Regioselective Formation of Imidazol-2-yllithium, Imidazol-4-yllithium, and Imidazol-5-yllithium Species†

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Representative imidazol-2-yllithium, imidazol-4-yllithium, and imidazol-5-yllithium species have been prepared via halogen–metal exchange, and the propensity of the latter two to undergo isomerization and quench by electrophilic reagents has been studied. The C2-unsubstituted imidazol-5-yllithium species **3** is generated within 10 min at −78 °C from 1-[(benzyloxy)methyl]-4,5-diiodoimidazole (**1b**) and affords the C5-formyl product **4** upon reaction with DMF, but gives the isomeric C2-formyl product **6** if allowed to equilibrate to the imidazol-2-yllithium species **5** for an additional 35 min at −78 °C before quench. The less reactive electrophile diethyl carbonate is unable to trap **3** and instead reacts with **5** to afford tris[1-[(benzyloxy)methyl]-4-iodo-2-imidazolyl]carbinol (**7**). In contrast, 1-[(benzyloxy)methyl]-4-iodoimidazole-5-carboxaldehyde ethylene acetal (**10**) metalates to give the C2-unsubstituted imidazol-4-yllithium species **13**, which undergoes a *very* rapid conversion to its imidazol-2-yllithium isomer **14**, even at −100 °C, giving the 2,5-dicarboxaldehyde 5-ethylene acetal **16** or the 2-deuterio-5-carboxaldehyde ethylene acetal **15** upon quench with DMF or D_2O, respectively. Thus, in the presence of C2 unsubstitution, C5 functionalization could be accomplished when the electrophile was sufficiently reactive, while C4 functionalization could not. Short- and long-range ^1H-^{13}C heteronuclear (Hetcor) 2D NMR spectroscopic analyses were instrumental in the structural assignments of key compounds.

Halogen–metal exchange approaches to the multifunctionalization of imidazoles have met with limited success, at best.[1-7] Because a halogen–metal exchange reaction occurs regioselectively,[8] one should, in theory, be able to lithiate and functionalize any of the three carbon atom positions of a suitably N-protected polyhaloimidazole. One of the more appealing variations of such an approach is the development of a synthetic route to 2-unsubstituted-4,5-unsymmetrically disubstituted imidazoles, especially for the preparation of imidazole precursors to new purine ring analogues (4,5-annelated imidazoles).

The results of previous investigations bearing on the viability of this variation are somewhat conflicting. It is known, for example, that the C2 position of N-protected imidazoles is the most readily lithiated, either by halogen-metal exchange or by deprotonation.[1] Several investigators have reported the necessity of blocking this position in order to lithiate and functionalize the C4 or C5 positions of polyhaloimidazoles.[2,3] Thus, in the absence of such C2 protection, only C4(5) reduction or C2-functionalized products were isolated. Others, however, have noted the ease with which 2,5-dilithiation occurs in suitably N-protected 2,5-dihaloimidazole derivatives, even when only 1 equiv of alkyllithium reagent is employed.[4,5] In these cases, product mixtures consisting mainly of 2-mono- and 2,5-difunctionalized imidazoles were obtained. Finally, there is a brief report on the sequential lithiation and alkylation of first the C5 and then the C4 position of a C2-*unsubstituted* 4,5-dihaloimidazole.[6] Because of the uncertainty involved,[7] we wished to establish definitively the extent to which imidazol-5-yllithium and imidazol-4-yllithium species could be generated and quenched with electrophilic reagents in the presence of an unsubstituted C2 carbon atom position.

Results and Discussion

We selected 4,5-diiodoimidazole (**1a**) and 2,4,5-triiodoimidazole (**2a**) as the starting materials for our study. The regioselectivity of the diiodination of imidazole under aqueous basic conditions was once a subject of controversy, but has been established to proceed with the formation

Scheme I

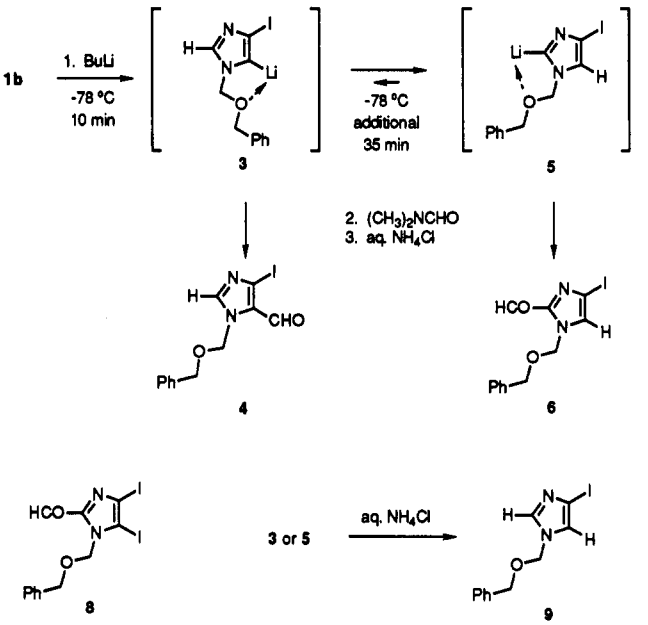

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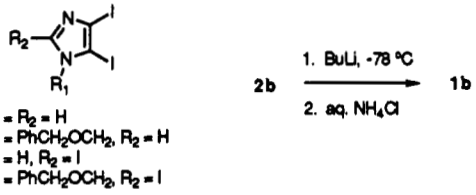
Table I. Selected ^{13}C Chemical Shift Values (δ) for Imidazoles in $CDCl_3$ Solution with $CDCl_3$ (δ 77.0) as Internal Reference

compd	C2	C4	C5
1b	142.0	97.6	82.0
2b	98.9	90.8	84.8
4	144.2	101.3	129.0
6	145.1	85.5	130.9
7	146.8	79.8	130.4
8	148.3	100.5	95.6
9	138.7	82.8	124.3
10	141.0	87.8	127.1
11	145.2	81.4	126.8
12	142.3	83.6	128.8
15	139.5	129.8	127.7
16	144.7	131.1	135.8
17	146.5	89.0	128.6

of 4,5-diiodoimidazole.[9-13] We used slight modifications of a literature procedure[10] to prepare **1a** and **2a**[14] and then

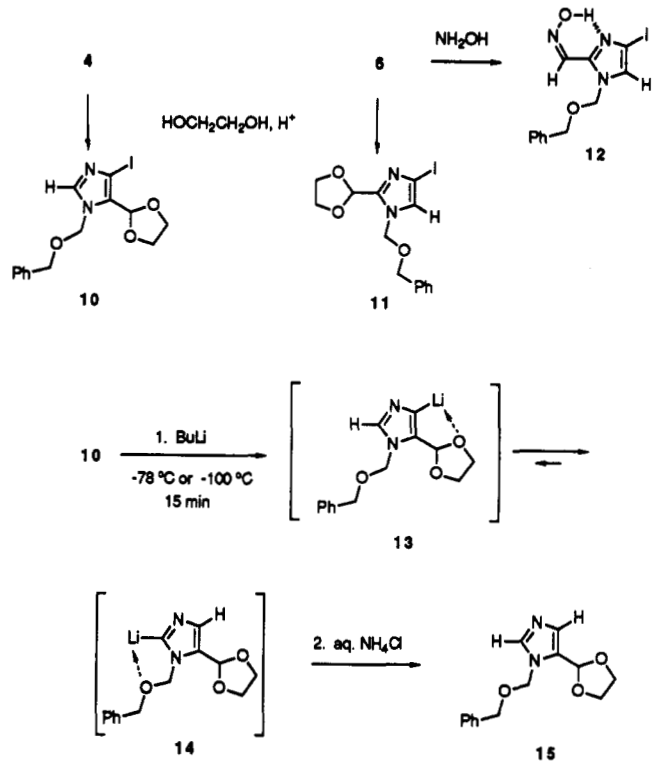


1a, $R_1 = R_2 = H$
b, $R_1 = PhCH_2OCH_2$, $R_2 = H$
2a, $R_1 = H$, $R_2 = I$
b, $R_1 = PhCH_2OCH_2$, $R_2 = I$

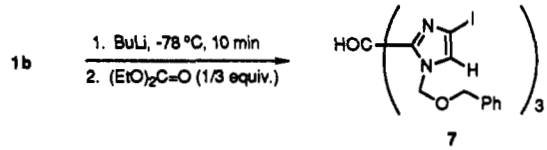
alkylated each of these with benzyl chloromethyl ether to afford imidazoles **1b** and **2b**, respectively. The (benzyloxy)methyl moiety is ultimately removable under mildly acidic conditions via protonation of the imidazole N3 nitrogen atom or under the essentially neutral conditions of hydrogenolysis.[15] In addition, as an ortho-lithiation directing group, this moiety provides for the stabilization of imidazol-2-yl- or 5-yllithium species via chelation of the ether oxygen atom to a 2- or 5-lithio substituent. As expected, **2b** underwent halogen–metal exchange exclusively at C2 to afford **1b** (99% yield) upon aqueous workup.

As shown in Scheme I, imidazole **1b** was found to undergo a regioselective halogen–metal exchange with butyllithium in dry THF at −78 °C within 10 min. Quench of the putative imidazol-5-yllithium species **3** with DMF afforded, after extractive workup and chromatographic purification, a 75% yield of 1-[(benzyloxy)methyl]-4-iodoimidazole-5-carboxaldehyde (**4**). The structural assignment of **4** was made with the assistance of a detailed ^1H and ^{13}C NMR spectroscopic analysis of its ethylene acetal derivative (vide infra) and by comparison of the ^{13}C chemical shifts of the imidazole ring carbon atoms with those of other compounds prepared in this study (see Table I). Interestingly, when the halogen–metal exchange reaction mixture of **1b** and butyllithium was allowed to equilibrate at −78 °C for a total of 45 min before quench with DMF, we obtained the isomeric 1-[(benzyloxy)methyl]-4-iodoimidazole-2-carboxaldehyde (**6**) in 68% purified yield and observed only a trace of **4** in the product mixture (TLC analysis). We believe that the initially formed imidazol-5-yllithium species **3** undergoes an

Scheme II



acid/base equilibration during the 45 min at −78 °C to afford the imidazol-2-yllithium species **5**, and that this process occurs via catalysis by a small amount of a 2,5-dilithioimidazole[4,5] produced by the slight excess of butyllithium reagent employed. On the basis of these findings, we suspected that electrophilic reagents weaker than DMF (e.g., the diethyl carbonate employed in one of Breslow's studies[2a]) would be unable to intercept the imidazol-5-yllithium species before equilibration to its imidazol-2-yllithium isomer occured under the conditions employed. In order to test this postulate, we prepared the putative imidazol-5-yllithium species **3** by equilibration of **1b** with butyllithium at −78 °C for 10 min and then allowed it to react with $^1/_3$ equiv of diethyl carbonate for 2 h at −78 °C. An aqueous workup of the reaction mixture afforded tris[1-[(benzyloxy)methyl]-4-iodo-2-imidazolyl]-carbinol (**7**; 59% yield), characterized by its ^1H and ^{13}C NMR and FD mass spectral properties. Thus, in contrast to that by DMF, the electrophilic quench by diethyl carbonate is unable to compete with the rapid conversion of **3** to **5** at −78 °C.



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Two minor byproducts invariably isolated (<10% yield) in the preparation of **4** or **6** were characterized as 1-[(benzyloxy)methyl]-4,5-diiodoimidazole-2-carboxaldehyde (**8**) and 1-[(benzyloxy)methyl]-4-iodoimidazole (**9**; Scheme I). The former imidazole may arise from a simple C2 deprotonation of **1b** by the butyllithium and then a formylation of the resulting imidazol-2-yllithium species by DMF, while the latter may result from the reaction of **3** or **5** with propitious water. We intentionally prepared compound **9** from **1b** (85% yield) by quenching imidazollithium intermediate **3** (or **5**) with aqueous NH_4Cl. The complete ^1H and ^{13}C NMR spectral peak assignments of **9** were made with the assistance of short- and long-range

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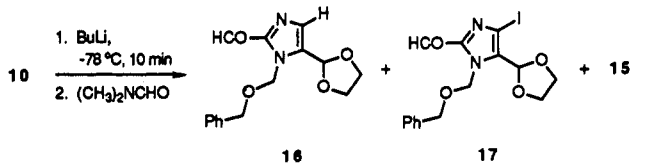
^1H–^{13}C 2D heteronuclear correlation (Hetcor) NMR spectroscopy. The observation of strong three-bond correlations of the CH_2N proton resonance to both the C2 and C5 carbon resonances in the long-range Hetcor spectrum allowed us to assign the structure of **9** as the 4-iodo regioisomer. The fact that the aqueous NH_4Cl quench of both **3** and **5** afforded imidazole **9** confirms our assignment of **5** as a 4-iodoimidazol-2-yllithium species, and thus of **6** as the 2-formyl-4-iodo regioisomer of **4**.

Imidazolecarboxaldehydes **4** and **6** were converted to their corresponding ethylene acetal derivatives **10** and **11** (91 and 81% yields, respectively; Scheme II). As before, Hetcor NMR spectroscopic analysis was employed to provide the key structural assignment criteria for **10**. Compound **6** was also converted to its oxime derivative **12** (93% yield). The observation of the extreme downfield shift (δ 11.75) of the D_2O-exchangeable hydroxyl resonance in the ^1H NMR spectrum of **12** leads us to conclude that this compound is the internally hydrogen-bonded *Z* isomer depicted in Scheme II.

Acetal **10** was treated with butyllithium at −78 °C and the reaction mixture quenched with aqueous NH_4Cl to afford 1-[(benzyloxy)methyl]imidazole-5-carboxaldehyde ethylene acetal (**15**), characterized with the assistance of Hetcor and dNOE NMR spectroscopic analysis. Treatment of **10** with butyllithium at −78 °C for 15 min followed by quench with D_2O gave [2-^2H]-**15** (contaminated with some unlabeled **15**), as identified by ^1H NMR spectral analysis. Similar results were obtained when the halogen–metal exchange reaction was conducted at −100 °C for 15 min before D_2O quench. The initially formed imidazol-4-yllithium species **13** apparently underwent an exceedingly rapid isomerization to the -2-yllithium species **14** under the various conditions employed. As expected, an attempt to trap the imidazol-4-yllithium species **13** with DMF as electrophile according to the procedure utilized previously in the successful trapping of **3** (Scheme I) did not afford any C4 formylated products. Instead, we obtained 1-[(benzyloxy)methyl]imidazole-2,5-dicarboxaldehyde 5-ethylene acetal (**16**; 25% yield) and 1-[(benzyloxy)methyl]-4-iodoimidazole-2,5-dicarboxaldehyde 5-ethylene acetal (**17**; 26% yield), along with a trace (6%) of **15**. Compounds **16** and **17**, characterized by their ^1H



and ^{13}C NMR and mass spectral properties, represent the products of formylation of the imidazol-2-yllithium species **14** and of C2-deprotonated **10**, respectively.

Conclusions

We have demonstrated that an imidazol-5-yllithium species can be prepared by halogen–metal exchange in the presence of an *unsubstituted* C2 carbon atom position and that this species can be used to obtain C5-functionalized imidazoles provided that the electrophilic reagent employed is sufficiently reactive to compete with the rapid conversion of the imidazol-5-yllithium species of its imidazol-2-yllithium isomer at −78 °C. However, a C2-unsubstituted imidazol-4-yllithium species undergoes much too rapid a conversion to its imidazol-2-yllithium isomer, even at −100 °C, to permit C4 functionalization. Thus, the presence of a C2 protecting group will be necessary in only some instances where C5 functionalization is desired, but in pratically all instances where C4 functionalization is desired. Assisted by these findings, we are now developing a new halogen–metal exchange based synthetic methodology to purine ring analogues from imidazole precursors. This will be the subject of a forthcoming paper.

Experimental Section

Materials and Methods. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA) using Merck silica gel-60 with fluorescent indicator as the adsorbent. Tetrahydrofuran was dried by distillation from sodium under nitrogen or argon, using benzophenone ketyl as indicator. *N,N*-Dimethylformamide was dried over P_2O_5 and then distilled under nitrogen or argon in vacuo. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-200 (200 and 50 MHz) or XL-300 (300 and 75 MHz), Nicolet NT-360 (360 and 90 MHz), or General Electric QE-300 (300 and 75 MHz), or GN-500 (500 and 125 MHz) instrument. These spectra were recorded with tetramethylsilane (δ 0.0 for ^1H), $CDCl_3$ (δ 77.0 for ^{13}C), or $(CD_3)_2SO$ (δ 39.5 for ^{13}C) as internal reference. Short- and long-range 2D ^1H–^{13}C Hetcor spectra were obtained on the Varian XL-300 or GE QE-300 or GN-500 instruments. Benzyl chloromethyl ether, butyllithium in hexanes, and diethyl carbonate were purchased from the Aldrich Chemical Co. The butyllithium was titrated with diphenylacetic acid in dry THF solution at 0 °C. Elemental microanalyses were performed by Joseph Nemeth or Tom McCarthy at the University of Illinois or obtained from Galbraith Laboraties, Knoxville, TN. Mass spectral analyses were obtained from Richard Milberg and his staff of the Mass Spectrometry facility at the University of Illinois. The purity of compounds **2b**, **7**, **16**, and **17** was judged to be >90% by ^1H and ^{13}C NMR spectral determinations.

1-[(Benzyloxy)methyl]-4,5-diiodoimidazole (1b). A solution of **1a** (9.0 g, 28.1 mmol) in 100 mL of anhydrous DMF was treated with powdered K_2CO_3 (39 g, excess) and stirred vigorously. The suspension was treated dropwise with benzyl chloromethyl ether (3.95 mL, 28.1 mmol) and stirred vigorously overnight. The reaction mixture was filtered by suction filtration, and the K_2CO_3 was washed with a small amount of fresh DMF. The combined DMF solutions were rotary evaporated in vacuo, and the oily residue was dissolved in 100 mL of CH_2Cl_2. The organic solution was evaporated onto 25 g of silica gel and pumped dry overnight, and the silica gel was washed with CH_2Cl_2 until no more product eluted (TLC analysis). The CH_2Cl_2 solution was reduced in volume to 125 mL, washed with saturated aqueous $NaHSO_3$ (75 mL) and saturated aqueous NaCl (75 mL), dried (Na_2SO_4), and rotary evaporated to give 11.1 g (90%) of nearly pure **1b** as a pale yellow solid: mp 88–89 °C (Et_2O/hexanes); ^1H NMR ($CDCl_3$) δ 7.69 (s, 1, H2), 7.40–7.29 (m, 5, PhH), 5.35 (s, 2, CH_2N), 4.50 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 142.0 (C2), 136.0 (Ph-quaternary C), 128.9, 128.6, and 128.2 (each Ph-C), 97.6 (C4), 82.0 (C5), 77.6 (CH_2N), 70.6 ($PhCH_2$); low-resolution ACE (alternating CI/EI) mass spectra EI *m/z* 439.9 (M^+), 409.8 ($M^+ - CH_2O$), 91.0 ($PhCH_2^+$); CI(NH_3) *m/z* 440.8 (MH^+), 410.8 ($MH^+ - CH_2O$), 91.0 ($PhCH_2^+$).

From 2b: A solution of **2b** (8.49 g, 15.0 mmol) in 150 mL of dry THF under Ar was cooled to −78 °C and was treated dropwise with BuLi (11.5 mL of a 1.30 M solution in hexanes, 15.0 mmol) over 5 min. The reaction mixture was stirred for an additional 25 min at −78 °C and was then quenched by the addition of 10 mL of saturated aqueous NH_4Cl while still cold. The mixture was allowed to warm slowly to room temperature and then was partitioned between 150 mL of EtOAc and 150 mL of water. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 200 mL). The EtOAc solutions were combined and rotary evaporated to dryness in vacuo, and the residue was purified by column chromatography (silica gel, 1% MeOH/CH_2Cl_2 as eluent) to afford 6.57 g (99%) of **1b** as a yellow solid: mp 88–91 °C (Et_2O/hexanes); ^1H NMR ($CDCl_3$) as above. Anal. Calcd for $C_{11}H_{10}I_2N_2O$: C, 30.03; H, 2.29; I, 57.68; N, 6.37. Found: C, 30.19; H, 2.11; I, 57.89; N, 6.29.

1-[(Benzyloxy)methyl]-2,4,5-triiodoimidazole (2b). A solution of **2a** (17.63 g, 39.5 mmol) in 200 mL of anhydrous DMF was treated with powdered K_2CO_3 (76 g, 548 mmol), and the resulting suspension was stirred vigorously with an overhead

benzyl chloromethyl ether (7.7 mL, 55.1 mmol) and stirred vigorously overnight. The suspension was suction filtered, and K_2CO_3 was washed with 50 mL of fresh DMF. The combined filtrate and washing was rotary evaporated in vacuo to an oil, which was dissolved in 200 mL of CH_2Cl_2 and evaporated onto 50 g of silica gel and pumped dry overnight. The product was eluted with CH_2Cl_2 (TLC monitoring) and the organic layer was washed with saturated aqueous $NaHSO_3$ (150 mL) and saturated aqueous NH_4Cl (50 mL), and rotary evaporated to afford 18.5 g (83%) of **2b** as a pale yellow solid. This compound was characterized according to its mp, ^1H and ^{13}C NMR spectral, and mass spectral data: mp 129–131 °C (aqueous Me_2CO); ^1H NMR ($CDCl_3$) δ 7.37–7.29 (m, 5, PhH), 5.42 (s, 2, CH_2N), 4.56 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 136.1 (Ph-quaternary C), 128.5, 128.2, and 127.7 (each Ph-C), 98.9 (C2), 90.8 (C4), 84.8 (C5), 79.1 (CH_2N), 70.9 ($PhCH_2$); low-resolution EI mass spectrum m/z 565.6 (M^+), 535.5 ($M^+ - CH_2O$), 91.1 ($PhCH_2^+$).

1-[(Benzyloxy)methyl]-4-iodoimidazole-5-carboxaldehyde (4). A solution of **1b** (1.73 g, 3.93 mmol) in 20 mL of anhydrous THF under N_2 was cooled to −78 °C and was treated dropwise with butyllithium (2.5 mL of a 1.62 M solution in hexanes, 4.28 mmol). The reaction mixture was stirred for 10 min at −78 °C and then was treated all at once with 2.0 mL of anhydrous DMF. The reaction mixture was allowed to warm slowly to room temperature over a 20-min period and then was quenched by the addition of 20 mL of saturated aqueous NH_4Cl. The product was isolated by extraction (EtOAc) and was purified by radial chromatography (50% EtOAc/hexanes) to afford 1.01 g (75%) of **4** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 9.63 (s, 1, CHO), 7.77 (s, 1, H2), 7.24–7.33 (m, 5, PhH), 5.71 (s, 2, CH_2N), 4.56 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 180.8 (CHO), 144.4 (C2), 135.9 (Ph-quaternary C), 129.0 (C5), 128.4, 128.4 and 127.8 (each Ph-C), 101.3 (C4), 74.8 (CH_2N), 71.2 ($PhCH_2$); low-resolution ACE mass spectra EI m/z 342.0 (M^+), 311.9 ($M^+ - CH_2O$), 91.0 ($PhCH_2^+$); CI(NH_3) m/z 360.9 (MNH_4^+), 342.9 (MH^+), 312.9 ($MH^+ - CH_2O$), 91.0 ($PhCH_2^+$); low-resolution FAB mass spectrum m/z 343.7 (MH^+). Anal. Calcd for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; I, 37.09; N, 8.19. Found: C, 42.00; H, 3.24; I, 37.16; N, 8.18.

1-[(Benzyloxy)methyl]-4-iodoimidazole-2-carboxaldehyde (6). This compound was prepared according to the procedure for compound **4**, except that the reaction mixture was stirred at −78 °C for 45 min before the addition of DMF. Extractive workup followed by radial chromatographic purification afforded **6** in 68% yield: ^1H NMR ($CDCl_3$) δ 9.50 (s, 1, CHO), 7.35–7.25 (m, 6, PhH and H5), 5.95 (s, 2, CH_2N), 4.60 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 181.2 (CHO), 145.1 (C2), 136.0 (Ph-quaternary C), 130.9 (C5), 128.6, 128.4, 127.8 (each Ph-C), 85.5 (C4), 75.1 (CH_2N), 71.7 ($PhCH_2$); low-resolution FAB mass spectrum m/z 343.0 (MH^+). Anal. Calcd for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; I, 37.09; N, 8.19. Found: C, 42.05; H, 3.17; I, 37.29; N, 8.19.

Tris[1-[(benzyloxy)methyl]-4-iodo-2-imidazolyl]carbinol (7). A solution of **1b** (880 mg, 2.0 mmol) in 15 mL of anhydrous THF was cooled to −78 °C and was treated with butyllithium (1.28 mL of a 1.57 M solution in hexanes, 2.0 mmol). The reaction mixture was stirred for 10 min at −78 °C, and then was treated dropwise with diethyl carbonate (82 μL, 0.67 mmol). The mixture was stirred for an additional 2 h at −78 °C. The solution was allowed to warm to room temperature over 2 h, and water (10 mL) was added to quench the reaction. The product was isolated by extraction (EtOAc) and was purified by radial chromatography (50% EtOAc/hexanes) to afford 380 mg (59%) of **7** as pale yellow crystals, characterized by its ^1H and ^{13}C NMR and mass spectral properties: mp 62–64 °C (EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 7.35–7.15 (m, 18, 15 PhH and three H5), 6.03 (s, exchanges with D_2O, 1, OH), 5.31 (s, 6, three CH_2N), 4.26 (s, 6, three $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 146.8 (C2) 136.6 (Ph-quaternary C), 130.4 (C5), 128.4, 128.0, and 127.6 (each Ph-C), 79.8 (C4), 76.6 (CH_2N), 71.1 ($PhCH_2$); low-resolution FD mass spectrum (MAT-731 spectrometer, 0 mA emission current, 8 kV acceleration potential, and −4 kV on extraction plate) m/z 968 (M^+).

1-[(Benzyloxy)methyl]-4,5-diiodoimidazole-2-carboxaldehyde (8). This compound was invariably isolated in small amounts (5–10% yield) from the preparations of **4** or **6**: mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 9.50 (s, 1, CHO), 7.33–7.26 (m, 5, PhH), 5.95 (s, 2, CH_2N), 4.60 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 127.5 (each Ph-CH), 100.5 (C4 or C5), 95.6 (C4 or C5), 76.9 (CH_2N), 71.4 ($PhCH_2$); low-resolution FAB mass spectrum m/z 468.9 (MH^+). Anal. Calcd for $C_{12}H_{10}I_2N_2O_2$: C, 30.80; H, 2.15; I, 54.23; N, 5.99. Found: C, 30.89; H, 2.12; I, 54.24; N, 5.88.

1-[(Benzyloxy)methyl]-4-iodoimidazole (9). A solution of **1b** (440 mg, 1.0 mmol) in 10 mL of anhydrous THF under nitrogen was cooled to −78 °C and treated dropwise with butyllithium (0.72 mL of a 1.44 M solution, 1.04 mmol). The solution was stirred at −78 °C for 30 min and then quenched while cold with 5 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and partitioned between EtOAc and water (50 mL of each). The layers were separated, and the organic phase washed once with water (25 mL), dried (Na_2SO_4), and rotary evaporated to a yellow oil. The crude product was purified by radial chromatography (EtOAc) to afford 268 mg (85%) of **9** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.46 (s, 1, H2), 7.36–7.25 (m, 5, PhH), 7.13 (s, 1, H5), 5.25 (s, 2, CH_2N), 4.42 (s, 2, $PhCH_2$); ^{13}C NMR ($CDCl_3$) δ 138.7 (C2), 135.6 (Ph-quaternary C), 128.5, 128.2, and 127.8 (each Ph-C), 124.3 (C5), 82.8 (C4), 74.8 (CH_2N), 70.2 ($PhCH_2$) (the assignments of the ^1H and ^{13}C resonances were made with the aid of short- and long-range heteronuclear correlation experiments. The correlations observed in the long-range (10-Hz optimized) experiment were $CH_2N/PhCH_2$, $PhCH_2/CH_2N$, $H2/C4$, $H5/C2$, $CH_2N/C2$, $CH_2N/C5$, $PhCH_2$/Ph-quaternary C, and CH_2O/Ph-o-CH); low-resolution FAB mass spectrum m/z 315.1 (MH^+). Anal. Calcd for $C_{11}H_{11}IN_2O$: C, 42.06; H, 3.53; N, 8.92. Found: C, 41.66; H, 3.33; N, 8.85.

1-[(Benzyloxy)methyl]-4-iodoimidazole-5-carboxaldehyde Ethylene Acetal (10). A solution of **4** (311 mg, 0.91 mmol) in 35 mL of dry C_6H_6 was treated with ethylene glycol (0.2 mL, 3.58 mmol), pyridine (40 μL, 0.5 mmol), and p-TsOH (95 mg, 0.5 mmol) and was heated at reflux in a Dean-Stark trap-equipped apparatus for 6 h. The reaction mixture was allowed to cool to room temperature and then was rotary evaporated to dryness in vacuo. The residue was purified by radial chromatography (40% EtOAc/hexanes) to afford 320 mg (91%) of **10** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.61 (s, 1, H2), 7.35–7.25 (m, 5, PhH, 5.88 (s, 1, acetal-CH), 5.41 (s, 2, CH_2N), 4.48 (s, 2, $PhCH_2$), 4.04–3.95 (m, 4, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 141.0 (C2), 136.2 (Ph-quaternary C), 128.4, 128.0 and 127.8 (each Ph-C), 127.1 (C5), 98.3 (acetal-CH), 87.8 (C4), 74.3 (CH_2N), 70.2 ($PhCH_2$), 65.0 (CH_2CH_2) (correlations observed in the long-range (10-Hz optimized) ^1H–^{13}C Hetcor spectrum were $CH_2N/C2$, acetal-$CH/C5$, $CH_2N/C5$, $CH_2N/PhCH_2$, and CH_2CH_2/acetal-CH); low-resolution ACE mass spectra EI m/z 386.1 (M^+), 91.1 ($PhCH_2^+$); CI(NH_3) m/z 387.0 (MH^+), 91.0 ($PhCH_2^+$). Anal. Calcd for $C_{14}H_{15}IN_2O_3$: C, 43.54; H, 3.92; I, 31.76; N, 6.87. Found: C, 43.84; H, 4.05; I, 31.76; N, 7.14.

1-[(Benzyloxy)methyl]-4-iodoimidazole-2-carboxaldehyde Ethylene Acetal (11). Substitution of **6** for **4** in the previous procedure for the preparation of compound **10** afforded acetal **11** (55% yield, 81% based on unrecovered starting material): mp 61–62 °C; ^1H NMR ($CDCl_3$) δ 7.40–7.27 (m, 5, PhH), 7.18 (s, 1, H5), 5.92 (s, 1, acetal-CH), 5.41 (s, 2, CH_2N), 4.50 (s, 2, $PhCH_2$), 4.06–3.98 (m, 4, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 145.2 (C2), 136.3 (Ph-quaternary C), 128.5, 128.2, 127.8 (each Ph-CH), 126.8 (C5), 98.0 (acetal-CH), 81.4 (C4), 74.5 (CH_2N), 70.4 ($PhCH_2$), 65.1 (CH_2CH_2); low-resolution ACE mass spectra EI m/z 386.1 (M^+), 313.1 ($M^+ - C_3H_5O_2$), 91.1 ($PhCH_2^+$); CI(CH_4) m/z 387.1 (MH^+), 313.1 ($MH^+ - C_3H_6O_2$), 91.1 ($PhCH_2^+$). Anal. Calcd for $C_{14}H_{15}IN_2O_3$: C, 43.54; H, 3.92; N, 7.26. Found: C, 43.71; H, 4.09; N, 7.07.

(*Z*)-1-[(Benzyloxy)methyl]-4-iodoimidazole-2-carboxaldehyde Oxime (12). A solution of **6** (0.48 g, 1.4 mmol) and hydroxylamine hydrochloride (0.15 g, 2.18 mmol) in a mixture of 10 mL of 95% EtOH and 5 mL of water was treated in several portions with 0.39 g (7.0 mmol) of powdered NaOH. The reaction mixture was heated at reflux for 1 h and was then poured onto ice. The pH of the aqueous mixture was adjusted to 7 by addition of 1 N HCl, and the product was extracted into EtOAc (3 × 10 mL). Evaporation of solvent followed by recrystallization of the crude product from water afforded 0.46 g (93%) of **12** as colorless crystals: mp 185–186 °C; ^1H NMR ($(CD_3)_2SO$) δ 11.75 (s, exchanges with addition of D_2O, 1, OH), 8.06 (s, 1, oxime-CH), 7.70 (s, 1 H5), 7.32 (m, 5, PhH), 5.66 (s, 2, CH_2N), 4.52 (s, 2, $PhCH_2$);

^{13}C NMR ($(CD_3)_2SO$) δ 142.3 (C2), 139.7 (oxime-CH), 137.1 (Ph-quaternary C), 128.8 (C5), 128.3, 127.7, and 127.6 (each Ph-C), 83.6 (C4), 75.3 (CH_2N), 70.1 ($PhCH_2$); low-resolution ACE mass spectra CI(CH_4) m/z 358.0 (MH^+), 310.0 ($MH^+ - CH_2O - H_2O$), 91.1 ($PhCH_2^+$). Anal. Calcd for $C_{12}H_{12}IN_3O_2$: C, 40.36; H, 3.39; N, 11.77. Found: C, 39.93; H, 3.33; N, 11.53.

1-[(Benzyloxy)methyl]imidazole-5-carboxaldehde Ethylene Acetal (15). A solution of **10** (292 mg, 0.76 mmol) in 5 mL of anhydrous THF was cooled to -78 °C and was treated with butyllithium (611 μL of a 1.41 M solution in hexanes, 0.86 mmol). The reaction mixture was stirred for 5 h at -78 °C, allowed to warm to room temperature, and was quenched with saturated aqueous NH_4Cl (10 mL). The product was isolated by extraction (EtOAc) and purified by radial chromatography (5% CH_3OH/CH_2Cl_2) to afford 150 mg (76%) of **15** as a yellow oil. The compound was characterized by its NMR and mass spectral properties: ^1H NMR ($CDCl_3$) δ 7.64 (s, 1, H2), 7.38-7.27 (m, 5, PhH), 7.18 (s, 1, H4), 6.05 (s, 1, acetal-CH), 5.42 (s, 2, CH_2N), 4.47 (s, 2, $PhCH_2$), 4.04-3.97 (m, 4, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 139.5 (C2), 136.2 (Ph-quaternary C), 129.8 (C4), 128.5, 128.0 and 127.8 (each Ph-C), 127.7 (C5) 97.2 (acetal-CH), 74.0 (CH_2N), 70.0 ($PhCH_2$), 64.8 (CH_2CH_2) (correlations observed in the long-range (10-Hz optimized) ^1H-^{13}C Hetcor NMR spectrum were *H2*/CH_2N, *H2*/*C4*, Ph-*H*/Ph-quaternary *C*, *H4*/*C2*, CH_2N/*C2*, $PhCH_2$/CH_2N, $PhCH_2$/Ph-*C*H, $PhCH_2$/Ph-quaternary *C*. A difference-spectra NOE (dNOE) experiment performed by irradiating the CH_2N proton resonance revealed an NOE interaction between these protons and the H2, acetal-CH, and $PhCH_2$ protons); low-resolution FAB mass spectrum m/z 261.2 (MH^+), 231.2 ($MH^+ - CH_2O$). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 63.85; H, 6.16; N, 10.38.

Treatment of **10** with butyllithium at -78 °C for 15 min followed by quench with D_2O gave a material which, by ^1H NMR analysis, was a mixture of [2-^2H]-**15** and unlabeled **15**. Similar results were obtained when the halogen-metal exchange reaction was conducted at -100 °C for 15 min.

Attempted C4 Formylation of 13. A solution of **10** (170 mg, 0.44 mmol) in 5 mL of anhydrous THF under argon was cooled to -78 °C and was treated dropwise with butyllithium (611 μL of a 1.41 M solution in hexanes, 0.86 mmol). The reaction mixture was stirred for 10 min at -78 °C and then was treated dropwise with anhydrous DMF (0.2 mL, 2.5 mmol). The mixture was stirred at -78 °C for 35 min, then was allowed to warm to room temperature and was quenched with saturated aqueous NH_4Cl (10 mL). The products were isolated by extraction (EtOAc) and purified by radial chromatography (5% CH_3OH/CH_2Cl_2) to afford 32 mg (25%) of 1-[(benzyloxy)methyl]imidazole-2,5-dicarboxaldehyde 5-ethylene acetal (**16**) as a yellow oil, 47 mg (26%) of 1-[(benzyloxy)methyl]-4-iodoimidazole-2,5-dicarboxaldehyde 5-ethylene acetal (**17**) as a yellow solid, and 7 mg (6%) of **15** as a yellow oil. **16**: ^{H} NMR ($CDCl_3$) δ 9.81 (s, 1, CHO), 7.37 (s, 1, H4), 7.35-7.25 (m, 5, PhH), 7.18 (s, 1, H4), 6.19 (s, 1, acetal-CH), 6.03 (s, 2, CH_2N), 4.55 (s, 2, $PhCH_2$), 4.05-4.00 (m, 4, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 182.8 (CHO), 144.7 (C2), 136.6 (Ph-quaternary C), 135.8 (C5), 131.1 (C4), 128.5, 128.0 and 127.7 (each Ph-C), 96.7 (acetal-CH), 73.7 (CH_2N), 71.1 ($PhCH_2$), 65.2 (CH_2CH_2); low-resolution ACE mass spectrum CI(CH_4) m/z 289.1 (MH^+), 259.1 ($MH^+ - CH_2O$), 91.1 ($PhCH_2^+$). **17**: mp 101-102 °C (Et_2O/hexanes); ^1H NMR ($CDCl_3$), δ 9.76 (s, 1, CHO), 7.38-7.25 (m, 5, PhH), 6.05 (s, 1, acetal-CH), 5.98 (s, 2, CH_2N), 4.57 (s, 2, $PhCH_2$), 4.11-4.00 (m, 4, CH_2CH_2); ^{13}C NMR ($CDCl_3$), δ 181.8 (CHO), 146.5 (C2), 136.7 (Ph-quaternary C), 128.6 (C5), 128.4, 128.0 and 127.8 (each Ph-C), 97.7 (acetal-CH), 89.0 (C4), 73.8 (CH_2N), 71.1 ($PhCH_2$), 65.5 (CH_2CH_2); low-resolution ACE mass spectra CI(CH_4) m/z 385.1 ($MH^+ - CH_2O$), 91.1 ($PhCH_2^+$). **15**: ^1H NMR ($CDCl_3$) identical with that of the sample prepared intentionally from **10**.

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Supplementary Material Available: Experimental procedures and data for **1a** and **2a**; ^1H and ^{13}C NMR spectra of **2b**, **7**, **16**, and **17**; short- and long-range 2D ^1H-^{13}C heteronuclear NMR shift correlation spectra for **9**, **10**, and **15** (15 pages). Ordering information is given on any current masthead page.

Synthesis and Catalytic Properties of Hydrophobically Modified Poly(alkylmethyldiallylammonium bromides)

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A series of hydrophobically modified homo- and copolymers of the poly(alkylmethyldiallylammonium bromide) type has been prepared by free-radical cyclo(co)polymerization of alkylmethyldiallylammonium bromide monomers in aqueous solution. Depending on the length of the alkyl side chain (varied between C_1 and C_{12}) and the conformational freedom of the polymeric main chain, polysoap behavior was found as indicated by the hypsochromic shift of the long-wavelength absorption band of Methyl Orange, noncovalently bound to the macromolecule. The formation of a compact coil results in the presence of hydrophobic microdomains. Polysoap formation, akin to intramolecular micellization, is also revealed by appreciable catalytic effects on the unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate at pH 11.3 and 30 °C.

Physicochemical studies, including viscosity measurements and fluorescence probing, have revealed that polyelectrolytes carrying sufficiently hydrophobic side chains often form compact coils in aqueous solution.[1,2] In a process which may be termed intramolecular micellization, a number of the side chains aggregate and form hydrophobic microdomains primarily stabilized by hydrophobic interactions. This type of polyelectrolytes has recently been characterized as "polysoaps".[3] Although the exact

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