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METALATIONS OF IMIDAZOLES. (POLY)FUNCTIONALIZATION AND CONVERSIONS TO IMIDAZOLONES

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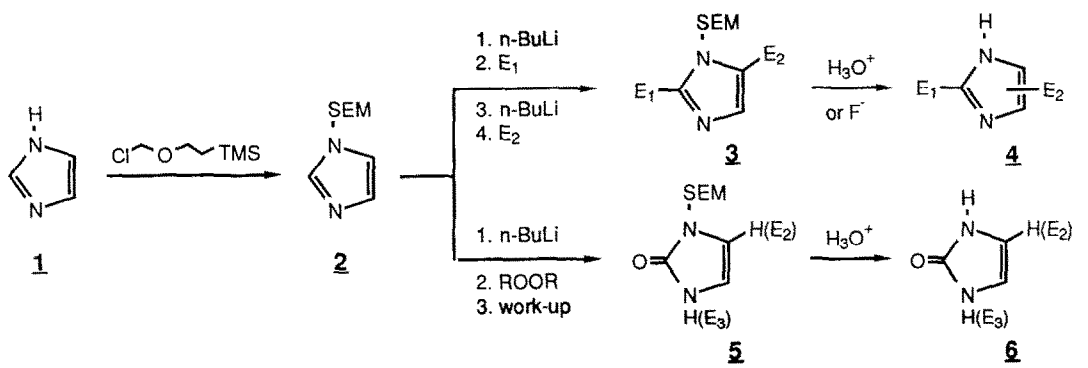
Summary: N-SEM protected imidazoles can be sequentially derivatized at the 2- and then 5-positions in a 1-pot operation. Quenching with selected peroxides following initial lithiation leads directly to imidazolones.

In the course of developing imidazoles as masked diamide/dipeptide equivalents,[2] we became interested in developing a streamlined route to 2,4(5)-disubstituted systems 4 via 3. The most direct approach is one in which both positions could be sequentially metalated and derivatized, preferably in a single pot. Moreover, by the judicious choice of a source of "O^+", direct conversion of imidazoles 2 to (substituted) imidazolones 6 via 5 which are well known to possess varied biological activity profiles,[3] should also be realizable. We now report that both of these objectives can be accomplished efficiently and with complete regiochemical control.

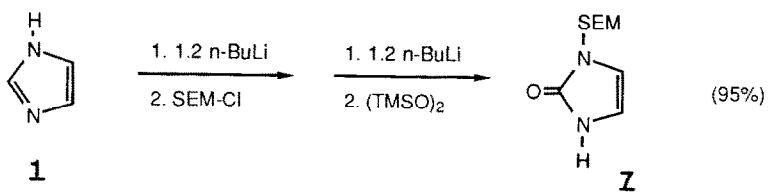


The choice of the SEM group for initial protection was predicated on earlier studies which suggested its removal could be promoted by fluoride ion or under conditions of mild alcoholic acid in good yields.[4] Chadwick's alternative, the N,N-dimethylsulfonamide derivative, which nicely permits sequential 2,5-lithiation/functionalization, requires aqueous H_2SO_4 or KOH over extended periods to effect deprotection.[5] While the MEM analog afforded similar results in terms of derivatization, deblocking under acidic conditions was considerably more difficult to achieve, in line with prior observations.[6] The recently reported use of the 1-(1-ethoxyethyl) moiety, while cleavable under milder conditions, introduces a new chiral center which can lead to product mixtures with aldehydes or unsymmetrical ketones as electrophilic partners.[7]

Formation of 2 from sublimed imidazole is best carried out using the preformed sodium salt in THF, followed by introduction of SEM-Cl (1.05 equiv., 0°C→rt, 1 h). Kugelrohr distillation (bp 115-118°, 0.15 mm Hg) affords pure material in usually >95% yield. While lithiation at C-2 with n-BuLi is straightforward, as is subsequent trapping with an electrophile, the whole process can be effected in one reaction vessel from imidazole. Thus, treatment of 1 with n-BuLi at -78° and then with SEM-Cl at room temperature generates 2, which is recooled to -78° and exposed to another equivalent of n-BuLi followed by electrophilic quenching. Alternatively, 2 may be sequentially converted to 3 by simple repetition of the lithiation/trapping protocol. Results are summarized in Table I.

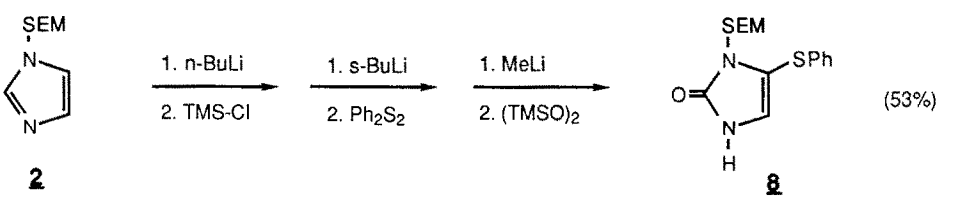
To obtain solely substitution at the 5-position, initial trapping with TMS-Cl allowed, e.g., sulfenylation (entry 3) or 5-formylation (entry 4) to occur with concommitant loss of the 2-Me_3Si moiety upon workup.

Oxidation of imidazoles to imidazolones[8] can also be accomplished using these procedures. From imidazole itself, N-SEM derivative 7 has been formed in 95% isolated yield in a 1-pot operation using $(TMSO)_2$[9] as electrophile. Peroxide $(PhCO_2)_2$[10] is also a known source of electrophilic oxygen which likewise leads to 7 in excellent yield (entries 5,6). Trapping at



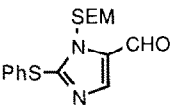
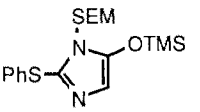
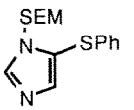
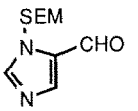
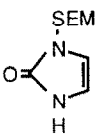
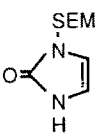
1 7

C-5 with $(TMSO)_2$ also works well (entry 2). Combining observations regarding the transient nature of 2-TMS substitution/5-functionalization with C-2 oxidation leads to a 5-substituted imidazolone. The intermediate 2-TMS-5-sulfenylated imidazole is susceptible to desilylation with MeLi thereby effecting 2-lithiation, which is then quenched to form 8.



2 8

Table I. Conversion of 2 to Substituted Imidazoles 3 and Imidazolones 5

Entry	Base[a]	E_1	Base[b]	E_2	Product[c]	Yield (%)[d]
1	n-BuLi	Ph_2S_2[e]	n-BuLi	DMF[f]		90
2	n-BuLi	Ph_2S_2[e]	n-BuLi	$(TMSO)_2$		79
3	n-BuLi	TMS-Cl[a]	s-BuLi	Ph_2S_2[e]		83
4	n-BuLi	TMS-Cl[a]	s-BuLi	DMF		83
5	n-BuLi	$(TMSO)_2$[g]	—	—		98
6	n-BuLi	$(PhCO_2)_2$[h]	—	—		91

[a] 1.2 equivalents were used in all cases.

[b] 1.3 equivalents of n-BuLi were employed.

[c] All products were fully characterized by IR, NMR, MS, and HRMS analyses.

[d] Yields refer to isolated, chromatographically pure or distilled materials.

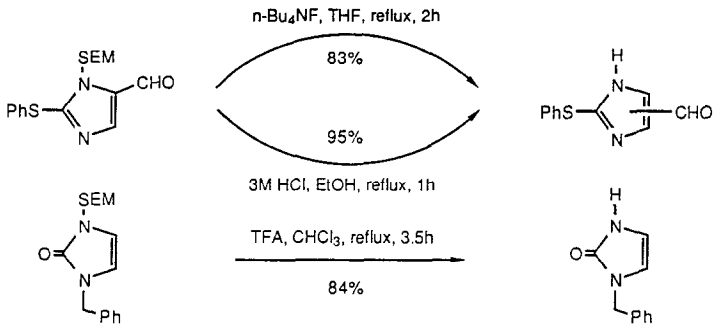
[e] 1.05 equivalents were used.

[f] An excess was used for quenching.

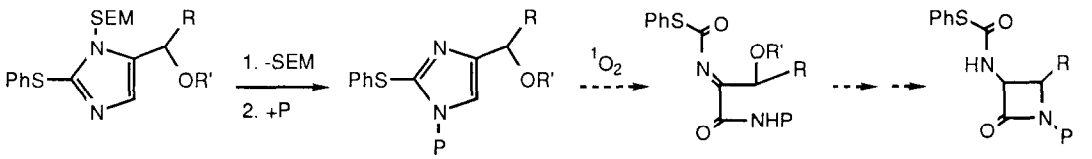
[g] 1.5 equivalents were used since $(TMSO)_2$ was less than 100% pure.

[h] 1.1 equivalents were used.

Removal of the SEM linkage from a functionalized imidazole was effected using 3M aqueous HCl in hot THF or EtOH, or with either of two fluoride sources (n-Bu_4NF or $LiBF_4$[11]), as illustrated below. SEM-protected imidazolones were best deblocked using TFA in $CHCl_3$.[12]



In conclusion, SEM-protected imidazoles, prepared *in situ* or as stable educts, provide ready access to 2- and/or 5-substituted analogs. Trapping 2-lithiated intermediates with stable peroxides leads directly to imidazolones. Deprotection of N-SEM-2,5-trisubstituted systems give 2,4(5)-dialkylated imidazoles which are known to N-alkylate to afford the 1,2,4-pattern required for singlet oxygenation to acyl imines,[13] potential precursors to β-lactams.



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