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SYNTHESIS OF 2-(2-ARYLETHYL)IMIDAZOLES BY DIRECT ALKYLATION OF 1-(*N,N*-DIMETHYLAMINOMETHYL)2-LITHIOMETHYLIMIDAZOLE

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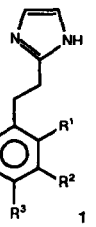
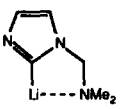
Abstract : Direct deprotonation of 1-(*N,N*-dimethylaminomethyl)2-methylimidazole **4** by *n*-butyllithium yields anion **5** which can readily undergo alkylation reactions. This finding provides immediate access to 2-(2-arylethyl)imidazoles, **1**, which are clumsy to prepare by other methods.

In our search for new agents for fertility control in males,[1] various 2-(2-arylethyl)imidazoles, **1**, were required for biological testings and for use as intermediates in further synthetic work. Out of the many documented methods for derivatization at C-2 of imidazole,[2] that based on Katritzky's approach[3] employing alkylation of 1-(*N,N*-dimethylaminomethyl)2-lithioimidazole, **2**, seemed to be the most direct, and one which should nicely lead to our target molecules. Indeed, in our hands, the dimethylaminomethyl protecting group proved far superior to others, not only in its ease of introduction and removal under mild conditions, but, more importantly, in promoting the ready formation of **2**, quite crucial to the success of subsequent reactions with electrophiles.



1

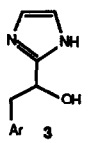
a. $R^1 = R^2 = R^3 = H$
b. $R^1 = Br$; $R^2 = R^3 = H$
c. $R^1 = R^2 = H$; $R^3 = Br$
d. $R^1 = R^2 = H$; $R^3 = Cl$
e. $R^1 = R^3 = Cl$; $R^2 = H$
f. $R^1 = R^3 = F$; $R^2 = H$
g. $R^1 = R^2 = H$; $R^3 = OMe$
h. $R^1 = H$; $R^2 = R^3 = OMe$



2

However, in applying **2** to the synthesis of **1**, a serious drawback intrinsic in the chemical nature of the necessary electrophiles became apparent. No alkylation takes place in the reaction of **2** with either 2-arylethyl halides or tosylates which eliminate to the corresponding styrenes in all cases. As for arylacetaldehydes, even though they do react with **2** to give alcohols **3** in good yields, the subsequent conversion to **1** (i.e. tosylation followed by reduction) is

considerably clumsy. We have studied this problem and are now pleased to report on the use of novel anion **5**, a higher homologue of **2**, which can readily be converted to our target molecules. Thus treatment of a THF solution of **4**, prepared from commercial 2-methylimidazole, with an equimolar amount of *n*-butyllithium at -78° for 10 minutes generates anion **5**, whose subsequent quenching with a benzyl halide followed by removal of the blocking group[3] leads smoothly to the required **1**.[4] The complete sequence is carried out in one pot and no intermediates are isolated. This method evades the use of arylethyl halides, and with them, the troublesome elimination reactions.



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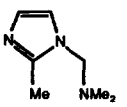

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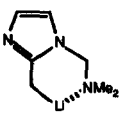

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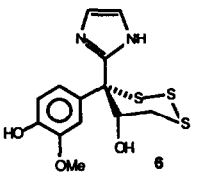

6

The facile metalation of **4** to give **5** is an attractive reaction and looks promisingly useful for further derivatizations of the imidazole skeleton. In fact we are currently applying this methodology to the synthesis of biologically active **6**, isolated from New Zealand ascidian *Aplidium* sp. D.,[5] and results will subsequently be reported.

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4. **1a** (59.1 %), **1b** (57.2 %), **1c** (59.7 %), **1d** (61.3 %), **1e** (50 %), **1f** (63.2 %), **1g** (56.8 %), **1h** (62.3 %) as calculated from **4**. All compounds are fully characterized. Elemental analyses were performed by the Scientific and Technological Research Equipment Center, Chulalongkorn University, Bangkok.
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