 2.02 (2H, br s), 2.20—2.30 (2H, m), 2.65—2.75 (1H, m), 2.90 (2H, d, J=12 Hz), 3.21 (2H, s), 4.12 (2H, t, J=7.5 Hz).

Butyl 4-[(4-Amino-5-chloro-2-methoxybenzoyl)amino]-1-piperidineacetate (1b) A mixture of **7** (1065 g, 5.28 mol), Et_3N (821 ml, 5.89 mol) and $ClCO_2Et$ (526 ml, 5.54 mol) in anhydrous THF (11 l) was stirred under ice cooling. After 1.5 h, a solution of **16** (1260 g, 5.88 mol) in anhydrous THF (2.4 l) was added dropwise to the mixture, and the mixture was stirred under ice cooling for 2 h. The insoluble substance was filtered off and the filtrate was concentrated. Methyl isobutyl ketone (MIBK) (12.6 l), water (4.2 l) and K_2CO_3 (73 g) were added to the resultant residue. The MIBK layer was washed with saturated NaCl, dried and concentrated. The residue was washed with iso-Pr_2O to give 1759 g (84%) of **1b** as a colorless crystal, mp 102—103 °C. *Anal*. Calcd for $C_{19}H_{28}ClN_3O_4$: C, 57.35; H, 7.09; N, 10.56. Found: C, 57.15; H, 7.09; N, 10.52. IR ν (KBr) cm^{-1}: 3488, 3388, 3316, 1754, 1642. ^{1}H-NMR ($CDCl_3$): 0.94 (3H, t, J=7.5 Hz), 1.38 (2H, sext, J=7.5 Hz), 1.60—1.75 (2H, m), 1.63 (2H, quint, J=7.5 Hz), 2.00—2.10 (2H, m), 2.30—2.40 (2H, m), 2.85—2.95 (2H, m), 3.23 (2H, s), 3.88 (3H, s), 4.00—4.10 (1H, m), 4.13 (2H, t, J=7.5 Hz), 4.38 (2H, s), 6.29 (1H, s), 7.65 (1H, d, J=8 Hz), 8.09 (1H, s).

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