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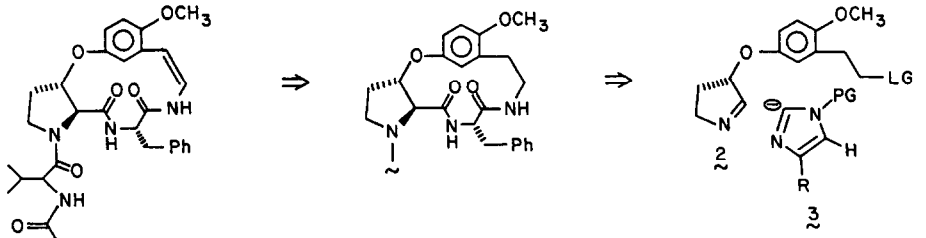
PROTECTION OF IMIDAZOLES AS THEIR β-TRIMETHYLSILYLETHOXYMETHYL (SEM) DERIVATIVES‡

Bruce H. Lipshutz*,[1] Wayne Vaccaro, and Bret Huff
Department of Chemistry, University of California
Santa Barbara, CA 93106

Summary: Monocyclic 4(5)-substituted imidazoles react with SEM-Cl to afford the corresponding N-SEM derivatives. These aminals readily metalate at C-2 with n-BuLi in THF at -78°C and react with various electrophiles. Deprotection may be achieved with either n-Bu_4NF or aqueous HCl.

As part of our program on cyclopeptide alkaloid total synthesis (e.g., 1) which utilizes heteroaromatic systems[2] as masked peptide equivalents, specifically including imidazoles[3] and oxazoles,[4] we required a protecting group (PG) for a monosubstituted imidazole which would fulfill several criteria. Aside from the obvious "on" and "off" steps, such a moiety was required to not only stand up to strong base, but direct metalation to the C-2 location (as in 3).[5] Since subsequent condensation was envisioned, in particular with a chiral α-alkoxyimine (e.g., 2), the group PG should be devoid of stereocenters as well. We now report that the β-trimethylsilylethoxymethyl (SEM) group[6] may be used, in fact, as a general solution for protection of an imidazole N-H.[7]

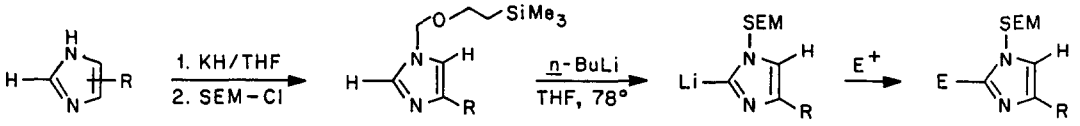


1, Amphibin-H

[Scheme 1]

‡Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

Although a number of imidazole protecting groups have been reported, including e.g., TMS,[8a] $EtOCH_2$,[8b] trityl,[8c] $CH(OEt)_2$,[8d] and SO_2NMe_2,[8e] those that direct lithiation at the 2-position usually require forcing conditions for deprotections. Since Chadwick[8e] has shown that MOM-derivatized imidazoles metalate readily, the fluoride lability of the SEM residue, as reported originally from our labs in 1980,[6] seemed like an obvious choice.[9] Treatment of a 4(5)-substituted imidazole 4, prepared in good yields (67 - 73%) in the classical manner[10] (from an α-haloketone and NaOCHO in DMF, rt, followed by formamide) with 1.2 equiv NaH or $Et_2N(i\text{-}Pr)$/cat. DMAP in DMF afforded the desired SEM-imidazoles. Unfortunately, their water solubility, together with the need for DMF as solvent, made isolation difficult and significantly lowered yields. Switching to NaH or KH in THF removed this obstacle and provided a very straightforward means of arriving at compounds 5 (70 - 75% after Kugelrohr distillation). The regiochemistry of the alkylation was apparent from the NMR data for 5,



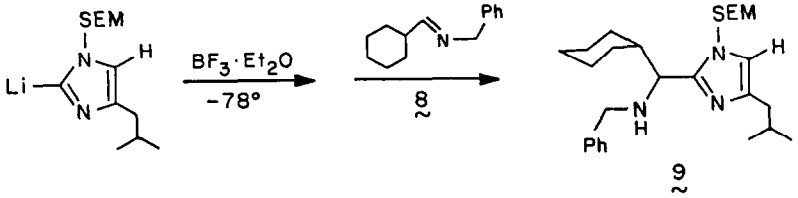
4 5 6 7

which show large differences in chemical shifts between the C-4 and C-5 protons in the 1,5- and 1,4-disubstituted isomers, respectively.[11]

Metalation of imidazoles 5 proceeds rapidly (<30 min) and quantitatively at -78°. An extensive study on the subsequent reactions of 6 with numerous electrophiles (E^+) was conducted which lead to some surprising observations (Table I). Introduction of aldehydes at -78° effectively and quickly "quenched" these intermediates to afford the expected alcohols (entries 2, 10, 13, 14). Aryl, heteroaromatic, and aliphatic aldehydes work equally well. Ketones (e.g., entry 3) give good yields as well, although starting SEM-imidazole was always isolated suggesting competitive enolization, not found where possible with aldehydes. Formylation, employing DMF as electrophile, proceeds quite efficiently (entry 6).

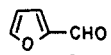
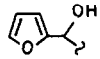
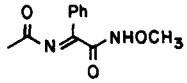
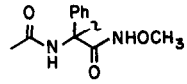
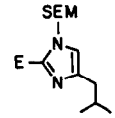
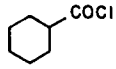
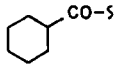
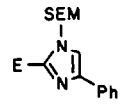
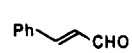
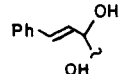
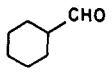
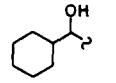
The big surprise came upon treatment of 6 with numerous alkylating and acylating agents. While MeI reacted in all cases, any other alkyl, as well as acid halide or anhydride including activated examples lead to essentially none ($PhCH_2Cl$, i-PrI) or little (entries 8, 9) of the desired products. Attempts to increase the reactivity of the imidazole by addition of HMPA, DMPU, 12-crown-4, TMEDA, $CuBr \cdot Me_2S$ (10 mol%) or CuCN (0.5 equiv) did not improve the situation. Surprisingly, PhS-SPh reacted smoothly at -78°C to give the sulfenylated imidazole in 95% yield (entry 12).

As a means of foreshadowing the specific applications of this chemistry to the target structures of interest (i.e., Scheme 1), an aldimine was added to 6 (1.2 equiv) at -78°.



9

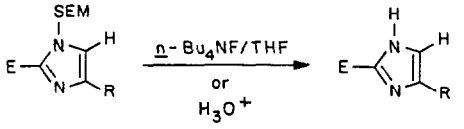
Table I. Preparation, C-2 Functionalization, and Deprotection of SEM-Imidazoles

Entry	Imidazole	Protection(%)[a] (4 → 5)	Electrophile	Product(%) (5 → 6 → 7)		Deprotection(%)[a] (7 → 10)
		71				
1			MeI	E = Me	(94)	
2					(82)	76[b,c]
3					(72)	
4						46[c,d]
		72				
5			MeI	E = Me	(64)	
6			DMF	CHO	(85)	86[e], 90[c]
7					(42)	
8			Ac_2O	CH_3CO	(40)	100[e], 52[c]
9			CH_3COCl		(20)	
10			PhCHO	PhCH(OH)	(99)	
		73				
11			D_2O	E = D	(100)	
12			Ph_2S_2	SPh	(95)	86[f]
13					(100)	
14					(86)	68[c]

[a] All yields refer to isolated, chromatographically pure materials. Satisfactory IR, NMR, MS, and HRMS data were obtained for all compounds. [b] Reaction was performed on the derived methyl ether. [c] n-Bu_4N-F in refluxing THF was used. [d] Overall yield for 2 steps. [e] 3N HCl in refluxing EtOH was used. [f] 3N HCl/EtOH, at 60°C.

Warming produced only minor amounts of the derived secondary amine. Prior exposure of 8, however, to 2 equiv $BF_3 \cdot Et_2O$ at -78° followed by cannula addition of the imine/Lewis acid solution to 6 at -78° led to the anticipated amine 9 in 87% isolated yield.

The deprotection step to 10 could be carried out using either 2-5 equiv of n-Bu_4NF, ca. 1 M in THF between 45° and reflux temperatures, or with 3N HCl in EtOH at 60-90°C.[12]



7 10

In summary, the SEM group has been shown to be an effective, general means of blocking the NH portion of an imidazole. SEM-imidazole derivatives can be easily metalated at low temperatures, and react rapidly with aldehydes, ketones, imines and selected alkylating agents. Unmasking takes place under the influence of either warm fluoride ion or aqueous acid.

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References and Notes

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12. See also, Jansson, K., Frejd, T., Kihlberg, J., Magnusson, G., Tetrahedron Lettters, 1986 27, 753.

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