Pergamon

Tetrahedron Letters 41 (2000) 2777–2779

TETRAHEDRON
LETTERS

Direct displacement of –OH by nucleophiles in hydroxymethylimidazoles

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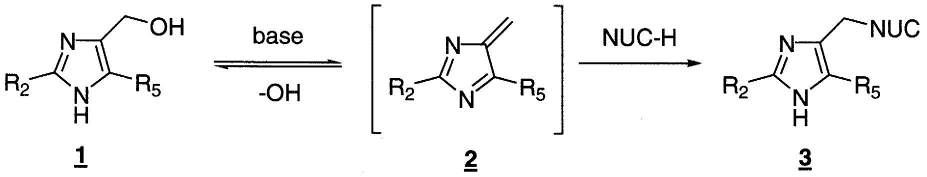
Received 13 December 1999; accepted 8 February 2000

Abstract

Direct displacement of –OH from 4- and 5-hydroxymethylimidazoles is achieved in good to excellent yields simply by heating a 4- or 5-hydroxymethylimidazole in the presence of an appropriate nucleophile in refluxing basic water. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aminomethylimidazole; hydroxymethylimidazole; imidazole; nucleophilic displacement.

Simple chemical transformations can be very powerful tools in organic synthesis. We needed to make a series of substituted imidazoles, and sought a direct method to access a multitude of imidazole derivatives from a common precursor. In addition to our needs for this class of compounds, 4-aminomethylimidazoles have recently been claimed as potent farnesyl transfer inhibitors for the treatment of cancer.[1] Thus, we sought an expedient method for functionalizing certain imidazoles using a readily available common starting material. Hydroxymethyimidazoles (**1**) came to mind, and using analogy with the instability of 3-hydroxymethylindoles,[2] we envisioned that we could develop conditions under which direct –OH displacement could be achieved from hydroxymethylimidazole (**1**, Scheme 1). Our hypothesis was further supported by the observation that naturally occurring 4-hydroxymethylimidazoles tended to racemize in solution,[3] thus supporting the hypothesized lability of the –OH group. Recognizing that an elimination/addition equilibrium of the HO– group in hydroxymethylimidazole would likely exist under



Scheme 1.

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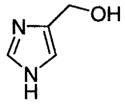
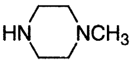
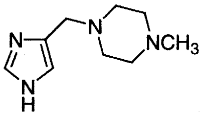
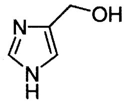
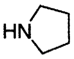
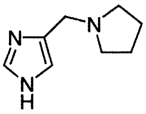
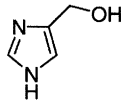
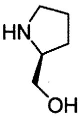
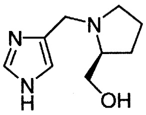
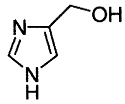
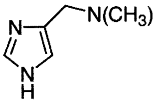
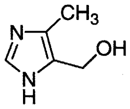
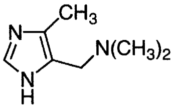
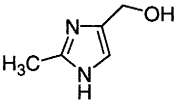
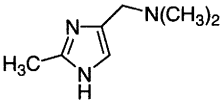
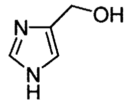
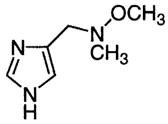
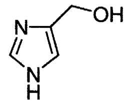
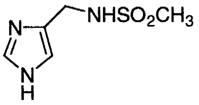
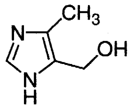
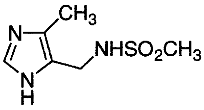
PII: S0040-4039(00)00262-8

Table 1
Synthesis of functionalized imidazoles

Entry	**Imidazole**	**Nucleophile**	**Product**	**Yield (%)**
A				**96**
B				**37**
C				**61**
D		$-NH(CH_3)_2$		**99**
E		$-NH(CH_3)_2$		**95**
F		$-NH(CH_3)_2$		**81**
G		CH_3ONH_2		**100**
H		$CH_3SO_2NH_2$		**79**
I		$CH_3SO_2NH_2$		**93**

basic conditions, we sought to establish the equilibrium such that a nucleophile present in the reaction would have an opportunity to capture the vinylogous iminium intermediate (**2**, Scheme 1). Using basic aqueous conditions (1 M K_2CO_3 or Na_2CO_3), we were able to directly displace the hydroxy group in hydroxymethylimidazoles with a variety of nitrogen nucleophiles forming functionalized imidazoles (**3**) in moderate to excellent yields (Table 1).

Table 1 summarizes the results of our methodological study. In a typical experiment,[4] the hydroxymethylimidazole hydrochloride (1 equiv.) is heated at reflux in an aqueous solution of K_2CO_3 (3 equiv.) along with the desired nucleophile (excess, typically 2 equiv.). Nucleophiles included amines (entries A–F), methoxylamine (entry G), and sulfonamides (entries H and I). Only water has been used as the reaction solvent, and for the cases studied, no other solvents were needed. Extremely volatile nucleophiles (i.e. dimethylamine) require the reaction to be run in a sealed tube, but generally no other special requirements are needed. Within 24 hours, the reaction is typically complete. Purification depends on the nature of the nucleophile. With most amines, the reaction could be simply evaporated under reduced pressure, and the desired product isolated via washing the solid residue with ethyl acetate; evaporation of the ethyl acetate afforded the desired aminomethylimidazole. Both 4- and 5-hydroxymethyimidazoles can participate in this reaction.

We have not attempted the reaction with a 2-hydroxymethyimidazole as yet. It should also be noted that no attempt has been made to optimize the conditions of the individual reactions. Furthermore, only nitrogen nucleophiles have been tested thus far in this method. We are presently exploring the activity of other nucleophiles (oxygen, sulfur and carbon nucleophiles), and will report those results upon their completion.

In summary, we have demonstrated an expedient synthesis of functionalized imidazole derivatives arising from the direct nucleophilic displacement of hydroxide from hydroxymethylimidazoles. We are presently studying the full scope of this powerful but simple transformation.

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4. A typical procedure was as follows: a solution of the hydroxymethylimidazole (10 mmol), amine (25 mmol, 2.5 equiv.), potassium or sodium carbonate (30 mmol, 3 equiv.) and water (20 mL) was heated at reflux under nitrogen for 24 h. Water was removed from the reaction via evaporation under reduced pressure, and the residue was vigorously stirred in ethyl acetate (50 mL). The ethyl acetate was removed and evaporated under reduced pressure to afford the desired aminomethylimidazole. Alternatively, the aqueous reaction solution could be extracted with 5% methanol in ethyl acetate (3×50 mL), the extracts combined, dried (Na_2SO_4) and evaporated under reduced pressure to afford the desired aminomethylimidazole. The sulfonamides were further purified by passing an aqueous solution of the sulfonamide through a column of acidic ion exchange resin (Bio-Rad AG 50W-X2, 35 g). The resin was then washed with water (2×200 mL, discarded), methanol (2×200 mL, discarded), and the product was obtained by releasing the imidazole from the acidic resin with methanolic ammonia (200 mL, 3.5 N). This solution was then evaporated under reduced pressure to afford the desired sulfonamide.