Carboxylate Protection for the Synthesis of 4,5-Disubstituted 1-Methylimidazoles

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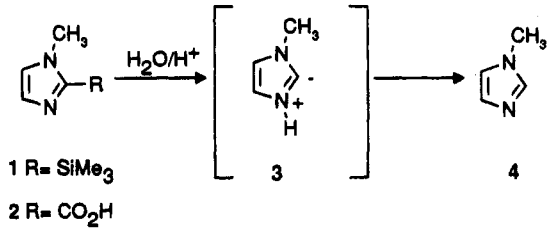
Summary: Using the carboxylate function as a readily removed blocking group for the 2-position, a regioselective synthesis of diverse 4,5-disubstituted 1-methylimidazoles has been developed starting from 1-methyltribromoimidazole, **5**.

The imidazole ring confers upon a compound that carries it the potential for a range of catalytic properties, liganding abilities, and quite often, biological activities. Therefore, substituted imidazoles are in great demand for designing artificial catalysts,[1] metal chelating agents,[2] and pharmaceutical agents.[3] This in turn creates the need for versatile methods for preparing imidazoles bearing multiple substitutions. Our interest in 4,5-disubstituted 1-methylimidazoles as pharmaceutical intermediates led us to develop a practical and flexible synthesis of this class of compounds employing a novel carboxylate protection strategy. Although the metalation chemistry of imidazoles has been extensively investigated,[4] there is a clear need for additional methodology for preparing polysubstituted derivatives. Our attention was directed to finding a simple blocking group for the 2-position which would be compatible with imidazole metalation chemistry and could be easily removed upon reaction workup. Recently,[5] we reported the 2- to 5-position migration of 2-(trialkylsilyl)-substituted 5-lithio-*N*-methylimidazoles making the silyl group unsuitable as a blocking group in this system. A 2-silyl group is easily removed from an alkylimidazole **1** with water alone (Scheme 1).[6] This has been proposed to be due to the favorable formation of ylide **3**, which is also the putative intermediate in the decarboxylation of *N*-methylimidazole-2-carboxylic acid to *N*-methylimidazole[7] **2**. Bearing this in mind we decided to investigate the suitability of the readily removed carboxylate function as a blocking group for the 2-position.[8]

Scheme 1



To arrive at 4,5-disubstituted 1-methylimidazoles we envisaged 1-methyl-4,5-dibromoimidazole-2-carboxylic acid (**6**) as an attractive starting material. We expected that the dilithium species **7** would be obtained upon treatment of **6** with 2 equiv of BuLi as a stable species at low temperature.[9,10] Electrophiles would then be readily introduced into the 5-position of **7**. Furthermore, the presence of a 4-bromine would allow subsequent elaboration of another substituent at the 4-position. The unknown 1-methyl-4,5-dibromoimidazole-2-carboxylic acid, **6**, was easily prepared[11] in good yield from the readily obtained **5**[4,12] by selective exchange of the 2-bromine with BuLi followed by trapping with CO_2 (Scheme 2). After 2 equiv of BuLi was added to **6** in THF at −70 °C a

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) (a) Benner, S. A.; Heeb N. V. *Tetrahedron Lett.* **1994**, *35*, 3045 and references therein. (b) Somayaji, V.; Skorey, K. I.; Brown, R. S.; Ball, R. G. *J. Org. Chem.* **1986**, *51*, 4866. (c) Bruice, T. C.; Schmir, G. L. *J. Am. Chem. Soc.* **1958**, *80*, 148. (d) Akiyama, M.; Hara, Y.; Tanabe, M. *J. Chem. Soc., Perkin Trans 2* **1978**, 288. (e) Wolfenden, R.; Jencks, W. P. *J. Chem. Soc.* **1961**, *83*, 4390.

(2) Knapp, S.; Albaneze, J.; Schugar, H. J. *J. Org. Chem.* **1993**, *58*, 997 and references therein.

(3) (a) For examples of 5-HT3 antagonists see: Rizzi, J. P.; Nagel, A. A.; Rosen, T.; McLean, S.; Seeger, T. *J. Med. Chem.* **1990**, *33*, 2721 and references therein. (b) For examples of adrenergic ligands see: Amemiya, Y.; Hong, S. S.; Burrah, V. V.; Patil, P. N.; Shams, G.; Romstedt, K.; Feller, D. R.; Hsu, F.; Miller, D. D. *J. Med. Chem.* **1992**, *35*, 750. (c) For a review of pilocarpine SAR see: Shapiro, G.; Enz, A. *Drugs Future* **1992**, *17*, 489. (d) For angiotensin II antagonists see: Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Peishoff, C. E.; Tucker, L. M.; Aiyar, N.; Griffin, E.; Ohlstein, E. H.; Stack, E. J.; Weidley, E. F.; Edwards, R. M. *J. Med. Chem.* **1993**, *36*, 1880 and references therein.

(4) (a) For recent examples of sequential metal–halogen exchange reactions for the preparation of polysubstituted imidazoles see: Lipschutz, B. J.; Hagen, W. *Tetrahedron Lett.* **1992**, *33*, 5865 and references therein. (b) For a review of imidazole metalation chemistry see: Iddon, B. *Heterocycles* **1985**, *23*, 417.

(5) Shapiro, G.; Marzi, M. *Tetrahedron Lett.* **1993**, *34*, 3401.

(6) Jutzi, P.; Sakriss, W. *Chem. Ber.* **1973**, *106*, 2815.

(7) (a) Haake, P.; Bausher, L. P.; McNeal, J. P. *J. Am. Chem. Soc.* **1971**, *93*, 7045. (b) An X-ray structure has been performed for the stable imidazole carbene (or ylide), imdiazole 1,3-di-1-adamantylimidazol-2-ylidene: Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(8) It has been shown that the dimethylamide of *N*-methylimidazole-2-carboxylic acid is readily deprotonated in the 5-position but the vigorous conditions of the amide hydrolysis–decarboxylation detract from this chemistry. Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645.

(9) It is known that for halogenated 1-methylimidazoles, lithium–halogen exchange proceeds more readily at the 5-position relative to the 4-position. El Borai, M.; Moustafa, A. H.; Anwar, M. and Abdel Hay, F. I. *Pol. J. Chem.* **1981**, *55*, 1659.

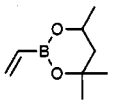
(10) BuLi-mediated metal–halogen exchange is rapid and quantitative precluding addition to the carboxylate function. Furthermore, with excess tBuLi in THF at −70 °C, partial double deprotonation of **2** to a dilithium species analogous to **7**, having hydrogen in place of the 4-bromine, could be achieved. Trapping with MeI followed by decarboxylation gave up to 20% 1,5-dimethylimidazole along with 1-methylimidazole. Thus, there was no indication of intrinsic instability or self-reactivity of this dilithium species with addition to the carboxylate.

(11) Lithium–bromine exchange was performed by adding 1.1 equiv of *n*-butyllithium to a stirred solution of tribromo-1-methylimidazole (15 g, 47 mmol) in THF at −70 °C under argon. After 30 min dry carbon dioxide (dry ice evaporated through H_2SO_4 tower) was bubbled into the solution for 1 h and it was allowed to warm to room temperature. The lithium carboxylate was precipitated by the addition of hexane and filtered under argon. The lithium salt proved difficult to work with and purify. Therefore, it was converted to the free acid by dissolving in 50% aqueous ethanol, acidifying to pH 2, and refrigeration. Compound **6** (7.40 g, 55%) crystallized as white needles (mp 112–113 °C). This material was dried under vacuum over P_2O_5 and was stored in a desiccator for several months without significant decarboxylation. Decarboxylation of **6** was observed in $CDCl_3$ presumably due to traces of HCl present; therefore, evaluation of **6** by ^{1}H-NMR analysis in this solvent must be avoided: ^{1}H-NMR (360 MHz, DMSO-d_6) δ = 3.93 (s, 3H); ^{13}C (100 MHz, DMSO-d_6) δ = 158.6, 137.9, 116.3, 111.4, 35.5.

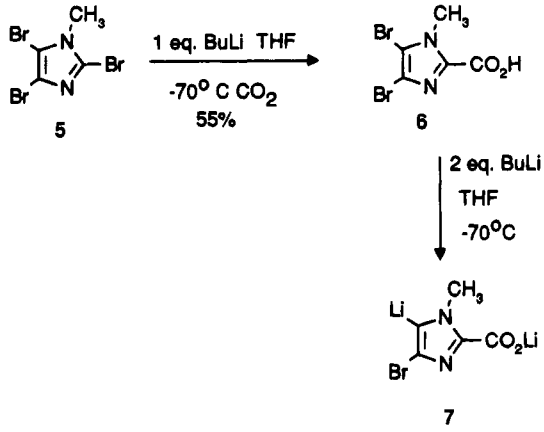
(12) Iddon, B.; Lim, B. L. *J. Chem. Soc., Perkin Trans 1* **1983**, 735.

0022-3263/94/1959-5524$04.50/0

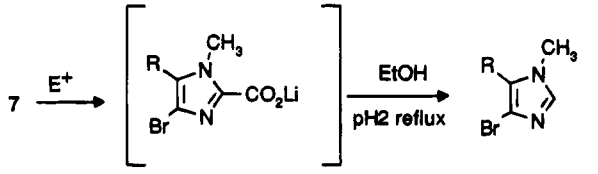
Table 1. Suzuki Couplings

starting material	boron reagent	R1	R2	product	base	yield (%)
9a	$PhB(OH)_2$	Me	Ph	**11a**	2 N Na_2CO_3	43
9b	$PhB(OH)_2$	CHO	Ph	**11b**	2 N Na_2CO_3	71
9b	(*E*)-PhCH=CHB($O_2C_6H_4$)	CHO	(*E*)-PhCH=CH–	**11c**	2 N NaOH	55
9b		CHO	H_2=CH–	**11d**	2 N NaOH	44

Scheme 2



Scheme 3



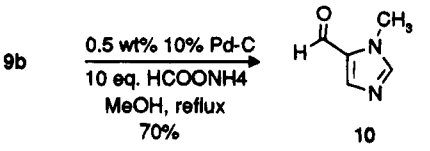
E^+ = MeI, DMF

8a R= CH_3 9a R= CH_3 45%

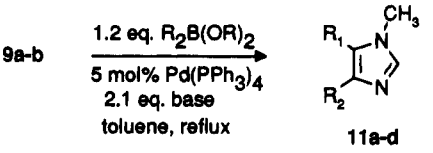
8b R= CHO 9b R= CHO 43%

virtually homogeneous solution was formed. Additon of MeI or DMF followed by decarboxylation gave the known methylation and formylation products **9a** (45%) and **9b** (43%), respectively.[13] In the formylation reaction the known 1-methylimidazole-4-carboxaldehyde[14] was characterized as a side product in 10–15% yield (Scheme 3). This compound presumably arises by the quenching of **7** by adventitious water followed by further bromine–lithium exchange and trapping at the 4-position.[15] Although the isolated yields of **9a** and **9b** are moderate, no attempts were made to optimize the reaction.

Scheme 4



Scheme 5



It remained to explore the possibilties for synthetic exploitation of the bromine at C-4.[16] Catalytic transfer hydrogenation of **9b** to the important starting material for pilocarpine synthesis,[17] imidazolecarboxaldehyde, **10**, proceeds cleanly in good yield (Scheme 4). More importantly, the Suzuki coupling[18] of **9a** and **9b** with phenylboronic acid in toluene at reflux with 5% $Pd(PPh_3)_4$ using sodium carbonate as the base proceeded cleanly giving **11a** in moderate and the unknown **11b** in good yield after chromatographic purification.[19] Also, couplings of β-(phenylethenyl)catecholborane[20] and a vinyl boronate ester (4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinate[21]) with **9b** were performed in an analogous fashion using sodium hydroxide as the base. These reactions proceeded smoothly to give the novel cinnamyl- and vinylimidazoles **11c** and **11d** in moderate yields after chromatographic purification (Scheme 5).[22]

Thus, defined 4,5 substitution representing a wide range of functionality is readily achievable for an *N*-alkylimidazole with this methodology. Although the yields are moderate, the chemistry is simple and the products are readily isolated in pure form in few steps.

(13) (a) **General Procedure.** 2 equiv of n-BuLi was added to a THF solution of **6** at −70 °C under argon giving a fine suspension. After 10 min 1.4 equiv of the corresponding electrophile (MeI or DMF) was added and the mixture was allowed to warm to 0 °C. A small amount of 2 N HCl was added to quench the reaction and the mixture concentrated on a rotary evaporator. The residue was dissolved in ethanol and HCl added to give pH 2. This mixture was heated at reflux for 1 h, concentrated in vacuo to a residue which was easily purified by column chromatography (SiO_2, 10% MeOH: 1% NH_3–CH_2Cl_2) the side products having greatly different R_f's. (b) **9a**: Pyman et al. *J. Chem. Soc.* **1910**, *97*, 1827. **9a**: ^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.32 (s, 1H), 3.59 (s, 3H), 2.18 (s, 3H); MS-EI M^+ = 174, 176. (c) The preparation of **9b** in four steps from 4-bromoimidazole has been described. Mukaihira, T.; Fujii, T. *Heterocycles* **1992**, *33*, 21. Our melting point of **9b** was identical to that reported. **9b**: mp 89–90 °C; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.52 (s, 1H), 3.93 (s, 3H); MS-EI M^+ = 188, 190.

(14) Our data for 1-methylimidazole-4-carboxaldehyde which exhibits a similar concentration dependent ^{1}H-NMR but very different melting point and R_f values relative to its regioisomer, compound **10**, were consistent with those reported: Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. H. *J. Org. Chem.* **1968**, *33*, 3758.

(15) In the case of **9b** the side products were not analyzed.

(16) For examples of introduction of a 4-substituent into 4-iodoimidazoles by Grignard reaction and also palladium-catalyzed couplings see: Turner, R. M.; Ley, S. V.; Lindell, S. D. *Synlett* **1993**, 748.

(17) Shapiro, G; Chengzhi, C. *Tetrahedron Lett.* **1992**, *33*, 2447.

(18) For a review using boronic acids see: Martin, A. R.; Yang Y. *Acta Chem. Scand.* **1993**, *47*, 221. For boronic ester see: Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. Miyura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(19) Phenylboronic acid was purchased from Fluka AG. Compound **11a** has been reported without characterization: Kikugawa, Y.; Cohen, L. A. *Chem. Pharm. Bull.* **1976**, *24*, 3205. **11a**: ^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.63 (dd, 2H, J = 2.4, 8.1 Hz), 7.52 (s, 1H), 7.40 (t, 2H, J = 8.1 Hz), 7.25 (tt, 1H, J = 8.1, 2.4), 3.60 (s, 3H), 2.40 (s, 3H); MS-EI M^+ = 172. **11b**: mp 103–105 °C; ^{1}H-NMR (360 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 7.62–7.68 (m, 3H), 7.43–7.50 (m, 3H), 4.00 (s, 3H); MS-EI M^+ = 186.

(20) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5429.

(21) 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane was purchased from Janssen.

(22) Compounds **11a–d** were purifed by chromatography over silica gel using 9:1 ethyl acetate–methanol as eluent. In pure form, vinyl imidazole **11d** was sensitive to polymerization. **11c**: mp 179–183 °C; ^{1}H-NMR (360 MHz, $CDCl_3$) δ = 10.10 (s, 1), 7.63 (d, 1H, J = 16.2 Hz), 7.55–7.57 (m, 3H), 7.30–7.41 (m, 4H), 3.93 (s, 3H); FAB-MS MH^+ = 213. **11d**: ^{1}H-NMR (360 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 7.53 (s, 1H), 6.97 (dd, 1H, J = 12.0, 18.0 Hz), 6.22 (dd, 1H, J = 2.4, 18.0 Hz), 5.33 (dd, 1H, J = 2.4, 12.0 Hz), 3.92 (s, 3H); FAB-MS MH^+ = 137.

The method is general and thus also well suited toward the preparation of a series of related analogs (e.g., for SAR studies). Further functionalization or substitution at the 2-position is clearly achievable on these products or derivatives thereof using established methods. Finally, the potential for expanding the application of this chemistry to other related heterocycles (thiazoles, oxazoles, etc.) is evident.

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