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Ti(III)-MEDIATED REDUCTIONS OF N-HYDROXY IMIDAZOLES TO 1-PROTIO-2,4(5)-DISUBSTITUTED DERIVATIVES

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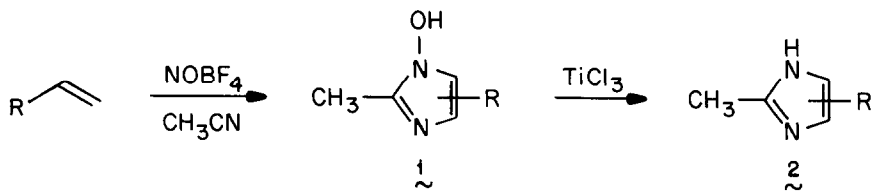
SUMMARY: *N-Hydroxy imidazoles are converted via $TiCl_3$ in $MeOH/H_2O$ to N-protio derivatives, useful precursors of chiral amino acids.*

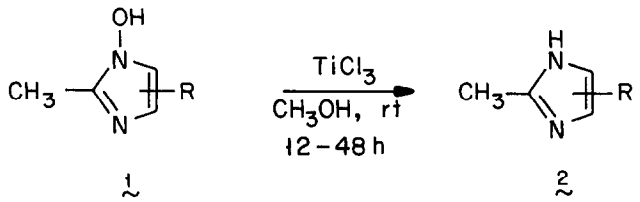
The unique role which appropriately functionalized imidazoles play as 'azabutadienes' in reactions with singlet molecular oxygen has led to their conversion to amino acid derivatives in optically active form.[1] This novel method, which equates an apparently simple heterocycle with either naturally occurring or synthetic amino acids, requires a 1,2,4-trisubstitution pattern on the ring. Although improvements on the well-established Weidenhagen route to 2,4(5)-disubstituted materials have been made,[2] we took note of a rather sketchy communication which surfaced over a decade ago describing the preparation of di- and trisubstituted imidazoles using commercially available nitrosonium tetrafluoroborate ($NOBF_4$) in nitrile media.[3] This protocol is especially attractive as it relies on olefin precursors and involves only two operations. Unfortunately, in our hands, while the N-hydroxy imidazoles mentioned in this report were easily realized, their reduction to the necessary 1-protio species failed completely under literature 'conditions' (Red-Al, rt), as well as upon examination of numerous other reagents and conditions.[4] Based on the



1 2

successful reduction of other N-hydroxy-containing compounds (e.g., pyrimidines,[5] oximes,[6] and hydroxamic acids[7]) with $TiCl_3$, it was hoped that imidazoles 1 would follow suit. Much

Table I. Reductions of 1 to 2 via Ti(III) Chloride



1 2

R	Yield (%)
$PhCH_2$	83
t-Bu	94
$(CH_3)_2CHCH_2$	87
n-C_4H_9	94
n-C_5H_{11}	92

to our delight, when a methanolic solution of 1 (ca. 0.2 M) was treated with $TiCl_3$ (2 equiv, 20% in H_2O) at room temperature, TLC analysis indicated complete consumption of starting material. Subsequent quenching with saturated aqueous $NaHCO_3$ and extractive workup (CH_2Cl_2) afforded the desired products (83 - 94 %, isolated) after filtration through SiO_2 (10% EtOH/$CHCl_3$). Typical substrates are illustrated in Table I and demonstrate the generality of the method. In light of this highly efficient conversion of 1 to 2,4(5)-disubstituted imidazoles, a straightforward two-step route to amino acid and dipeptide precursors [1,2] is now in hand.

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References and Notes

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