SEQUENTIAL C-2 LITHIATION/ACYLATION OF *N*-1 FUNCTIONALIZED IMIDAZOLES: SYNTHESIS OF NOVEL TETRAHYDROIMIDAZO[1,2-*a*][1,4]DIAZEPINES†

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Abstract- 5,6,7,9-Tetrahydroimidazo[1,2-*a*][1,4]diazepines (**4a-c**) are prepared by conversion of 2-acylimidazoles (**2a-c**) to cyclic imines (**3a-c**) followed by hydride reduction. In the key step, a masked primary amine (**1**) is acylated in good yield employing an alkyllithium base to afford acylimidazoles (**2a-c**) after acid hydrolysis of the imines. This reaction avoids use of transient *N*-1 (im) protecting groups.

Regiospecific transmetallation and subsequent substitution of imidazole at the 2-position has previously been accomplished without perturbation of its sp^3 *N*-1 nitrogen by the use of temporary blocking groups such as MOM,[1] SEM,[2,3] and trityl.[4] Herein, we report the first such transformation in which this critical *N*-1 position bears a permanent functional group amenable to subsequent manipulation, i.e. the 3-aminopropyl moiety. Further elaboration of these resultant 1,2-disubstituted imidazoles provides novel 5,6,7,9-tetrahydroimidazo[1,2-*a*]-[1,4]diazepines (**4a-c**). The regiospecific lithiation of these functionalized substrates, usually effected with n-butyllithium, represents an attractive, versatile approach to imidazole-based heterocyclic systems.

Masked primary amine (**1**) is prepared from 1-(3-aminopropyl)imidazole by the method of O'Donnell *et al.*[5] in high yield (Scheme 1). Lithiation of **1** (n-BuLi, THF, -78°C) and acylation (ArCOCl, -78°C) gives exclusively a 2-aroylimidazole product (71-90%).[6] Use of Boc or Cbz instead of diphenylmethylidene protection results in a

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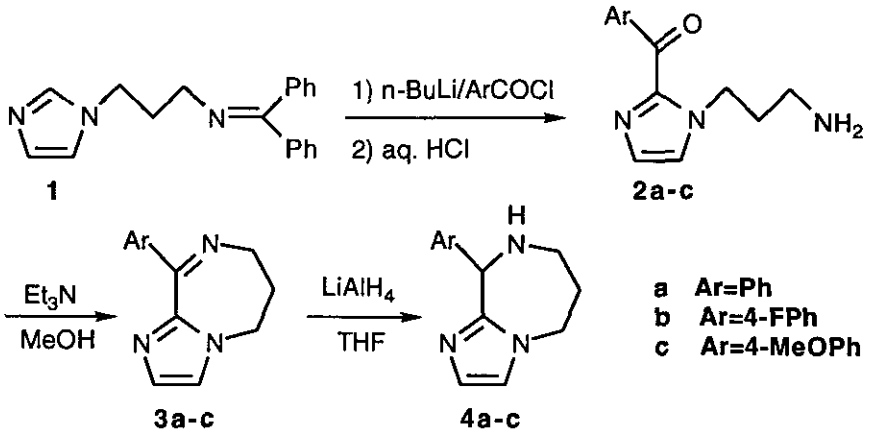
heterogenous reaction medium which yields a mixture of mono- and diacyl products. Although TMEDA is employed to maintain solubility of all these metallated intermediates, yields and solubility in the diphenylmethylidene cases are unaffected by the absence of TMEDA.[7] Methyllithium or n-butyllithium may be used interchangeably without affecting yield.

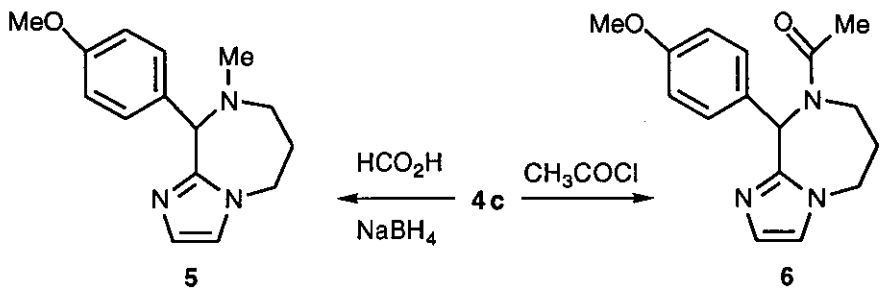
Removal of the diphenylmethylidene group (aqueous HCl, THF) gives the 2-aroylimidazole derivatives (**2a-c**) as dihydrochloride salts.[8] Dehydrative cyclization of **2a-c** under basic, protic conditions (2 eq. Et_3N, MeOH) occurs readily with either electron-donating or -withdrawing substituted aromatic derivatives to produce novel, stable imines (**3a-c**)[9] (60-73%). Lithium aluminum hydride reduction of **3a-c** (1 eq. $LiAlH_4$, THF, room temperature) cleanly affords the title compounds (**4a-c**)[10] (86-93%).

Scheme 1



In preliminary investigations into the reactivity of **4c** (Scheme 2), derivatization at the 8-*N* position is effected with both alkylating (for **5**: MeI, NaH, DMF, 5°C, 63% or HCO_2H, $NaBH_4$, room temperature, 88%)[11] and acylating (for **6**: CH_3COCl, CH_2Cl_2, room temperature, 95%)[12] agents. Reductive alkylation of **4c**[13] produces **5** cleanly without formation of quaternary by-products, and is the superior method to alkylate these systems. Interestingly, the ^1H nmr spectra of both **5** and **6** exhibit a large chemical shift difference (0.3-0.7 ppm) between the seven-ring pseudoaxial and pseudoequatorial protons of each methylene site. These ^1H nmr shift differences are characteristic of medium-sized rings.[14]

Scheme 2



In conclusion, these results expand lithiation/substitution methodology of imidazole chemistry. Furthermore, the application of this methodology produces the novel 5,6,7,9-tetrahydroimidazo[1,2-*a*][1,4]diazepines as new examples of seven-membered ring-fused imidazoles.

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6. Lipshutz *et al.* (reference 3) have sequentially lithiated/trapped at the 2- and then 5-position of SEM-protected imidazole. We have not observed 5-acyl or 2,5-diacyl product formation. For additional references on regiocontrolled 5-lithiation, see B. T. Phillips, D. A. Claremon, and S. L. Varga, *Synthesis*, **1990**, 761; T. P. Demuth, D. C. Lever, L. M. Gorgos, C. M. Hogan, and J. Chu, *J. Org. Chem.*, 1992, **57**, 2963.
7. Use of TMEDA as a coordinating solvent to enhance reactivity of organometallic reagents is well-documented. Exclusion of TMEDA in our system, however, does not diminish reactivity.
8. A typical procedure for acylation of 1-(3-*N*-diphenylmethylideneiminopropyl)imidazole (**1**) is: A solution of **1** (5.00 g, 17.0 mmol) in dry THF (400 ml) was cooled to -78°C and treated with n-BuLi (10.2 ml, 2.5 M in hexanes, 1.5 eq.) dropwise over 5 min to give a deep-red solution. This solution was stirred for 55 min and treated with benzoyl chloride (3.0 ml, 1.5 eq.), stirred another 30 min at -78°C, and quenched with sat'd NH_4Cl (50 ml). Warming to room temperature and standard work-up (extraction with EtOAc (2x100 ml) and water (50 ml), separation, drying of the combined organic layers ($MgSO_4$), and evaporation gave an oil which was purified by chromatography (silica gel, 0.5% NH_4OH/2% EtOH/CH_2Cl_2) to afford 1-(3-*N*-

diphenylmethylideneiminopropyl)-2-benzoylimidazole as a gold oil. Dissolution in THF (50 ml) at room temperature and treatment with 1N HCl (30 ml), stirring for 8 h, and concentration gave a solid which was triturated with Et_2O (5x50 ml) and dried to give **2a**•dihydrochloride (3.29 g, 64% for two steps) as a tan powder, mp 176-177°C; ms m/z 230 (MH^+); ^1H nmr (DMSO-d_6) δ 8.78(2H, br s, NH) 8.26(2H, s, NH) 8.16(2H, d, J=7.8 Hz, Ar-H) 7.92(1H, s, Im-H) 7.69(1H, t, J=7.4 Hz, Ar-H) 7.56(2H, t, J=7.7 Hz, Ar-H) 7.41(1H, s, Im-H) 4.53(2H, t, J=6.7 Hz) 2.80(2H, dd, J=7.4, 13.6 Hz) 2.16(2H, m). Anal. Calcd for $C_{13}H_{15}N_3O$•2HCl: C, 51.67; H, 5.67; N, 13.90. Found: C, 51.26; H, 5.75; N, 13.63.

9. For **3c**: Ms m/z 242 (MH^+); ir (neat) 2955, 2858, 1598, 1253 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.85(2H, d, J=7.8 Hz, Ar-H) 7.19(1H, s, Im-H) 7.07(1H, s, Im-H) 6.88(2H, d, J=7.9 Hz, Ar-H) 4.07(2H, t, J=8.0 Hz) 3.81(3H, s, OMe) 3.63(2H, t, J=8.1 Hz) 2.4(2H, m). Anal. Calcd for $C_{14}H_{15}N_3O$•0.5 H_2O: C, 67.18; H, 6.44; N, 16.79. Found: C, 67.51;H, 6.41; N, 16.63.
10. For **4c**: Ms m/z 244 (MH^+); ir (neat) 3290, 2934, 2837, 1610, 1512, 1247 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.16 (2H, d, J=7.9 Hz, Ar-H) 6.87(2H, d, J=7.8 Hz, Ar-H) 6.85(1H, s, Im-H) 6.82(1H, s, Im-H) 5.29(1H, s, ArC-H) 4.00(2H, m) 3.77(3H, s, OMe) 3.30(1H, m) 3.10(1H, m) 1.90(2H, m) 1.80(1H, br s, NH). Anal. Calcd for $C_{14}H_{17}N_3O$•0.25 H_2O: C, 67.84; H, 7.13; N, 16.96. Found: C, 67.82; H, 6.99; N, 16.46.
11. For **5**: Ms m/z 258 (MH^+); ir (neat) 2930, 2839, 1610, 1510, 1246 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.03(2H, d, J=7.9 Hz, Ar-H) 6.96(1H, s, Im-H) 6.84(2H, d, J=7.9 Hz, Ar-H) 6.80(1H, s, Im-H) 5.28(1H, s, ArC-H) 4.00(1H, m, Im-CH_2, eq) 3.70(3H, s, OMe) 3.60(1H, m, Im-CH_2, ax) 3.20(1H, m, MeN-CH_2, ax) 2.90(1H, m, MeNCH_2, eq) 2.47(3H, s, NMe) 2.05(1H, m, C-CH_2-C, ax) 1.40(1H, m, C-CH_2-C, eq). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.28; H, 7.60; N, 16.10.
12. For **6**: Ms m/z 286 (MH^+); ir (neat) 2936, 2838, 1639, 1512, 1253 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.96(1H, s, Im-H) 6.80(5H, m, Ar-H, Im-H) 6.48(1H, s, ArC-H) 4.63(1H, d, J=10.4 Hz, CON-CH_2, eq) 4.08(1H, d, J=10.6 Hz, Im-CH_2, eq) 3.83(1H, t, J=8.4 Hz, CON-CH_2, ax) 3.76(3H, s, OMe) 2.86(1H, t, J=8.1 Hz, Im-CH_2, ax) 2.33(3H, s, COMe) 1.90(2H, m, C-CH_2-C). Anal. Calcd for $C_{16}H_{19}N_3O_2$•H_2O: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.90; H, 6.64; N, 13.35.
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14. J. B. Hendrickson, R. K. Boeckman, J. D. Glickson, and E. Grunwald, *J. Am. Chem. Soc.*, 1973, **95**, 494. We have assigned the time-averaged pseudoaxial and pseudoequatorial proton resonances based upon precedented, seven-membered heterocycle coupling patterns.

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