Tetrahedron Letters, Vol. 34, No. 4, pp. 595-598, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Novel Synthesis of N-Unsubstituted Imidazoles Using N-Trimethylsilylimines

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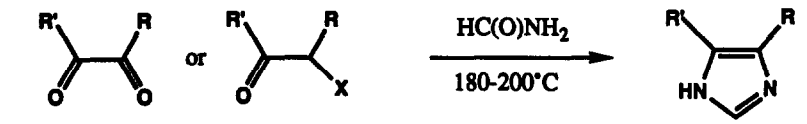
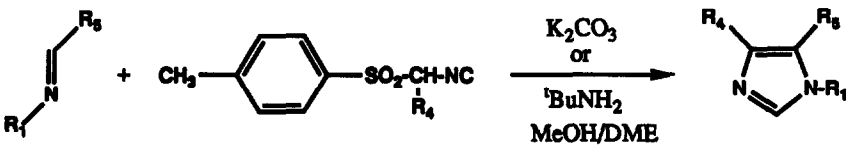
Summary: Cycloaddition of N-trimethylsilylimines **3** with the lithiotosylmethylisocyanates **4** is described. This provides a novel synthesis of 4-substituted and 4,5-disubstituted imidazoles from easily accessible aldehydes or organolithium reagents, under mild conditions and in a one-pot operation.

Imidazoles play an important role in many biologically interesting processes and many useful therapeutic agents contain the imidazole moiety. During the course of our investigation of agonists and antagonists of the histamine-H3 receptor, we required a mild and efficient synthesis of 4-substituted and 4,5-disubstituted imidazoles. The well known Brederick reaction,[1] while providing imidazoles in many cases, is conducted under harsh reaction conditions [eq. 1], and therefore, is not generally applicable to functionally complex molecules. In 1977, van Leusen, et al.[2] reported a mild synthesis of 1,5-disubstituted and 1,4,5-trisubstituted imidazoles via the cycloaddition of aldimines **1** with tosylmethylisocyanates **2** [eq. 2]. In an attempt to extend this methodology to the synthesis of imidazoles in which the N-1 and N-3 nitrogens of the imidazole ring are free of substitution, we investigated the cycloaddition of tosylmethylisocyanates **2** with N-trimethylsilylimines **3**. Herein we report the preliminary results of this study, which provides a novel synthesis of 4-monosubstituted and 4,5-disubstituted imidazoles in a one-pot operation.



(X= halogens, OH, OAc, NH_2 etc.)

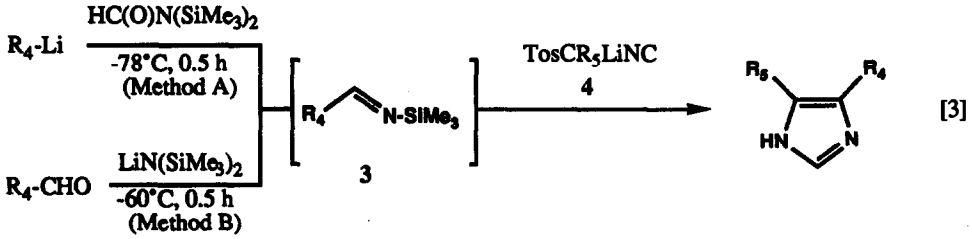
[1]



1 **2**

(R_1= alkyl)

[2]



[3]

The N-trimethylsilylimines **3**, which have been employed in β-lactam and primary amine syntheses,[3] can be generated by two methods (eq. 3): reaction of an organolithium with N,N-bis(trimethylsilyl)-formamide[4] (Method A), or reaction of an aldehyde with lithium bis(trimethylsilyl)amide (Method B). Without isolation the silylimine **3** can then be trapped by the anion of tosylmethylisocyanate (**4**, $R_5 = H$) or of a substituted tosylmethylisocyanate[5] (**4**, $R_5 \neq H$) to form the 4-substituted imidazole ($R_5 = H$) or the 4,5-disubstituted imidazole ($R_5 \neq H$), respectively. Application of the above protocols provided the N-unsubstituted imidazoles[6] in Table. Athough the yields of this one-pot imidazole synthesis are moderate, two points deserve comment. In Method A, it may be possible to replace the organolithiums by the corresponding Grignard reagents. In Method B, both enolizable as well as nonenolizable aldehydes (see entries 2 and 5) can be employed in this imidazole synthesis. In summary, we have demonstrated that both the 4-substituted and 4,5-disubstituted imidazoles can be synthesized from the easily accessible aldehydes or organolithium reagents, under mild conditions (-78°C to r.t.) in a one-pot operation.

Table. Preparation of 4-substituted and 4,5-disubstituted imidazoles from organolithiums or aldehydes

entry	starting material	R4	R5	method	yield, %[a]
1	CH_3Li	CH_3	H	A	55
2	CH_3CHO	CH_3	H	B	25
3	n-C_4H_9Li	n-C_4H_9	H	A	51
4	C_6H_5Li	C_6H_5	H	A	23
5	C_6H_5CHO	C_6H_5	H	B	24
6	n-C_4H_9Li	n-C_4H_9	CH_3	A	51
7	n-C_4H_9Li	n-C_4H_9	$C_6H_5CH_2$	A	66

a. isolated yield; reaction conditions are not optimized.

Typical reaction procedures for both Method A (organolithium and N,N-bistrimethylsilylformamide) and Method B (aldehyde and lithium bis(trimethylsilyl)amide) are described below.

Method A (Preparation of 5-benzyl-4-butylimidazole). To a cold (-78°C) solution of N,N-bis(trimethylsilyl)formamide (1.63 mL, 7.5 mmol) in anhydrous tetrahydrofuran (10 mL) was added slowly a solution of n-butyllithium in hexane (4.7 mL, 1.6 N, 7.5 mmol). The mixture was stirred at -78°C for 30 min and then a solution of the anion of tosylbenzylmethylisocyanate [prepared by the addition of a solution of lithium bis(trimethylsilyl)amide (7.15 mL, 1.0 N, 7.16 mmol) to a cold (-55°C) solution of tosylbenzylmethyl-isocyanate (2.035 g, 7.16 mmol) in anhydrous tetrahydrofuran (5 mL) followed by stirring for 30 min at -50 to -60° C] was transferred via cannula. The resultant solution was stirred for 30 min at -78°C, allowed to warm to 0°C (2 h) and then stirred at room temperature for 16 h. The reaction mixture was concentrated, the residue was diluted with 30 mL of distilled water, and the solution was adjusted to pH = 10 ~ 11 by the addition of 1N HCl. Sodium chloride was added to saturate the aqueous solution and this solution was extracted with ethyl acetate/methylene chloride (4 : 1). The combined organic extracts were dried over anhydrous sodium sulfate and potassium carbonate, concentrated, and purified by flash chromatography on silica gel to give 5-benzyl-4-butylimidazole[5] (1.01 g, 66%).

Method B (General procedure). To a solution of an aldehyde (1.5 mmol) in anhydrous tetrahydrofuran (2 mL) at -60°C was added dropwise a solution of lithium bis(trimethylsilyl)amide (1.5 mmol). The resulting solution was warmed to -30°C (20 min), and then a solution of the anion of tosylmethylisocyanate (1.4 mmol) was added (prepared as described in Method A). The resultant solution was stirred for 30 min at -78°C, allowed to warm to 0°C (2 h), and then stirred at room temperature for 16 h. The reaction mixture was then worked-up as described in Method A.

Acknowledgements. The author thanks Mr. Steven Orlando for the preparation of mono-substituted tosylmethyl isocyanates, and is very grateful to Drs. Andrew T. Lupo, Jr., John Piwinski, and Michael J. Green for their helpful discussions.

References and Notes

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(6) All compounds reported herein gave ^{1}H NMR, IR, and MS or combustion analytical data consistent with the assigned structures.

(Received in USA 28 September 1992; accepted 27 October 1992)