4-Lithio-1-tritylimidazole as a Synthetic Intermediate. Synthesis of Imidazole-4-carboxaldehyde

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Reaction of 4-iodo-1-tritylimidazole with *n*-butyllithium at −79°, followed by rapid quenching of the reaction mixture with DMF, gives good yields of 1-tritylimidazole-4(5)-carboxaldehyde, the isolation of which demonstrates the intermediacy of 4-lithio-1-tritylimidazole. This species should be destabilized by repulsive interaction of the negative charge on C-4 with the adjacent lone pair electrons on N-3 (the ALP effect). The isolation of 1-tritylimidazole-4(5)-carboxaldehyde in good yield and the versatility of the aldehyde functionality make 4-lithio-1-tritylimidazole a useful synthetic intermediate.

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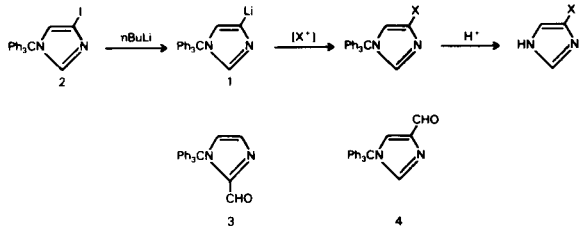
While the imidazole ring readily undergoes electrophilic halogenation and nitration in position-4(5), electrophilic alkylation and acylation reactions generally fail [1]. For this reason, routes to imidazoles having carbon substituents in position-4(5) often involve total synthesis of the imidazole ring [2]. We recently reported a method for the preparation of a series of 2-substituted imidazoles by lithiation of 1-tritylimidazole and electrophilic attack on the resulting C-2 carbanion [3]. The generality and convenience of this method suggested that extension to 4-substituted imidazoles would be a worthwhile effort, particularly in view of the paucity of synthetic alternatives. Accordingly, we have explored the feasibility of using 1-trityl-4-lithioimidazole (**1**), generated from 1-trityl-4-iodoimidazole (**2**) by metal-halogen exchange, as a precursor of 4(5)-substituted imidazoles (Scheme 1).

Scheme 1



Steric considerations suggest that tritylation of 4(5)-iodoimidazole yields the 4-iodo derivative, **2**, rather than the 5-iodo isomer. This expectation, in itself, is a complicating factor since a carbanion at C-4 should be destabilized by repulsive interaction with the adjacent lone pair at N-3 (the ALP effect) [4]. The importance of this consideration follows from earlier work. For example, Noyce, *et al.* [5], report that 5-bromo-1-methylimidazole undergoes lithium-halogen exchange, and that alkylation of the resulting carbanion with acetaldehyde yields 5-(1-hydroxyethyl)-1-methylimidazole. Under the same conditions, however, 4-bromo-1-methoxyimidazole gives 4-bromo-2-(1-hydroxyethyl)-1-methylimidazole, this result demonstrating the failure of lithium-halogen exchange [5]. Furthermore, Breslow, *et al.* [6] reported failure in attempts to lithiate *N*-protected 4(5)-bromo- or iodoimidazoles by reaction with butyllithium, obtaining instead products resulting from C-2 metalation or from reduction. The same workers demonstrated that, when the 2-position of 1-(methoxymethyl)- or 1-(ethoxymethyl)imidazole was blocked with the thiophenyl group, a C-5 carbanion was generated by LDA deprotonation. Again, there seemed to be no evidence for the formation of a C-4 carbanion. These workers ascribed the exclusive formation of the C-5 carbanion to coordination of lithium with the ether group on N-1. In their syntheses of alkynyl substituted 1-methylimidazoles, Shvartsberg, *et al.* [7] treated 4-iodo-1-methylimidazole with a 3-fold excess of *n*-butyllithium. Quenching with iodine produced a mixture of 4-iodo-1-methylimidazole and 2,4-diiodo-1-methylimidazole. The authors interpreted this result as suggesting the intermediacy of 4-lithio-1-methylimidazole, along with the 2,4-dilithio species, and possibly 2-lithio-4-iodo-1-methylimidazole. More recent studies of Iddon, *et al.*, on the metal-halogen exchange reactions of mono- and poly-halogenoimidazoles emphasize the difficulty in forming the C-4 lithium derivative [8a-b]. In the latter work, in an effort to functionalize the imidazole ring at position 4(5), positions 1 and 2 were blocked prior to metalation [9]. Consistent with the ALP affect, 4,5-dibromo-1-ethoxymethyl-2-phenylthioimidazole, on treatment with butyllithium and dimethyl disulfide, gave 4-bromo-1-ethoxymethyl-5-methylthio-2-phenylthioimidazole, and apparently none of the 5-bromo isomer [8b]. However, these same workers prepared an imidazol-4-yl lithium derivative (demonstrated by trapping with dimethylformamide or carbon dioxide) by treatment of 4-bromo-1-ethoxymethyl-5-methylthio-2-phenylthioimidazole with *n*-butyllithium at −70° [8a].

In our studies on the generation of imidazole C-2 carbanions, we found it convenient to monitor the extent of anion formation by quenching aliquots of the reaction mixture with excess dimethylformamide [10]. We found

the formation of 1-tritylimidazole-2-carboxaldehyde (**3**) to be rapid and quantitative and applied a similar strategy for detection of **2**. Rapid addition of a hexane solution of *n*-butyllithium to a solution of **2** in THF at −79° resulted in complete lithium-halogen exchange in less than 2 seconds, as evidenced by formation of an imidazole-carboxaldehyde in good yield after quenching of the reaction mixture with DMF. Furthermore, the nonidentity of the main product aldehyde with **3** (shown by tlc) suggested that it was the isomeric 4-aldehyde **4** *i.e.* the product of trapping of **1**. Elemental analysis, comparison with the literature [10,11] mp and nmr spectral data, and formation of imidazole-4(5)-carboxaldehyde after acid-catalyzed detritylation confirmed the structural assignment.

While our finding suggest that the ALP effect can be overcome, significant covalent character of the carbon-lithium bond may decrease a repulsive interaction with the N-3 lone-pair electrons. Our ability to achieve acylation of **1** with DMF stands in contrast to the results of Breslow, *et al.* It is perhaps significant that DMF appears particularly effective in the reaction compared to other electrophiles (see below), a point we are investigating further. This procedure has provided a very convenient synthesis of **4**, since the reaction can be scaled up and the product is easily purified.

Two features of the reaction deserve note. If a stoichiometric amount of *n*-butyllithium is used, the yield of **4** is reduced to around 50%. This product is accompanied by significant amounts of 1-tritylimidazole (19%), unreacted **2** (8%), **3** (7%), and a product tentatively identified as 4-iodo-1-tritylimidazole-2-carboxaldehyde (16%). We assume that reduction probably results from dehydrohalogenation of *n*-butyl iodide by the imidazole carbanion, and, indeed, use of a 2- to 3-fold excess of *n*-butyllithium (which excess should react with the *n*-butyliodide [15]) increased the yield of **4** to 83%, and no 1-tritylimidazole was detected. Under these conditions, **3** (11%) and a product tentatively identified as 1-tritylimidazole-4,5-dicarboxaldehyde (2%) were also isolated.

The mechanism for the formation of **3** remains unclear. That no 2-iodo-1-trityl imidazole [3] is detectable as a contaminant of **2**, and that 4-iodo-1-tritylimidazole-2-carboxaldehyde can be isolated when a stoichiometric quantity of *n*-butyllithium is used suggest that **3** is formed by reduction of 4-lithio-1-tritylimidazole-2-carboxaldehyde even in the presence of excess *n*-butyllithium. Furthermore, the relative amount of **3** formed does not appear to increase significantly with longer reaction times, suggesting that **3** is not derived from **1** by prototopic shift to the C-2 carbanion.

Yields and regioselectivities in the reactions of **1** with other electrophiles have been less impressive [12]. We are continuing to investigate the chemistry of **1** with the aim of extending the utility of the intermediate, and of determining the significance of the ALP effect in these reactions. From a synthetic point of view, **4** provides a convenient starting point for many imidazoles derivatives, by virtue of the versatility of the aldehyde functionality and the ease of removal of the trityl group [13].

EXPERIMENTAL

4(5)-Iodoimidazole was prepared by sodium sulfite reduction of a mixture of di- and triiodoimidazole, as described by Bensusan, *et al.* [14]. The polyiodinated imidazoles were conveniently prepared by iodination of imidazole with a 3-fold excess of iodine using a chloroform, 2*N*-sodium hydroxide two phase system. After removal of the chloroform layer, the aqueous phase was neutralized with hydrochloric acid, was decolorized with sodium thiosulfate and was filtered to give crude di- and triiodoimidazole; the solid mixture was suitable for the sulfite reduction.

4-Iodo-1-tritylimidazole (**2**).

To a solution of 3.38 g (0.017 mole) of 4-iodoimidazole in 15 ml of dimethylformamide was added 5.56 g (0.02 mole) of triphenylmethyl chloride and 1.5 ml of triethylamine. The solution was stirred at ambient temperature overnight and was then poured into 200 ml of ice water. The solid was filtered and dried to give **1**, 7.04 g (95%), recrystallized from ethyl acetate/cyclohexane, mp 224-225°.

Anal. Calcd. for $C_{22}H_{17}IN_2$: C, 60.56; H, 3.93; N, 6.43. Found: C, 60.73; H, 3.63; N, 6.47.

1-Tritylimidazole-4-carboxaldehyde (**4**).

(1) Stoichiometric *n*-Butyllithium.

A solution of 436 mg (1.0 mmole) of **2** in 10 ml of dry tetrahydrofuran (Aldrich) was stirred under argon with cooling in a dry ice acetone bath. To this solution was added with a syringe 0.65 ml (1.04 mmoles) of a 1.6 *M* solution of *n*-butyllithium in hexane (Aldrich). After 5 seconds, the reaction was quenched by addition of 0.5 ml of dry dimethylformamide. The solution was allowed to warm to ice temperature, water was added and most of the tetrahydrofuran was removed by rotary evaporation. The solid product that formed was collected by filtration. The crude product was chromatographed on a silica gel column, eluting with a 1:1 mixture of petroleum ether/ether. There was obtained, in order of elution from the column, 78 mg (16%) of a product tentatively identified as 4-iodo-2-formyl-1-tritylimidazole [15], unreacted **2** (37 mg, 8%), 1-tritylimidazole-2-carboxaldehyde **3** (21 mg, 7%), **4** (158 mg, 51%), and 1-tritylimidazole (59 mg, 19%).

The main product, **3** was recrystallized from ethanol to give colorless crystals, mp 197-198°, lit [10] mp 196-197°. The nmr spectrum was in complete agreement with literature data [11].

(2) Excess *n*-Butyllithium.

A solution of 436 mg (1.0 mmole) of **2** in 10 ml of dry tetrahydrofuran was treated, as above, with 2 ml (3.2 mmoles) of a 1.6 *M* solution of *n*-butyllithium in hexane. After 2 seconds the carbanion was quenched with 0.5 ml of dry dimethylformamide. Chromatography of the crude product, isolated as above, gave 1-tritylimidazole-2,4-dicarboxaldehyde, 8 mg [15], **3**, 38 mg (11%) and **4** 281 mg (83%).

Imidazole-4(5)-carboxaldehyde.

A solution of 169 mg (0.5 mmole) of **4** in methanol containing 5% acetic acid was refluxed for 7 hours. Water was added and triphenylcarbinol was removed by filtration. Evaporation of the filtrate gave homogeneous imidazole-4(5)-carboxaldehyde as an off-white solid, 47 mg (98%), mp 163-165°; sublimation gave colorless crystals, mp 172.5-173° (lit [16] mp 170°).

REFERENCES AND NOTES

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[12] For example, rapid quenching of **1** with an excess of ethyl chloroformate gave a 3:1 mixture of 4- (ref [9]) and 2-carboethoxy-1-tritylimidazole (ref [3]) in a total yield of 32%.

[13] For example, see A. Burger, M. Bernabé and P. W. Collins, *J. Med. Chem.*, **13**, 33 (1970). We are using **4** in the synthesis of α-substituted urocanic acid derivatives as potential urocanase inhibitors.

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[15] The identity of 4-iodo-2-formyl-1-tritylimidazole and 1-tritylimidazole-2,4-dicarboxaldehyde were based on hydrolyses to the deprotected imidazoles, identified by chemical ionization mass spectrometry. The structures of **2**, **3** and 1-tritylimidazole were confirmed by comparison with authentic materials (mp, tlc and nmr data). The aldehyde proton of **3** is erroneously reported at 9.40 ppm in reference [3]. The correct value is 9.20 ppm.

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