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Single-flask Polyfunctionalization of the Imidazole Ring; A Streamlined Route to the Antitumor Agent Carmethizole

Bruce H. Lipshutz* and William Hagen

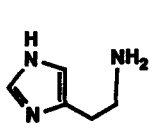
Department of Chemistry

University of California, Santa Barbara, CA 93106

[FAX: 805/893-4120]

Summary: *Three sequential treatments of an N-protected tribromoimidazole with n-BuLi / electrophile in a 1-pot process leads to N-protected 2,4,5-trisubstituted imidazoles. The method can be applied to the preparation of the immediate precursor of carmethizole.*

The chemistry of the imidazole ring occupies an extremely important niche within the family of 5-membered ring heteroaromatics.[1] And yet, in spite of its central role in numerous molecules of established bioactivities, of natural origin or otherwise (*e.g.*, histamine (1), nucleosides (2),[2] girolline (3),[3] carmethizole (4),[4] etc.), a general procedure for the rapid elaboration of the basic skeleton has not materialized as yet.



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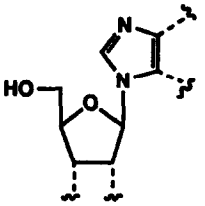

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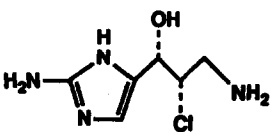

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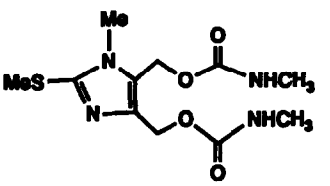
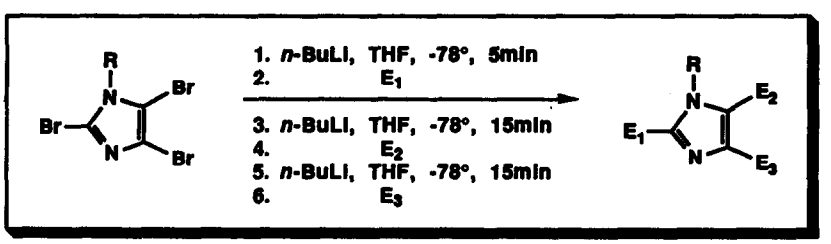


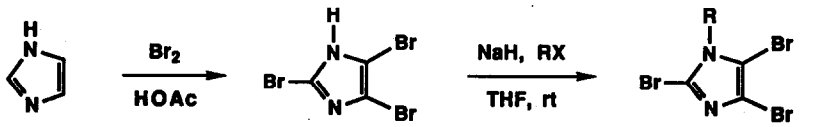
4

Conversion of an N-derivatized tribromide[5] and iodide[6] to the corresponding metallated intermediates has been documented, most extensively by Iddon,[7] as well as by several other groups.[8] However, we are aware of only a single report describing the replacement of all three halogens with three identical electrophiles in a single pot operation.[9] Based on our interest in the manipulation of appropriately substituted systems as β-lactam precursors,[10] we set out to develop a protocol for the polyfunctionalization of simple imidazoles. We now report on such a method, along with its use as an entry to the diol precursor associated with the potent antineoplastic agent carmethizole.[4]



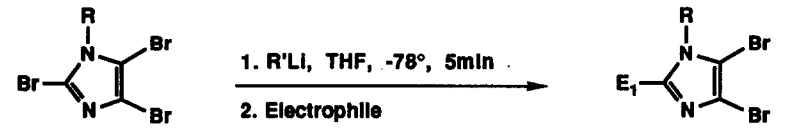
(Eq. 1)

The starting tribromide **5** is available in quantity *via* polybromination of imidazole[11] followed by straightforward N-alkylation (Eq. 2). Metal-halogen exchange using *n*-BuLi was initially shown to occur, as



5 **[R = Bn, SEM, CH_3]** (Eq. 2)

expected,[12] at the 2-position with a variety of trapping agents (Eq. 3). Double replacement at the 2- and 5-positions, likewise, was not problematic, with isolated yields for these 2-substituted and 2,5-disubstituted

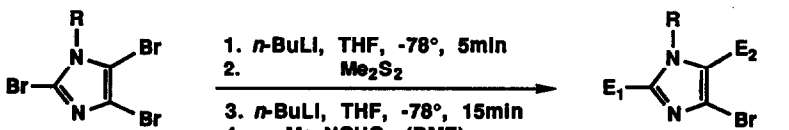


R = Me; R' = *n*-Bu
R = Bn; R' = Ph

E_1 = MeS (93%)
E_1 = PhS (97%)

(Eq. 3)

imidazoles obtained routinely in the 85-97% range (*e.g.*, Eq. 4). Extension of the double lithiation-electrophile quench to the remaining C-4 bromide afforded overall yields on the order of 51-71% for the



R = Me

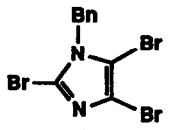
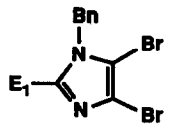
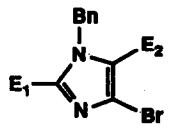
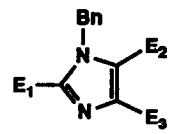
E_1 = MeS
E_2 = CHO **(85%)**

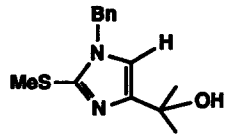
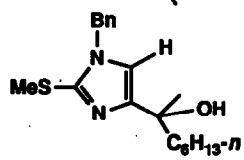
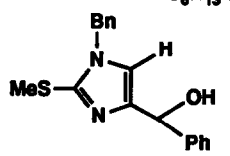
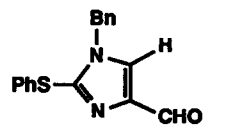
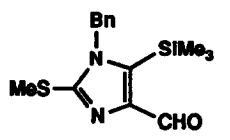
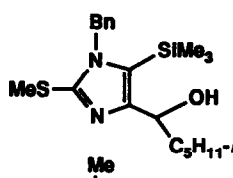
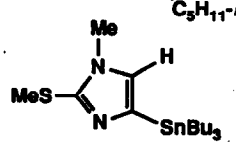
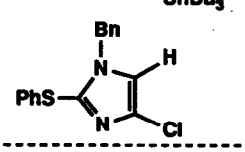
(Eq. 4)

1-pot, 6-step sequence. The final lithium-bromine exchange was noticeably less facile than those at the C-2 and C-5 sites. Numerous attempts to improve the rate and overall efficiency using, *e.g.*, *s*-BuLi, *t*-BuLi, *n*-BuNa, etc. were not fruitful. Several examples of the resulting triply derivatized materials are illustrated in Table 1, concerning which the following salient features deserve mention: (1) Using *i*-PrOH (1 eq) as E_2 (*cf.* Eq. 1) allows for generation of the 1,2,4-trisubstitution pattern which has been found receptive toward [4+2] singlet oxygenation *en route* to nonracemic peptides.[13] When used together with a C-4 DMF quench/$NaBH_4$ reduction, suitable materials result for eventual β-lactam construction;[10] (2) Anionic trapping is not limited to disulfides and aldehydes; introduction of three distinct electrophiles, including these as well as ketones, protons, and trialkylsilanes, halides and stannanes can be achieved.

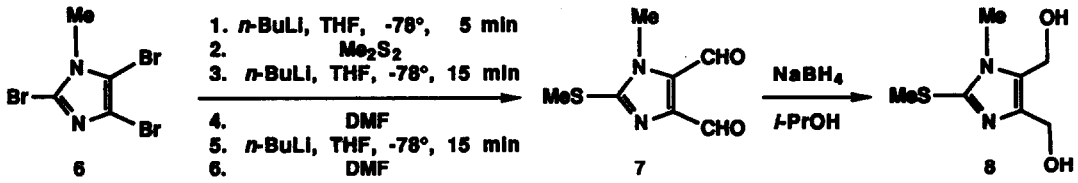
Lastly, the ability to control the sequence for insertion of electrophiles onto the ring has allowed us to prepare the key N-methyl-2-thiomethyl-4,5-dihydroxymethylimidazole precursor **8** to its *bis*-carbamate derivative, carmethizole (4).[4] Starting with N-methyltribromoimidazole **6**, initial installation of the MeS-moiety at C-2, followed by formylation at C-5 and then at C-4 led to dialdehyde **7** (51%). Double reduction with $NaBH_4$ afforded target diol **8** (91%). This path to **8** compares quite favorably (overall yield from **6** to **8** is 45%) with literature procedures which proceed *via* a thioimidazolone intermediate.[4] Given the (postulated) critical role played by the sulfide residue in **4**,[4] our carbanion approach should permit (using various disulfides) realization of several analogs not readily prepared *via* sulfur alkylation chemistry (*e.g.*, the thiophenyl case).

Table 1. 1-Pot generation of N-protected-2,4,5-trisubstituted imidazoles

Entry	E1	E2	E3	Final Product[a] (%)[b]
1	Me_2S_2	*i*-PrOH	acetone	 (71)
2	Me_2S_2	*i*-PrOH	$C_6H_{13}CHO$	 (66)
3	Me_2S_2	*i*-PrOH	PhCHO	 (55)
4	Ph_2S_2	*i*-PrOH	DMF	 (64)
5	Me_2S_2	Me_3SiCl	DMF	 (59)
6	Me_2S_2	Me_3SiCl	$C_5H_{11}CHO$	 (61)
7	Me_2S_2	*i*-PrOH	Bu_3SnCl	 (40)[c]
8	Ph_2S_2	*i*-PrOH	$Cl_3C\text{-}CCl_3$	 (44)

[a]Fully characterized by IR, NMR, MS, & HRMS data. [b]Isolated. [c]By quantitative NMR.



In conclusion, using a readily available trihaloimidazole, a single flask multiple metalation/anion trapping protocol has been developed which leads to an imidazole ring containing a variety of substitution patterns (*e.g.*, Table 1, entry 1; see typical procedure).[14] Further applications of this chemistry *en route* to girolline and monocyclic β-lactams of interest will be reported in due course.

Acknowledgement. Financial support provided by the Committee on Research, UCSB, is gratefully acknowledged.

References and Notes

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14. N-Benzyl-2,4,5-tribromoimidazole (200mg, 0.51 mmmol), was dried azeotropically with toluene, dissolved in 5 mL of THF, cooled to -78°, and *n*-BuLi (2.45M, 0.21 mL, 0.51 mmol), was added *via* syringe and the solution stirred 5 minutes at -78°. Dimethyldisulfide (45.6 μL, 0.51 mmol), was then added and stirred 5 minutes at -78°. The second aliquot of *n*-BuLi (2.45M, 0.21 mL, 0.51 mmol), was then added and stirred 15 minutes at -78° prior to the introduction of 2-propanol (38.8 μL, 0.51 mmol). After another 5 minutes at -78°, the third aliquot of *n*-BuLi (2.45M, 0.21 mL, 0.51 mmol), was added and following another 15 minute period at -78°, acetone (37.2 μL, 0.51 mmol), was added and stirred for 15 minutes at -78°. The solution was then poured into 30mL of water saturated with NH_4Cl, extracted with 3x30mL of ethyl acetate and dried over Na_2SO_4. The solvent was removed *in vacuo* to give 0.1687g of an orange oil. The residue was purified by flash chromatography (silica gel, 8:2 hexane/ethyl acetate), to give 0.0948g (71%), of a clear oil; ^1H NMR (500 MHz $CDCl_3$) 1.50 (s, 6 H), 2.50 (s, 3 H), 2.92 (br s, 1 H), 5.05 (s, 2 H), 6.72 (s, 1 H), 7.20-7.33 (m, 5 H); IR (neat) cm^{-1}: 3400 2975 2925 1740 1670 1560 1540 1495 1450 1420 1355 1210 1165 950 850 725 690 660; MS (EI) m/e (rel int): 244 (32.9), 229 (3.3), 153 (16.6), 91 (100), 65 (13.5); HREIMS: calcd for $C_{14}H_{16}N_2S$-H_2O 244.1034, found 244.1022.

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