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A Scalable Synthesis of a Histamine H_3 Receptor Antagonist

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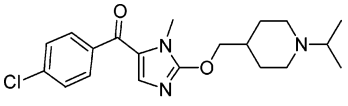
Abstract: Starting from 1-methylimidazole, a concise, scalable, three-step synthesis of the title compound is described. The required 2-chloroimidazole was prepared in very good yield by halogen−metal exchange between the 2-lithio derivative and hexachloroethane.

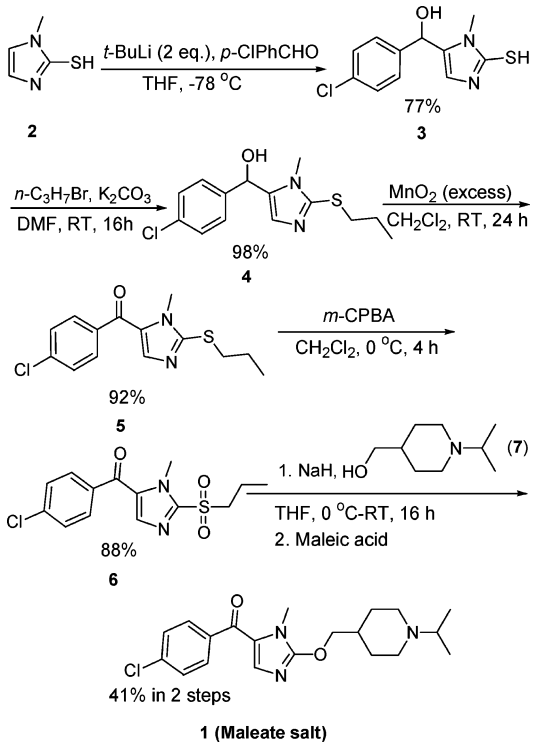
The third histamine (H_3) receptor was first described as a presynaptic autoreceptor located in the central nervous system.[1] Subsequently, H_3 receptors were also shown to be located presynaptically as heteroreceptors on nonhistamine-containing neurons.[2] A number of potential therapies for disorders associated with sleep−wake cycle, cognition, memory, food intake, and thermoregulation using modulators of H_3 receptors have been proposed on the basis of animal pharmacology experiments. The successful cloning of the human histamine H_3 receptor[3] led to an intensive medicinal chemistry effort in this area, and a number of novel H_3 antagonists have been identified in our laboratories. Compound **1** was identified as one of the most promising among a number of potent H_3 antagonists for further pharmacological evaluation.[4] Toward this purpose, multigram quantities of **1** were needed. Our initial laboratory synthesis appeared to be unsuited for this purpose. As outlined in the Scheme 1, it involved a six-step synthetic sequence including reagents undesirable for large-scale work, hazardous reaction conditions, and chromatographic purifications. Herein we describe a shorter, more efficient, and scalable synthesis of **1**.



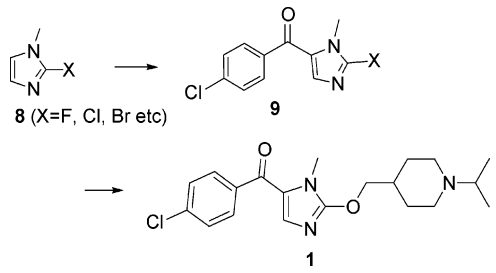
1

The discovery synthesis started from *N*-methylimidazole-2-thiol and employed a selective metalation strategy[5] to install the required 4-chlorobenzoyl group at the C-5 position (Scheme 1). Through a sequence of alkylation and oxidation steps, the thiol moiety at the C-2 position was then transformed to a reactive propylsulfonyl leaving group, which underwent nucleophilic substitution with (1-isopropylpiperiden-4-yl)methanol (**7**) to furnish the final product.

SCHEME 1



SCHEME 2



In the scale-up synthesis, our strategy relied on regioselective metalation of an imidazole to install the 4-chlorobenzoyl group at the C-5 position. Since metalation at C-5 requires masking the C-2 position of the imidazole, our concept was to employ a suitable group that not only blocked the C-2 position during the metalation at C-5 but also functioned as a reactive leaving group in a nucleophilic substitution reaction directly in the next step as depicted in Scheme 2. Among the halogens, chlorine and fluorine were considered to play this dual role since they are most likely to be stable to metalating reagents such as *n*-butyllithium.[6] Chlorine appeared most suitable, due

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SCHEME 3

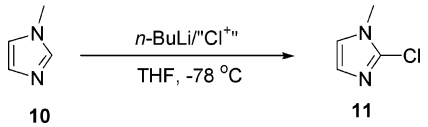


TABLE 1. Preparation of 2-Chloro-1-methyl-1*H*-imidazole (11)

chlorine source	solvent	*T* (°C)	yield (%)
CCl_3COCl	THF	−78	20
Cl_2	THF	0	10
CCl_4	THF	−78	38
C_2Cl_6	THF	−78	80

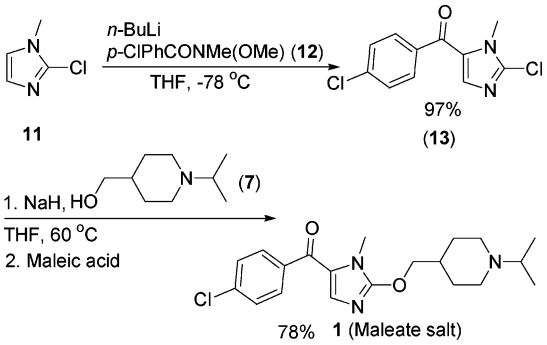
to the ease of its introduction, particularly when required in large scale. In addition, use of chlorine as a protecting group at C-2 during lithiation at C-5 of some imidazole derivatives has been reported.[7,8c] Thus, 2-chloro-1-methylimidazole was chosen as the key synthon for preparing **1** and related analogues.

Preparation of 2-chloroimidazole derivatives has been reported.[8] The most efficient method appeared to be lithiation of *N*-methylimidazole and reaction of the 2-lithio derivative with a positive halogen source (Scheme 3). The reported procedures using trichloroacetyl chloride and carbon tetrachloride[8b,c] gave moderate yields (30−40%) of the required 2-chloro derivative in our hands (Table 1). In addition, these reagents posed significant difficulties for large-scale preparations. Both trichloroacetyl chloride and CCl_4 generated highly reactive intermediates (dichloroketene and dichlorocarbene, respectively), which decomposed under the reaction and workup conditions and made isolation very difficult. Hexachloroethane, readily available and inexpensive, proved a more useful chlorine source for the halogen−metal exchange reaction. Tetrachloroethylene, the byproduct formed during the reaction, was quite stable to the reaction and workup conditions and was easily removed by distillation (bp 121 °C).

Thus, treatment of *N*-methylimidazole with *n*-butyllithium generated the 2-lithio derivative, which on quenching with hexachloroethane gave the 2-chloro derivative in very good yield as a colorless liquid.

Introduction of the 4-chlorobenzoyl substituent at C-5 by regioselective lithiation strategy also worked efficiently. Thus, treatment of 2-chloro derivative **11** with *n*-butyllithium generated the 5-lithio derivative, which on treatment with Weinreb amide **12**[9] furnished the desired 4-chlorobenzoyl analogue **13** in excellent overall yield as a crystalline solid. Nucleophilic substitution[10] of the activated 2-chloro-5-benzoylimidazole **13** with the sodium salt of 4-piperidinylmethanol **7**[11] proceeded smoothly to furnish the free base of **1** in 78% yield (Scheme 4).

SCHEME 4



In conclusion, we have developed a concise, three-step synthesis of **1** starting from 1-methylimidazole. Consistently good to excellent yields were obtained in all steps, and all the intermediates were purified by distillation and/or crystallization. Use of a 2-chloroimidazole derivative, in which the chlorine plays a dual role—blocking the C-2 position during metalation and reacting as a leaving group in subsequent step—as illustrated in our synthesis, provides a unique and general strategy to a range of substituted imidazoles.

Experimental Section

Preparation of 2-Chloro-1-methyl-1*H*-imidazole (11). To a 300-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet were added *N*-methylimidazole (4.1 g, 0.05 mol) and anhydrous THF (25 mL). The stirrer was started, and the solution was cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 22 mL, 0.055 mol) was added via syringe resulting in a golden yellow solution. This solution was stirred for 30 min whereupon a solution of hexachloroethane (13 g, 0.055 mol) in THF (25 mL) was added dropwise via syringe. The reaction mixture was stirred for 1 h and then quenched with saturated aqueous ammonium chloride (25 mL). The cooling bath was removed, and when the reaction flask reached room temperature the contents were transferred to a 500 mL separatory funnel, washing with ethyl acetate (150 mL). The organic layer was separated, washed with water and brine, and dried over anhydrous sodium sulfate. After filtration, the solvents were evaporated under reduced pressure resulting in an oily residue. This crude product was distilled under reduced pressure to afford 2-chloro-1-methyl-1*H*-imdazole (4.75 g, 80%) as a colorless liquid, bp 136 °C/5 Torr. Purity was determined to be 97.3% by GC analysis (HP-5MS 30 m × 0.25 mm × 0.25 μm column; oven temperature 55 °C; ramp 10 °C/min; final temperature 270 °C; mass selective detector; retention time 5.6 min). IR (film): 1515, 1420, 1367, 1277, 1127, 912, 740, 689, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J = 1.6 Hz, 1 H), 6.89 (d, J = 1.6 Hz, 1 H), 3.55 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.2, 127.9, 121.8, 33.1. HRMS (EI): *m/z* calcd for $C_4H_6ClN_2$ $[M + H]^+$ 117.0223, found 117.0220.

Preparation of 4-Chloro-*N*-methoxy-*N*-methylbenzamide (12). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet, and an addition funnel was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (20 g, 0.20 mol) and dichloromethane (250 mL). The mixture was cooled to 0 °C, and triethylamine (24 g, 0.20 mol) was added, followed by a solution of 4-chlorobenzoyl chloride (35.8 g, 0.2

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(11) Compound **7** was prepared by treating 4-piperidenemethanol with acetone and sodium triacetoxyborohydride. For detailed experimental procedures, see the Supporting Information.

mol) in dichloromethane (100 mL). After the addition was complete, the cooling bath was removed, and the reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (200 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were washed with aqueous sodium bicarbonate and brine and then dried over anhydrous magnesium sulfate. After filtration, the solvents were evaporated under reduced pressure to afford the benzamide **12** (37 g, 92%) as a colorless oil. IR (film): 2935, 1639, 1593, 1460, 1415, 1212, 1090, 1015, 887, 838, 747, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.6 Hz, 2 H), 7.32 (d, J = 8.6 Hz, 2 H), 3.55 (s, 3 H), 3.11 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 137.3, 132.9, 130.5, 128.8, 61.7, 34.1. HRMS (EI): *m/z* calcd for $C_9H_{11}ClNO_2$ $[M + H]^+$ 200.0478, found 200.0484.

(2-Chloro-3-methyl-3*H*-imidazol-4-yl)(4-chlorophenyl)-methanone (13). To a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet, and an addition funnel were added 2-chloro-1-methyl-1*H*-imidazole (15 g, 0.128 mol) and THF (250 mL). The reaction mixture was cooled to −78 °C, and *n*-BuLi (2.5 M in hexanes, 54 mL, 0.135 mol) was added. The pale yellow suspension that formed was stirred for 1 h, and a solution of 4-chloro-*N*-methoxy-*N*-methylbenzamide (27 g, 0.135 mol) in THF (50 mL) was then added dropwise. After the addition was complete, the cooling bath was removed, and the reaction was allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride (150 mL), transferred to a separatory funnel, and extracted with ethyl acetate (1.5 L). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. After filtration, the solvents were evaporated under reduced pressure to yield the product as a crystalline solid. Recrystallization from ethyl acetate−hexanes afforded the desired ketone (31.2 g, 97%) as a white crystalline solid. Mp: 173−174 °C. IR (film): 1639, 1589, 1517, 1395, 1377, 1253, 1186, 902, 841, 756, 738, 695, 676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 2 H), 7.44 (s, 1 H), 7.44 (d, J = 8.6 Hz, 2 H), 3.97 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 140.3, 139.5, 139.2, 136.3, 131.2, 130.4, 128.9, 33.5. HRMS (EI): *m/z* calcd for $C_{11}H_9Cl_2N_2O$ $[M + H]^+$ 255.0092, found 255.0104. Anal. Calcd for $C_{11}H_8Cl_2N_2O$: C, 51.8; H, 3.06; N, 10.93. Found: C, 52.08; H, 3.16; N, 10.90.

(4-Chlorophenyl)-[2-(1-isopropylpiperidin-4-ylmethoxy)-3-methyl-3*H*-imidazol-4-yl]methanone (1). To a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and an addition funnel were added NaH (1.45 g, 0.061 mol) and THF (300 mL). The stirred suspension was cooled to 0 °C, and (1-isopropylpiperidin-4-yl)methanol (9.5 g 0.06 mol) was added. The cooling bath was removed and the reaction mixture warmed to room temperature. After 2 h, a solution of (2-chloro-3-methyl-3*H*-imidazol-4-yl)(4-chloro-phenyl)methanone (15.56 g, 0.061 mol) in dry THF (100 mL) was added. The reaction mixture was stirred at 60 °C and monitored by HPLC every 4−8 h. After 36 h, the reaction was judged complete. The reaction mixture was cooled to room temperature, poured into ice-cold water, and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to provide the crude material as a brown solid. Recrystallization from ethyl acetate afforded the desired product (17.5 g, 78%) as a white crystalline solid. Mp: 126−127 °C. IR (film): 2963, 1615, 1585, 1529, 1481, 1362, 1287, 1213, 1173, 1104, 1020, 897,846, 727, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 7.13 (s, 1 H), 4.22 (d, J = 6.0 Hz), 3.68 (s, 3 H), 2.84 (m, 2 H), 2.61 (m, 1 H), 2.09 (m, 2 H), 1.74 (m, 3 H), 1.30 (m, 2 H), 0.97 (d, J = 6.5 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.4, 157.0, 138.3, 138.2, 137.3, 130.2, 128.7, 127.1, 74.9, 54.6, 48.4, 35.9, 30.7, 29.1, 18.3. HRMS (EI): *m/z* calcd for $C_{20}H_{27}ClN_3O_2$ $[M + H]^+$ 376.1792, found 376.1801. Anal. Calcd for $C_{20}H_{26}ClN_3O_2$: C, 63.91; H, 6.97; N, 11.17. Found: C, 63.55; H, 6.77; N, 11.05.

(4-Chlorophenyl)-[2-(1-isopropylpiperidin-4-ylmethoxy)-3-methyl-3*H*-imidazol-4-yl]methanone (1) Maleate Salt. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, reflux condenser, and an addition funnel was charged with (4-chlorophenyl)[2-(1-isopropylpiperidin-4-ylmethoxy)-3-methyl-3*H*-imidazol-4-yl]methanone (15.4 g, 40.96 mol), ethanol (170 mL), and maleic acid (4.75 g, 40.96 mol). The mixture was heated on a heating mantle at 70−75 °C until a clear solution was obtained. The heat source was removed, and the reaction mixture was cooled to room temperature. The solution was transferred to a 2-L beaker, washing with 25 mL of ethanol. The solution was diluted with 750 mL of ether with vigorous stirring. The white precipitate that formed was filtered and dried in vacuo to afford the maleate salt as a white powder. Recrystallization from water afforded the maleate salt (18.8 g, 93%) as colorless needles. Mp: 161−162 °C. IR (film): 2963, 1625, 1586, 1532, 1466, 1361, 1257, 1172,1087, 1025, 956, 757, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.6 Hz, 2 H), 7.43 (d, J = 8.6 Hz, 2 H), 7.17 (s, 1 H), 6.27 (s, 2 H), 4.36 (d, J = 6.0 Hz, 2 H), 3.73 (s, 3 H), 3.53 (m, 3 H), 2.74 (bt, J = 11.6 Hz, 2 H), 2.24−1.92 (m, 5 H), 1.34 (d, J = 6.8 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 169.7, 156.6, 138.8, 138.2, 137.5, 136.0, 130.6, 129.1, 127.7, 73.2, 57.9, 48.3, 34.4, 31.1, 26.0, 17.0. Anal. Calcd for $C_{24}H_{30}ClN_3O_6$: C, 58.21; H, 6.07; N, 8.35. Found: C, 58.6; H, 6.07; N, 8.35.

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Supporting Information Available: General experimental methods, experimental details for the preparation of **7**, and copies of ^1H and ^{13}C NMR spectra for compounds **1**, **7**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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