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Synthesis of substituted 2-phenylhistamines via a microwave promoted Suzuki coupling

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Abstract—Substitutions on the 2-position of the imidazole ring of histamine have proven useful in a number of biochemical settings. Current art for the synthesis of these constructs relies upon a cumbersome and low-yielding condensation reaction. Here-in we report a new procedure for the synthesis of a series of substituted 2-phenylhistamines utilizing a microwave-promoted Suzuki coupling.
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The utility of histamine analogues in various biochemical settings is firmly established. Derivatives of histamine based upon alterations to the 2-aminoethyl side chain have been employed as substrates for histamine *N*-methyltransferase and as antagonists of the H_1-receptor.[1,2] Methyl substitution at the 4-position of histamine generates a potent agonist of the histamine H_4-receptor.[3] Substitutions at the 2-position of histamine have been widely explored both synthetically and biochemically, primarily as pharmacological tools for the histamine receptors. Of particular interest has been the use of 2-phenylhistamines as potent agonists of the H_1-receptor.[4,5] Recent efforts by Leurs and co-workers have identified 2-(3-trifluoromethyl)phenylhistamine (**3a**) as the sole agonist of a mutant form of the histamine H_1-receptor.[6] This combination of a synthetic ligand and mutant receptor provides researchers with a tool to study the relationship between function and phenotype of a cellular target free of the selectivity issues which plague studies utilizing the native ligand and unaltered protein.

Modified native ligands such as the aforementioned histamine analogues have proven to be among the most frequently explored pharmacological tools. A key to this strategy is the ability to quickly explore numerous alterations and structural sub-types to ascertain the effectiveness of these constructs in a variety of biochemical settings. It is imperative that the strategies employed to construct these compounds are appropriately convergent to maximize synthetic efficiency. The full understanding of the biochemical utility of substituted 2-phenylhistamine analogues is likely unknown given the limited number of analogues explored to date. The synthesis of substituted 2-phenylhistamines has relied upon a condensation between amidines/imidates and 2-oxo-4-phthalimido-1-butyl acetate to afford phthalimide protected histamine analogues.[5,7] Thus, a separate syntheses of substituted amidines or imidates are required for individual substituted 2-phenylhistamine analogues. Recognizing the biochemical utility of these constructs and the need for efficient methods to generate larger numbers of related analogues, we sought out alternate synthetic methods.

The utility of palladium-catalyzed cross-coupling reactions has evolved to become a major foundation by which new carbon-carbon bonds are formed.[8] The inclusion of microwave heating has aided the speed and efficiency of these transformations, particularly in the case of aryl–aryl Suzuki couplings.[9] It was our goal to develop a synthetic method for the formation of substituted 2-phenylhistamines utilizing a microwave-promoted Suzuki coupling between substituted phenyl boronic acids and a common 2-halohistamine derivative. Suzuki couplings between halo-heteroaromatic

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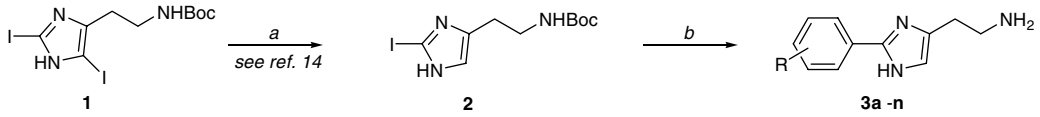


Scheme 1. Reagents and conditions: (a) 1 N HCl, reflux 72 h; then $(Boc)_2O$, 4 M NaOH, dioxane/H_2O (50% over two steps); (b) $PdCl_2(PPh_3)_2$ 5 mol %, DME, 30 min; then **4a**–**n** (3 equiv), aq Na_2CO_3, microwave irradiation (110 °C, 2 h); then 4 N HCl microwave irradiation (110 °C, 30 min).

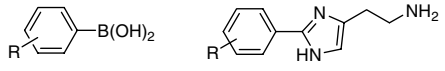
constructs and aryl-boronic acids are frequently reported and successful examples include couplings between aryl-boronic acids and benzimidazoles,[10] imidazoles,[11] pyrimidines,[12] and oxazoles.[13] A method for the construction of substituted 2-phenylhistamines using this approach would allow for the rapid advancement of numerous analogues via a final stage coupling from a common precursor.

Our method relies upon the facile synthesis of a 2-halohistamine derivative for the implementation of the final Suzuki reaction (Scheme 1). To achieve this a protocol from Cohen and co-workers[14] was utilized whereby Boc protected (α-nitrogen) histamine was iodinated with 2.2 equiv of *N*-iodosuccinimide to achieve N^{α}-Boc-2, 4-diiodohistamine (**1**) in quantitative yield. Monoiodinations utilizing stoichiometric quantities of *N*-iodosuccinimide resulted in complex mixtures of the mono and diiodinated products. Treatment of **1** in refluxing 1 N HCl for 72 h followed by replacement of the Boc protecting group effectively yielded the necessary N^{α}-Boc-2-iodohistamine (**2**) in modest yields over two steps. This key intermediate was then subjected to Suzuki type conditions {$PdCl_2(PPh_3)_2$ [5 mol %] in DME for 30 min followed by 3 equiv of boronic acids **4a**–**n** in aqueous sodium bicarbonate}.[15] The mixture was heated via microwave irradiation to 110 °C for 2 h at which time a 4 N solution of HCl in DME was added to the reaction mixture and microwave irradiation was continued for an additional 0.5 h. Higher temperatures with shorter reaction times resulted in decomposition of the iodohistamine and an inability to recover the coupled biaryl product. The resulting products (**3a**–**n**) were purified immediately (failure to immediately purify the final products was consistently detrimental to the overall yield). Table 1 describes the scope and generality of the procedure utilizing variously substituted phenyl boronic acids to yield numerous substituted 2-phenylhistamine analogues.[16] Yields were consistently greater than 60% for the two step, one-pot synthetic procedure.

Various catalysts were explored, as well as surveys of the inorganic base, solvent combinations and temperature ranges. While the results from these appraisals were not universal, the end choice of 5 mol % $PdCl_2(PPh_3)_2$ and aqueous sodium bicarbonate consistently gave the best results. Further, we considered the need for protection of the τ-nitrogen and found that such attempts were detrimental to the Suzuki coupling. Protection of the α-nitrogen was essential for the reaction to progress. Use of alternate protecting groups for the α-nitrogen was also noted to confer unfavorable results on the procedure.

In summary, we have developed a concise, efficient, and general method for the synthesis of substituted 2-phenylhistamine analogues from a common precursor.

Table 1.



4a -n 3a -n

Reactant	Product	R	Yield[a] (%)
4a	**3a**	*m*-CF_3	62
4b	**3b**	H	66
4c	**3c**	*o*-OCH_3	69
4d	**3d**	*p*-OCH_3	67
4e	**3e**	*p*-CH_3	61
4f	**3f**	*p-tbutyl*	64
4g	**3g**	*o-F*	60
4h	**3h**	*p-F*	66
4i	**3i**	*3,5-*CF_3	42
4j	**3j**	*o*-OCH_3, *5-F*	66
4k	**3k**	*3,5-F*	51
4l	**3l**	*m*-NO_2	58
4m	**3m**	*m*-NO_2, *p*-CH_3	59
4n	**3n**	*o-Cl*	59

[a] Yields calculated from intermediate **2** following the one-pot Suzuki coupling and Boc deprotection.

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15. *General experimental*: All microwave reactions were performed in a Biotage 0.5–2.0 mL vessel with a crimped top. 1,2-Dimethoxyethane (DME) was used as purchased. The 4 M hydrochloric acid in dimethoxyethane (HCl in DME) solution was used as purchased. The 2 M aqueous sodium carbonate solution was freshly prepared for each iteration. All organic reagents were used as purchased. The catalyst, trans-dichlorobis(triphenylphosphine) palladium(II) $[Pd(PPh_3)_2Cl_2]$ was purchased from Strem Chemicals and stored in a desiccator. The products were purified via flash chromatography, using 32–63 μm silica gel. Methylene chloride for chromatography (CH_2Cl_2) was used as purchased. Saturated ammonia/methanol (CH_3OH/(NH_3)) was prepared by sparging methanol with ammonia gas for approx. 1 h. A Biotage Initiator 1.2 microwave was utilized for the Suzuki coupling reactions. HRMS were obtained by The Proteomics and Mass Spectrometry Facility at NIDDK/NIH/DHHS on a Waters LCT Premier time-of-flight (TOF) mass spectrometer, using the internal reference standard method. *General procedure for Suzuki coupling*: To a solution of *N*-tertbutylcarbonyl-2-iodohistamine (1 equiv) in dimethoxyethane (0.04 M) was added $PdCl_2(PPh_3)_2$ (5 mol %). The solution was sparged with nitrogen and stirred at room temperature for 0.5 h, at which time the boronic acid (3 equiv) and aq sodium carbonate (2 M) were added. The reaction solution was sparged again with nitrogen and then placed in the microwave and heated for 2 h at 110 °C. When TLC and LC–MS showed full consumption of starting materials, HCl/dioxane (4 M) was added and the reaction tube was again placed in the microwave and heated for 0.5 h. The crude product was directly purified by column chromatography (without additional work-up; 0–20% $CH_3OH(NH_3)/CH_2Cl_2$) to isolate the histamines as free bases. All products showed greater than 95% purity by LCMS analysis, however, it should be noted that each product eluted in the void volume of a 100% buffered aqueous gradient.
16. *2-(3-Trifluoromethylphenyl)-histamine* (**3a**): Using the general procedure and starting with 0.10 g (0.297 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.047 g (62%) of **3a** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.29 (s, 1H) 8.21–8.17 (m, 1H), 7.78–7.72 (m, 2H), 7.10 (s, 1H), 3.09 (t, $J = 6.9$ Hz, 2H), 2.92 (t, $J = 6.9$ Hz, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ 144.8, 131.1, 130.8, 129.4, 128.1, 125.0, 124.6, 124.5, 123.2, 121.4 40.7, 28.9; HRMS calcd for $C_{12}H_{13}N_3F_3$ (M+H) 256.0983, found 256.1060. *2-(Phenyl)-histamine* (**3b**): Using the general procedure and starting with 0.030 g (0.089 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0011 g (66%) of **3b** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.86–7.81 (m, 2H), 7.47–7.32 (m, 3H), 6.94 (s, 1H), 2.98 (t, $J = 6.9$ Hz, 2H), 2.80 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{11}H_{14}N_3$ (M+H) 188.1109, found 188.1185. *2-(2-Methoxyphenyl)-histamine* (**3c**): Using the general procedure and starting with 0.031 g (0.093 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.014 g (69%) of **3c** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.00 (dd, $J = 1.7$, 7.7 Hz, 1H), 7.34 (ddd, $J = 1.7$, 7.3, 8.3 Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.03 (ddd, $J = 1.0$, 7.4, 7.7 Hz, 1H), 7.07 (s, 1H), 4.08 (s, 3H), 3.15 (t, $J = 6.9$ Hz, 2H), 2.95 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{12}H_{16}N_3O$ (M+H) 218.1215, found 218.1296. *2-(4-Methoxyphenyl)-histamine* (**3d**): Using the general procedure and starting with 0.027 g (0.082 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.012 g (67%) of **3d** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.88–7.85 (m, 2H), 7.11–7.07 (m, 3H), 6.97 (s, 1H), 3.93 (s, 3H), 3.05 (t, $J = 6.9$ Hz, 2H), 2.88 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{12}H_{16}N_3O$ (M+H) 218.1215, found 218.1292. *2-(4-methylphenyl)-histamine* (**3e**): Using the general procedure and starting with 0.030 g (0.090 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.011 g (61%) of **3e** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.82 (d, $J = 8.1$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.00 (s, 1H), 3.06 (t, $J = 6.9$ Hz, 2H), 2.95 (t, $J = 6.9$ Hz, 2H), 2.47 (s, 3H); HRMS calcd for $C_{12}H_{16}N_3$ (M+H) 202.1266, found 202.1342. *2-(4-tert-Butylphenyl)-histamine* (**3f**): Using the general procedure and starting with 0.028 g (0.083 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.013 g (64%) of **3f** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.76 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.7$ Hz, 2H), 6.91 (s, 1H), 2.99 (t, $J = 6.9$ Hz, 2H), 2.81 (t, $J = 6.9$ Hz, 2H), 1.42 (s, 9H); HRMS calcd for $C_{15}H_{22}N_3$ (M+H) 244.1735, found 244.1823. *2-(2-fluorophenyl)-histamine* (**3g**): Using the general procedure and starting with 0.030 g (0.089 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.011 g (60%) of **3g** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.53 (ddd, $J = 1.5$, 7.5, 9.3 Hz, 1H), 7.55–7.47 (m, 1H), 7.40–7.30 (m, 2H), 7.09 (s, 1H), 3.07 (t, $J = 6.9$ Hz, 2H), 2.92 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{11}H_{13}N_3F$ (M+H) 206.1015, found 206.1098. *2-(4-Fluorophenyl)-histamine* (**3h**): Using the general procedure and starting with 0.029 g (0.088 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.012 g (66%) of **3h** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.98–7.93 (m, 2H), 7.31–7.26 (m, 2H), 7.04 (s, 1H), 3.11 (t, $J = 6.9$ Hz, 2H), 2.92 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{11}H_{13}N_3F$ (M+H) 206.1015, found 206.1101. *2-(3,5-bis-Trifluoromethylphenyl)-histamine* (**3i**): Using the general procedure and starting with 0.030 g (0.088 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.012 g (42%) of **3i** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.58 (s, 1H), 8.05 (app. s, 2H), 7.18 (s, 1H), 3.15 (t, $J = 6.9$ Hz, 2H), 2.97 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{13}H_{12}N_3F_6$ (M+H) 324.0857, found 324.0932. *2-(2-Methoxy-5-fluorophenyl)-histamine* (**3j**): Using the general procedure and starting with 0.028 g (0.084 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.013 g (66%) of **3j** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.75 (dd, $J = 2.7$, 9.6 Hz, 1H), 7.14–7.03 (m, 2H), 6.98 (s, 1H), 3.98 (s, 3H), 3.03 (t, $J = 6.9$ Hz, 2H), 2.84 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{12}H_{15}N_3OF$ (M+H) 236.1121, found 236.1207. *2-(3,5-Difluorophenyl)-histamine* (**3k**): Using the general procedure and starting with 0.030 g (0.088 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.010 g (51%) of **3k** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.49–7.44 (m, 2H) 7.04 (s, 1H), 7.0–6.92 (m, 1H), 3.10 (t, $J = 6.9$ Hz, 2H), 2.88 (t, $J = 6.9$ Hz,2H); HRMS calcd for $C_{11}H_{12}N_3F_2$ (M+H) 224.0921, found 224.1007. *2-(3-Nitrophenyl)-histamine* (**3l**): Using the general procedure and starting with 0.030 g (0.089 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.012 g (58%) of **3l** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.77–8.76 (m, 1H), 8.32–8.22 (m, 2H), 7.84–7.78 (m, 1H), 7.10 (s, 1H), 3.17 (t, $J = 6.9$ Hz, 2H), 2.93 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{11}H_{13}N_4O_2$ (M+H) 233.0906, found 233.1038. *2-(3-Nitro-4-methylphenyl)-histamine* (**3m**): Using the gen-

eral procedure and starting with 0.028 g (0.083 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.012 g (59%) of **3m** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.57 (d, $J = 1.8$, 1H), 8.15–8.09 (m, 1H), 7.67–7.62 (m, 1H), 7.13 (s, 1H), 3.15 (t, $J = 6.9$ Hz, 2H), 2.97 (t, $J = 6.9$ Hz, 2H), 2.69 (s, 3H); HRMS calcd for $C_{12}H_{15}N_4O_2$ (M+H) 247.1117, found 247.1201. *2-(2-Chlorophenyl)-histamine* (**3n**): Using the general procedure and starting with 0.031 g (0.092 mmol) of *N*-tertbutylcarbonyl-2-iodohistamine, 0.012 g (59%) of **3n** was obtained; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71–7.68 (m, 1H), 7.53–7.50 (m, 1H), 7.42–7.38 (m, 2H), 6.99 (s, 1H), 2.98 (t, $J = 6.9$ Hz, 2H), 2.81 (t, $J = 6.9$ Hz, 2H); HRMS calcd for $C_{11}H_{13}ClN_3$ (M+H) 222.0720, found 222.0797.