Directed *ortho*-Lithiation on Solid Phase

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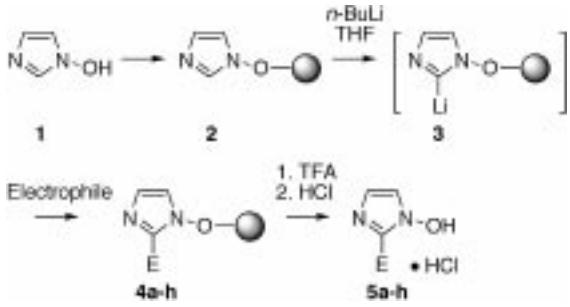
Received June 17, 1998

Resin-bound 1-hydroxyimidazole, obtained by alkylation of the sodium salt of 1-hydroxyimidazole with chloromethyl polystyrene, was lithiated at C-2 with *n*-butyllithium. Subsequent treatment with carbon, halogen, or sulfur electrophiles followed by detachment from the solid support by heating with trifluoracetic acid at 100 °C for 20 h gave 2-substituted 1-hydroxyimidazoles in 52−93% yields.

Solid-phase synthesis[1−3] and combinatorial chemistry[4,5] have recently received much interest due to their potential to accelerate the drug discovery process.[6,7] The repertoire for synthesis on solid support is still inadequate, especially if compared with conventional solution-phase chemistry. In solution, metalation of aromatic compounds followed by reaction with an electrophile has a broad potential and has been used extensively.[8,9] Consequently, lithiated solid-phase-bound aromatic substrates could be useful for the introduction of a variety of functional groups by subsequent trapping with a broad range of electrophiles. Direct lithiation of unsubstituted polystyrene via proton−lithium exchange has been reported.[10−12] In addition, aromatic lithiation by halogen−lithium exchange of bromopolystyrene[10,12] and polymer-bound substrates has been described.[13] Recently, lithiation of polymer-bound 3-furyl- and 3-thienylmethanol has been reported.[14] In many cases, proton−lithium exchange provides the most direct route to the target structure and is preferred over halogen−lithium exchange. Reactions involving proton−lithium exchange are well suited for the introduction of substituents of high diversity and therefore useful in the production of substance libraries for biological evaluation.

We report what seems to be the first systematic investigation of directed *ortho*-lithiation through deprotonation of a substrate bound to a polymer support.[15,16]

Scheme 1



Recently, we have shown that the 1-benzyloxy group in 1-benzyloxyimidazole serves as a directing metalation group in directed *ortho*-metalation, giving access to 2-substituted 1-benzyloxyimidazoles.[17] This process has now been adapted to a solid-state protocol using chloromethyl polystyrene to immobilize the *N*-hydroxyimidazole.

The resin-bound 1-hydroxyimidazole (**2**) was obtained by reaction of commercially available chloromethyl polystyrene with the sodium salt of *N*-hydroxyimidazole (**1**) in DMF (Scheme 1). The attachment of 1-hydroxyimidazole (**1**) to the polymer could easily be performed on a 50-g scale and was optimized to require an excess of only 0.5 equiv of 1-hydroxyimidazole (**1**). The loading of the resin was 0.90 mmol/g, corresponding to 74% of the maximum theoretical loading of 1.22 mmol/g, as determined by cleavage with TFA at 100 °C for 20 h.

Resin-bound 1-hydroxyimidazole (**2**) was lithiated and reacted with a series of representative electrophiles. Lithiation was performed using 3 equiv of *n*-BuLi at −50 °C. Subsequent addition of carbon, halogen, or sulfur electrophiles produced resin-bound 2-substituted imidazole derivatives (**4a**−**h**). The substituted imidazoles were cleaved from the support by heating with TFA at 100 °C for 20 h in a screw-cap sealed reaction vessel.[18] Yields were determined by stripping off the TFA with HCl, followed by weighing of the resulting 2-substituted

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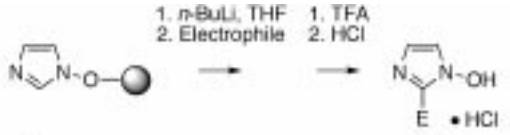
S0022-3263(98)01145-1 CCC: $15.00
Published on Web 09/24/1998

Table 1. Preparation of 2-Substituted 1-Hydroxyimidazoles



2 **5a-h**

	Electrophile	E	Conversion [a] %	Yield [b] %
a	MeI	Me	93	92
b	PhCHO	PhCHOH	96	52
c	$HCONMe_2$	$CH(OH)_2$	97	81
d	C_2Cl_6	Cl	97	93
e	CBr_4	Br	95	77
f	Me_2S_2	SMe	97	90
g	Ph_2S_2	SPh	97	74
h [c]	PhCOCl	COPh	100	58

[a] Conversion determined from relative peak areas of ^{1}H-NMR spectra
[b] Isolated yield determined using the loading level of starting resin **2**
[c] Using LDA instead of *n*-BuLi

1-hydroxyimidazole hydrochlorides (**5a**−**h**) (Table 1). The purity of the products was 92−100% as determined by ^{1}H NMR analysis. The only contaminant observed was 1-hydroxyimidazole as the consequence of incomplete lithiation or incomplete reaction with the electrophile. The identity of the products **5a**−**h** was established by elemental analysis and by ^{1}H and ^{13}C NMR spectra.

Benzoylation of **3** with benzoyl chloride was performed by generation of **3** using LDA instead of *n*-BuLi in order to avoid the addition of *n*-BuLi to **4h**. The fact that benzoylation did occur without formation of the tertiary alcohol demonstrated the advantage of solid-phase lithiation. In solution, the tertiary alcohol was a byproduct formed by the attack of lithioimidazole on the initially formed ketone.

Lithiation of **2** followed by treatment with benzaldehyde proceeded almost quantitatively since oxidation of the resin-bound product **4b** with 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide[16,19] followed by cleavage from the resin produced 1-hydroxy-2-benzoylimidazole·HCl (**5h**) in 97% yield. However, cleavage of resin-bound 1-hydroxy-2-phenylhydroxymethylimidazole **4b**, even under forcing conditions, gave only 52% of **5b** and left a resin which contained bound nitrogen in an amount corresponding to the loss of product **4b**. Presumably **4b** under the acidic cleavage conditions forms a benzylic carbocation which then is irreversibly reattached to the resin by a Friedel−Crafts type alkylation.

In conclusion, we have demonstrated that directed *ortho*-lithiation on resin-bound 1-hydroxyimidazole is a powerful synthetic method for the introduction of substituents at C-2 of 1-hydroxyimidazoles. The present procedure also provides access to 2-substituted imidazoles since 1-hydroxyimidazoles can easily be reduced to the corresponding imidazoles by $TiCl_3$ or palladium-catalyzed hydrogenolysis.[17,20]

Experimental Section

General Methods. All reactions involving air-sensitive reagents were performed under nitrogen using syringe−septum cap techniques. All glassware was flame-dried prior to use. All new compounds were colorless, unless otherwise stated. Melting points of the hygroscopic products were recorded in closed capillaries and are uncorrected. NMR spectra were recorded on a 300 MHz instrument.

Materials. The resin used was chloromethyl polystyrene 100−200 mesh, capacity 1.3 mmol/g, from Rapp Polymere. THF was distilled from Na/benzophenone under nitrogen, and DMF was sequentially dried with and stored over 3 Å molecular sieves.[21] *n*-Butyllithium 1.6 M in hexanes was titrated prior to use.[22]

Coupling of 1-Hydroxyimidazole (1) to Chloromethyl Polystyrene. In a two-necked flask and in a nitrogen atmosphere, sodium hydride (55% suspension in mineral oil, 4.60 g, 0.11 mol) was suspended in dry DMF (0.90 L). After the suspension cooled to 0 °C, 1-hydroxyimidazole (**1**)[17] (8.25 g, 0.098 mol) was added in a nitrogen counterstream over approximately 3 min. Stirring was continued at 0 °C for 20 min. Chloromethyl polystyrene (1.3 mmol/g, 50.0 g) was then added, and the mixture was stirred at 20 °C under nitrogen for 16 h. Filtration and washing with water (0.5 L), methanol (0.5 L), water (0.5 L), THF−methanol 1:1 (2 × 0.5 L), and dichloromethane (2 × 0.5 L) followed by drying at 0.1 mmHg at 20 °C for 24 h afforded resin-bound 1-hydroxyimidazole (**2**). The loading determined by cleavage of 1-hydroxyimidazole from the resin (see below) was 0.90 mmol/g.[23]

Cleavage of 1-Hydroxyimidazole (1) from Resin. Standard Procedure. Resin-bound 1-hydroxyimidazole (**2**) (1.0 g) and TFA (10 mL) were heated with stirring in a screw-cap sealed reaction vessel[18] to 100 °C for 20 h. Filtration and extraction with water (10 mL), TFA (3 mL), and water (10 mL); combination of all extracts and evaporation to dryness; evaporation twice with 37% aqueous hydrochloric acid (3 mL); addition of water (5 mL), filtration through activated carbon; and removal of the water *in vacuo* gave 109 mg of 1-hydroxyimidazole·HCl (**1**·HCl) as deliquescent crystals. The ^{1}H and ^{13}C NMR spectra were identical with those of an authentic sample.[17] On the basis of the amount of **1** obtained, the loading of polymer **2** was calculated to be 0.90 mmol/g corresponding to 74% of the maximal theoretical loading of 1.22 mmol/g.

Metalation of Resin-Bound 1-Hydroxyimidazole (2) Followed by Reaction with an Electrophile. Standard Procedure. In a Schlenck flask and in a nitrogen atmosphere, resin-bound 1-hydroxyimidazole (**2**) (1.00 g, 0.90 mmol) was suspended in dry THF (20 mL). Cooling to −60 °C; addition of *n*-butyllithium (2.70 mmol, 3.0 equiv) over 2 min, stirring at −50 to −60 °C for 20 min; addition of the electrophile (9.0 mmol, 10 equiv), stirring at −60 °C for 1 h followed by heating to 20 °C over 1 h and stirring at 20 °C for another 1 h; filtration and washing with methanol (2 × 15 mL), THF (2 × 15 mL), and dichloromethane (2 × 15 mL) followed by drying at 0.1 mmHg and 20 °C for 1 h afforded the resin-bound 2-substituted 1-hydroxyimidazoles **4a**−**g**. The products were cleaved from the resin using the procedure described above. The purity of the crude products (**5a**−**h**) were determined from relative peak areas of ^{1}H NMR spectra. The products were purified by recrystallization and identified by elemental analysis and by ^{1}H and ^{13}C NMR.

1-Hydroxy-2-methylimidazole (5a). After the addition of methyl iodide and stirring at −50 to −60 °C for 1 h, the mixture was cooled to −78 °C. To destroy excess methyl iodide, 33% dimethylamine in ethanol (3 mL) was added at such a rate that the internal temperature did not exceed −50 °C. Stirring was continued at −60 °C for 30 min and at 20 °C for 1 h before workup. The standard procedure was followed with the difference that additional washing with TFA (2 × 1 mL) was performed prior to washing with dichloromethane. This afforded 119 mg of a 93:7 mixture of **5a** and 1-hydroxyimidazole·HCl (**1**·HCl) corresponding to a 92% yield of **5a**. Recrystallization (ethanol−ethyl acetate) gave pure **5a**: mp

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(23) If the procedure was performed on a smaller scale (with ca. 5 g of resin), a loading of 1.07 mmol/g corresponding to 88% of the maximal theoretical loading was attained.

123−125 °C; δ_H (D_2O) 7.40 (1H, d, J = 2.10 Hz, H-4 or H-5), 7.20 (1H, d, J = 2.10 Hz, H-5 or H-4), 2.53 (3H, s, CH_3); δ_C (D_2O) 141.4, 119.9, 116.0, 9.0. Anal. Found: C, 35.93; H, 5.26; N, 20.88. Calcd for $C_4H_7N_2OCl$: C, 35.70; H, 5.24; N, 20.82.

1-Hydroxy-2-phenylhydroxymethylimidazole (5b). The standard procedure using benzaldehyde as the electrophile afforded 109 mg of a 92:8 mixture of 1-hydroxy-2-phenylhydroxymethylimidazole·HCl (**5b**) and **1**·HCl corresponding to 52% yield of **5b**. Recrystallization (ethanol−ethyl acetate) gave pure **5b**: mp 162−163 °C. δ_H (D_2O) 7.46−7.38 (6H, m, H-5 or H-4 and Ph), 7.33 (1H, d, J = 2.10 Hz, H-4 or H-5), 6.22 (1H, s); δ_C (D_2O) 144.2, 137.6, 130.5, 130.2, 127.9, 121.2, 117.1, 67.4. Anal. Found: C, 53.19; H, 4.86; N, 12.30. Calcd for $C_{10}H_{11}N_2O_2Cl$: C, 52.99; H, 4.89; N, 12.36. Elemental analysis of the resin after the cleavage with TFA gave C, 81.75; H, 6.75; N, 1.08 corresponding to 0.77 mmol of N/g resin, which is equivalent to 0.39 mmol of imidazole/g resin.

1-Hydroxy-2-formylimidazole (5c). The standard procedure using DMF as the electrophile gave 123 mg of a 97:3 mixture of 1-hydroxy-2-formylimidazole·hydrate·HCl (**5c**) and **1**·HCl as an oil, corresponding to 81% yield of **5c**: δ_H (D_2O) 7.48 (1H, d, J = 1.8 Hz, H-4 or H-5), 7.30 (1H, d, J = 1.8 Hz, H-5 or H-4), 6.27 (1H, s); δ_C (D_2O) 141.8, 121.5, 116.7, 82.8. Anal. Found: C, 28.13; H, 4.02; N, 15.74. Calcd for $C_4H_7N_2O_3Cl$, 35% H_2O: C, 27.79; H, 4.49; N, 16.20.

1-Hydroxy-2-chloroimidazole (5d). The standard procedure using hexachloroethane as the electrophile gave 130 mg of a 97:3 mixture of 1-hydroxy-2-chloroimidazole·HCl (**5d**) and **1**·HCl, corresponding to 93% yield of **5d**. Recrystallization (methanol−ethyl acetate) gave deliquescent crystals. ^{1}H and ^{13}C NMR spectra were identical with those of an authentic sample.[17]

1-Hydroxy-2-bromoimidazole (5e). The standard procedure using tetrabromomethane as the electrophile gave 142 mg of a 95:5 mixture of 1-hydroxy-2-bromoimidazole·HCl (**5e**) and **1**·HCl, corresponding to 77% yield of **5e**. Recrystallization (ethanol−ethyl acetate) gave pure **5e**: mp 160−175 °C (dec); δ_H (D_2O) 7.59 (1H, d, J = 2.40 Hz, H-4 or H-5), 7.40 (1H, d, J = 2.40 Hz, H-5 or H-4); δ_C (D_2O) 122.5, 119.6, 115.2. Anal. Found: C, 18.31; H, 1.96; N, 13.79. Calcd for $C_3H_4N_2OBrCl$: C, 18.07; H, 2.02; N, 14.05.

1-Hydroxy-2-methylthioimidazole (5f). The standard procedure using dimethyl disulfide as the electrophile gave 134 mg of a 97:3 mixture of 1-hydroxy-2-methylthioimidazole·HCl (**5f**) and **1**·HCl, corresponding to 90% yield of **5f**. Recrystallization (ethanol−ethyl acetate) gave pure **5f**: mp 160−162 °C; δ_H (D_2O) 7.50 (1H, d, J = 2.40 Hz, H-4 or H-5), 7.31 (1H, d, J = 2.40 Hz, H-5 or H-4), 2.62 (3H, s, CH_3); δ_C (D_2O) 140.2, 121.9, 118.4, 15.5. Anal. Found: C, 29.07; H, 4.15; N, 16.84. Calcd for $C_4H_7N_2OSCl$: C, 28.83; H, 4.23; N, 16.81.

1-Hydroxy-2-phenylthioimidazole (5g). The same procedure using diphenyl disulfide as the electrophile gave 154 mg of a 97:3 mixture of 1-hydroxy-2-phenylthioimidazole·HCl (**5g**) and **1**·HCl, corresponding to 74% yield of **5g**. Recrystallization (ethanol−ethyl acetate) gave pure **5g**: mp 169−171 °C; δ_H (D_2O) 7.54−7.41 (6H, m, H-4 or H-5 and Ph), 7.32 (1H, d, J = 2.40 Hz, H-5 or H-4); δ_C (D_2O) 136.4, 133.5, 131.2, 131.0, 128.1, 122.5, 119.1. Anal. Found: C, 47.54; H, 4.08; N, 12.30. Calcd for $C_9H_9N_2OSCl$: C, 47.27; H, 3.97; N, 12.25.

1-Hydroxy-2-benzoylimidazole (5h). Method a. The standard procedure using resin-bound 1-hydroxyimidazole (**2**), (200 mg, 0.18 mmol), freshly prepared lithium diisopropylamide in hexane−THF (3 equiv) for metalation, and benzoyl chloride as the electrophile gave a mixture which was quenched by the cautious addition of TFA (3.8 mL per g of **2**) over 5 min. The mixture was stirred at 20 °C for 1 h and worked up as described for the reaction with methyl iodide to give 41 mg of 1-hydroxy-2-benzoylimidazole·HCl (**5h**) contaminated with an unidentified byproduct. Flash chromatography (heptane−dichloromethane−acetic acid, 1:1:1 % → 1:4:1 %) afforded 20 mg (58%) of pure 1-hydroxy-2-benzoylimidazole: mp 112−113 °C; R_f 0.11 (heptane−dichloromethane−acetic acid, 1:3:1 %); δ_H ($CDCl_3$) 8.62 (2H, d, J = 7.20 Hz, H-2′), 7.66 (1H, t, J = 7.20 Hz, H-4′), 7.54 (2H, t, J = 7.20 Hz, H-3′), 7.38 (1H, s, H-4 or H-5), 7.23 (1H, s, H-5 or H-4); δ_C ($CDCl_3$) 184.9, 134.9, 134.5, 133.9, 131.3, 128.8, 126.9, 118.9. Anal. Found: C, 64.06; H, 4.41; N, 14.87. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89.

1-Hydroxy-2-benzoylimidazole (5h). Method b. A solution of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide[24,25] (0.65 g, 2.32 mmol) in DMSO (11 mL) was added at 20 °C to a suspension of resin-bound 1-hydroxy-2-phenylhydroxymethylimidazole (**4b**) (600 mg, 0.49 mmol) in THF (9 mL). Stirring at 20 °C for 2.5 h; filtration and washing with DMSO (5 × 10 mL), *i*-PrOH (3 × 10 mL), THF (3 × 10 mL), and dichloromethane (3 × 10 mL) followed by cleavage from the resin as described above gave 113 mg (97%) of crude 1-hydroxy-2-benzoylimidazole·HCl (**5h**). The free base,[26] identical with the material above, was obtained by dissolving **5h** in water (3 mL), extracting the solution with dichloromethane (6 × 3 mL), drying the extract ($MgSO_4$), removing the dichloromethane, and recrystallizing (ethyl acetate−heptane) the product.

Acknowledgment. This work was supported by the Danish Council for Technical and Scientific Research and the Lundbeck Foundation.

JO981145F

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