SHORT PAPER

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Functionalization of 1-methyl-1*H*-imidazole-5-carboxylic acid at the C-2 position: efficient syntheses of 2-substituted *t*-butyl 1-methyl-1*H*-imidazole-5-carboxylates†

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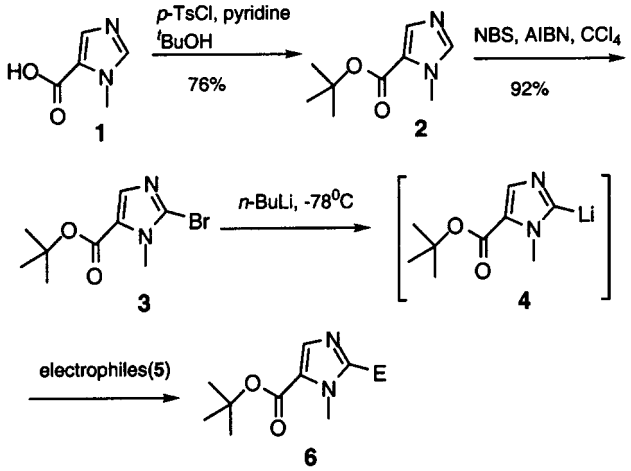
A number of 2-substituted *t*-butyl 1-methyl-1*H*-imidazole-5-carboxylates, which can be readily converted to the corresponding acids, were efficiently prepared from *t*-butyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate *via* bromine-lithium exchange or palladium-catalysed coupling.

In the course of developing biomimetic models of the heme a_3/Cu_b site of cytochrome *c* oxidase,[1] we have established a straightforward method for attaching structurally diverse imidazole-based pickets on the porphyrin template *via* an amide link.[1a–c] Our experience indicates that subtle structural variations in the substitution pattern of such imidazoles usually have profound effects on chemical and electrocatalytic properties of the resulting compounds. Therefore, we set forth to develop efficient methods that would allow us to obtain a variety of 2-substituted 1-methyl-1*H*-imidazole-5-carboxylic acids. Herein, we report a convenient synthesis of various 2-substituted *t*-butyl 1-methyl-1*H*-imidazole-5-carboxylates employing *t*-butyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate as the starting material.

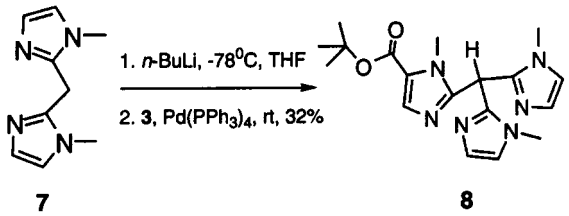
As shown in Scheme 1, esterification of readily available 1-methyl-1*H*-imidazole-5-carboxylic acid (**1**)[2] in a *p*-TsCl/pyridine/*t*-BuOH system[3] gave *t*-butyl ester **2** in 76% yield. Ester **2** was formed in only low yields by reactions of the acid chloride of **1** with *t*-BuOH in the presence of a base or with *t*-BuOLi.[4] Bromination of **2** with NBS in the presence of AIBN[2b] afforded bromide **3** in 92% yield.



Scheme 1

In a preliminary study of the bromine-lithium exchange reaction of **3** (Scheme 1), dry DMF was applied to quench carbanion **4**, which formed the desired aldehyde **6a** in 69% yield (Table 1). Subsequently, a number of structurally and electronically diverse electrophiles were treated with carbanion **4** to test the generality of this method. In an attempt to prepare the 2-fluorinated derivative, carbanion **4** was treated with N-fluorobenzene sulfonamide (**5b**). However, a benzenesulfonyl group rather than a fluorine atom was introduced onto the C-2 position. Reaction of carbanion **4** with chlorotrimethylsilane afforded the 2-trimethylsilyl derivative. Its subsequent reaction with methyl chloroformate yielded imidazoledicarboxylate **6e**. The *t*-butyl ester group can be easily hydrolyzed by mild acid; thus, the two esters can be easily distinguished. The imidazole derivatives described herein possess functional group combinations that are not readily prepared by other methods, and are useful precursors for further selective synthetic elaboration at the C-2 and C-5 positions. For example, compound **6h** is a potential chelating ligand for model studies of cytochrome *c* oxidase; imidazoles **6c** and **6f** can serve as precursors to potential antimicrobial[5a] and anti-inflammatory[5b] agents.

Moreover, compound **3** is also a precursor to the tripodal ligand **8**. This type of trisimidazole ligand is known to form stable complexes with Cu(I).[6] Thus, treatment of bisimidazolylmethane (**7**)[7] with *n*-BuLi, followed by addition of $Pd(PPh_3)_4$[8] and **3**, gave trisimidazole **8** in 32% yield (Scheme 2).



Scheme 2

In summary, we have established an efficient method for functionalizing 1-methyl-1*H*-imidazole-5-carboxylic acid (**1**) *via* bromine-lithium exchange or palladium-catalyzed coupling of its 2-bromo derivative (**3**).

Experimental

All melting points were recorded on a MEL-TEMP apparatus and are uncorrected. Infrared spectra were recorded on a Matttson Infinity 60AR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer. Mass spectra were performed by the Mass Spectrometry Facility at the University of California, San Francisco.

t-*Butyl 1-methyl-1*H-*imidazole-5-carboxylate* (**2**): A mixture of 1-methyl-1*H*-imidazole-5-carboxylic acid (**1**)[2] (10 mmol), dry pyridine (70 mmol), and *p*-TsCl (20 mmol) in dry *t*-butanol (0.2 mol) was stirred at rt overnight. The solvent was removed and the residue was subjected to chromatography to give **2** in 76% yield. mp 80–82 °C; ν_{max}/cm^{-1} (KBr): 1707 (C=O); δ_H ($CDCl_3$): 7.61 (s, 1H), 7.49 (s, 1H),

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

3.86 (s, 3H), 1.54 (s, 9H) ppm; HRMS: calcd. for $C_9H_{14}N_2O_2$ (M^+) 182.106, found 182.106.

t-*Butyl 2-bromo-1-methyl-1*H-*imidazole-5-carboxylate* (**3**): A mixture of *t*-butyl 1-methyl-1*H*-imidazole-5-carboxylate (**2**) (10mmol), NBS (11mmol), and AIBN (0.5 mmol) in CCl_4 (250 ml) was stirred at 60 °C overnight. The reaction mixture was filtered. The filtrate was concentrated and the residue was subjected to chromatography to give **3** in 92% yield. mp 54–56 °C; ν_{max}/cm^{-1} (KBr): 1717 (C=O); δ_H ($CDC1_3$): 7.56 (s, 1H), 3.86 (s, 3H), 1.53 (s, 9H)ppm; HRMS: calcd. for $C_9H_{13}{}^{79}BrN_2O_2$ (M^+) 260.016, found 260.016.

General procedure for the bromine-lithium exchange of t-*Butyl 2-bromo-1-methyl-1*H-*imidazole-5-carboxylate* (**3**): A solution of **3** (1mmol) in dry THF (10 ml) was treated with 1 equivalent of *n*-BuLi (2.5M in THF) at –78 °C for several minutes, followed by addition of an electrophile (**5**) (1 mmol). The resulting mixture was allowed to warm to rt and stirred overnight. The solvent was removed and the residue was subjected to chromatography to yield **6**.

t-*Butyl 2-formyl-1-methyl-1*H-*imidazole-5-carboxylate* (**6a**): mp 38–40 °C; ν_{max}/cm^{-1} (CCl_4): 1697 (C=O), 1722 (C=O); δ_H ($CDCl_3$): 9.87 (s, 1H), 7.73 (s, 1H), 4.24 (s, 3H), 1.55 (s, 9H) ppm; HRMS: calcd. for $C_{10}H_{14}N_2O_3$ (M^+) 210.100, found 210.100.

t-*Butyl-2-benzenesulfonyl-1-methyl-1*H-*imidazole-5-carboxylate* (**6b**): mp 126–128 °C; ν_{max}/cm^{-1} (KBr): 1718 (C=O); δ_H ($CDCl_3$): 8.00 (d, 2H, *J*=7.6Hz), 7.65 (t, 1H, *J*=7.6 Hz), 7.58 (s, 1H), 7.55 (d, 2H, *J*=7.6 Hz), 4.19 (s, 3H), 1.51 (s, 9H)ppm; HRMS: calcd. for $C_{15}H_{18}{}^{79}BrN_2O_4S$($M^+$) 322.099, found 322.099.

t-*Butyl-2-(1′-(2″-methoxyphenyl)hydroxymethyl)-1-methyl-1*H-*imidazole-5-carboxylate* (**6c**): mp 176–178 °C; ν_{max}/cm^{-1} (KBr): 3151 (OH), 1706 (C=O); δ_H ($CDCl_3$): 7.58 (s, 1H), 7.29 (td, 1H, *J*=9.1, 1.6 Hz), 7.14 (dd, 1H, *J*=7.5, 1.6 Hz), 6.90–6.95 (m, 2H), 6.22 (s, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 1.54 (s, 9H), ppm; HRMS: calcd. for $C_{17}H_{22}N_2O_4$ (M^+) 318.158, found 318.158.

t-*Butyl 1-methyl-2-(1′-(2″-nitrophenyl)hydroxymethyl)-1*H-*imidazole-5-carboxylate* (**6d**): mp 156–158 °C; ν_{max}/cm^{-1} (KBr): 3124 (OH), 1707 (C=O); δ_H ($CDCl_3$): 8.08 (dd, 1H, *J*=8.2, 1.0 Hz), 7.92–7.93 (m, 1H), 7.72 (t, 1H, *J*=7.8 Hz), 7.52 (t, 1H, *J*=7.7Hz), 7.44 (s, 1H), 6.58 (s, 1H), 4.00 (s, 3H), 1.56 (s, 9H) ppm; HRMS: calcd. for $C_{16}H_{19}N_3O_5$ (M^+) 333.132, found 333.132.

t-*Butyl 2-methoxycarbonyl-1-methyl-1*H-*imidazole-5-carboxylate* (**6e**): ν_{max}/cm^{-1} (CCl_4): 1714 (C=O), 1731 (C=O); δ_H ($CDCl_3$): 7.66 (s, 1H), 4.27 (s, 3H), 3.95 (s, 3H), 1.56 (s, 9H) ppm; HRMS: calcd. for $C_{11}H_{16}N_2O_4$ (M^+) 240.111, found 240.111.

t-*Butyl 1-methyl-2-(3′-methylphenylcarbonyl)-1*H-*imidazole-5-carboxylate* (**6f**): ν_{max}/cm^{-1} (film): 1716 (C=O), 1653 (C=O); δ_H ($CDC1_3$): 7.76 (s, 1H), 7.93–7.96 (m, 2H), 7.36–7.74 (m, 2H), 4.25 (s, 3H), 2.43 (s, 3H), 1.60 (s, 9H) ppm; HRMS: calcd. for $C_{17}H_{20}N_2O_3$ (M^+) 300.147, found 300.147.

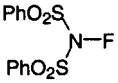
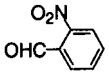
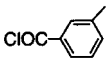
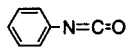
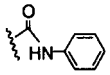
t-*Butyl 1-methyl-2-phenylcarbamoyl-1*H-*imidazole-5-carboxylate* (**6g**): mp 114–116 °C; ν_{max}/cm^{-1} (KBr): 3235 (NH), 1718 (C=O), 1678 (C=O); δ_H ($CDCl_3$): 9.41 (s, 1H), 7.67 (d, 2H, *J*=8.2 Hz), 7.63 (s, 1H), 7.37 (t, 2H, *J*=7.6 Hz), 7.15 (t, 1H, *J*=7.6 Hz), 4.40 (s, 3H), 1.59 (s, 9H) ppm; HRMS: calcd. for $C_{16}H_{19}N_3O_3$ (M^+) 301.143, found 301.143.

t-*Butyl 1,2-dimethyl-1*H-*imidazole-5-carboxylate* (**6h**): ν_{max}/cm^{-1} (film): 1703 (C=O); δ_H ($CDC1_3$): 7.55 (s, 1H), 3.81 (s, 3H), 2.44 (s, 3H), 1.59 (s, 9H) ppm; HRMS: calcd. for $C_{10}H_{16}N_2O_2$ (M^+) 196.121, found 196.121.

t-*Butyl 2-cyano-1-methyl-1*H-*imidazole-5-carboxylate* (**6i**): mp 112–114 °C; ν_{max}/cm^{-1} (KBr): 2240 (C=N), 1718 (C=O) cm^{-1}; δ_H ($CDCl_3$): 7.68 (s, 1H), 4.07 (s, 3H), 1.58 (s, 9H) ppm; HRMS: calcd. for $C_{10}H_{13}N_3O_2$ (M^+) 207.101, found 207.101.

*Bis(1-methyl-1*H-*imidazol-2-yl)(1-methyl-5-*t-*butoxycarbonyl-1*H-*imidazol-2-yl)methane* (**8**): A solution of bis(1methyl-1*H*-imidazol-2-yl)methane (**7**) (3 mmol) in dry THF (20 ml) was treated with *n*-BuLi (3 mmol) at –78 °C under N_2. The mixture was allowed to warm to –20 °C over 1h, and then $Pd(PPh_3)_4$ (0.3 mmol) and a solution of *t*-butyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate (**3**) (3 mmol) in dry THF (2 ml) were added respectively. The resulting mixture was stirred at rt for 24h. The solvent was removed and the residue was purified by chromatography to give **8** in 32% yield. ν_{max}/cm^{-1} (CCl_4): 1710 (C=O); δ_H ($CDCl_3$): 7.57 (s, 1H), 6.98 (d, 2h, *J*=1.2 Hz), 6.86 (d, 2H, *J*=.2 Hz), 5.97 (s, 1H), 3.69 (s, 3H), 3.43 (s, 6H), 1.51 (s, 9H) ppm; HRMS: calcd. for $C_{18}H_{24}N_6O_2$ (M^+) 356.196, found 356.196.

Table 1 Synthesis of 2-substituted t-butyl 1-methyl-1*H*-imidazole-5-carboxylates (**6**) by the reaction of carbanion **4** with electrophiles (**5**)

Electrophile	**5**	Product		Yield (%)
		E	**6**	
DMF	**5a**	-CHO	**6a**	69
	**5b**	$-SO_2Ph$	**6b**	31
	**5c**		**6c**	73
	**5d**		**6d**	77
ClCOOMe	**5e**	-COOMe	**6e**	51
	**5f**		**6f**	66
	**5g**		**6g**	79
CH_3I	**5h**	$-CH_3$	**6h**	67
p-TsCN	**5i**	-CN	**6i**	75

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