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1-[2'-(Trimethylsilyl)ethoxymethyl]-2-phenylsulfonylimidazole: A New Reagent for the Preparation of C-4 Substituted Imidazoles

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Abstract: The title compound provides for the efficient C-4 metallation of the imidazole nucleus. Further reactions lead to trisubstituted imidazoles which can be selectively deprotected at the N_1 and C_2 positions under mild conditions to maximize the potential for further elaboration.
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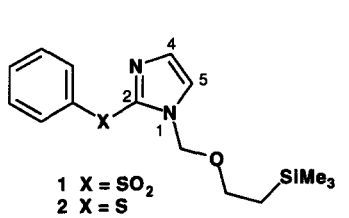
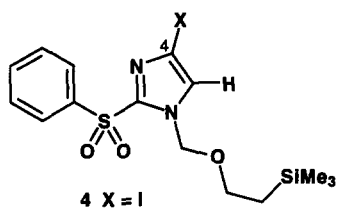
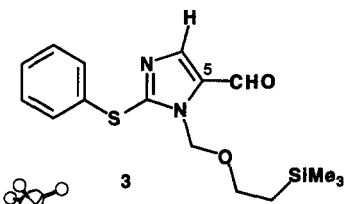
The incorporation of the imidazole nucleus is an important strategy in medicinal chemistry. Techniques which efficiently permit the direct attachment of the intact heterocycle have been the focus of recent investigations.[1] Nevertheless, there is a clear need for advances in methodology toward a general solution particularly for preparation of substituted derivatives.[2] As a part of our program directed towards the design and synthesis of novel H_3 histamine receptor agonists and antagonists, the chemistry of 1-[2'-(trimethylsilyl)ethoxymethyl]-2-phenylsulfonylimidazole (**1**), has been explored. Herein we communicate the selective C-4 metallation of the imidazole ring and the general utility of this approach for imidazole synthesis.







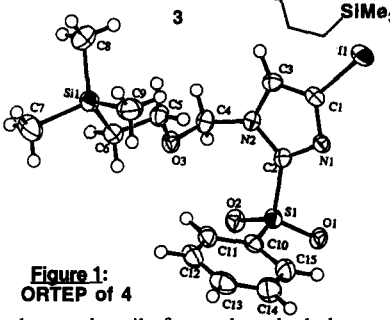
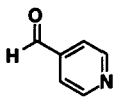
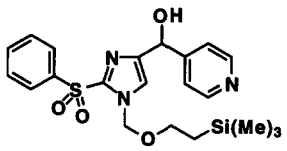
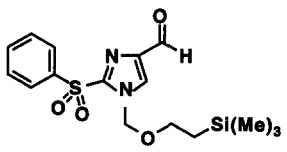
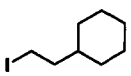
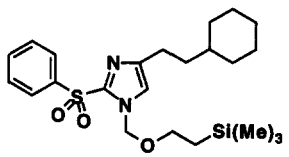
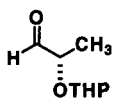
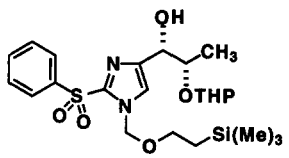
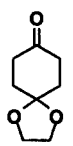
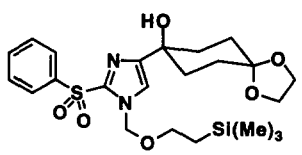
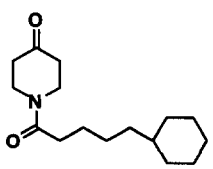
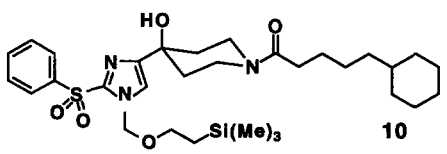


Figure 1: ORTEP of 4

Efforts to prepare C-4 substituted imidazoles have been primarily focused on the halogen-metal exchange reactions of 4 (or 5)-haloimidazoles. These approaches are not without complications and limitations.[1,3] Direct deprotonation for C-4 lithiation has been reported to occur in low yields from 1-trityl-2-phenylimidazole.[4] However, the characteristic relative acidity of ring hydrogens[5] is anticipated to follow the trend: C_2-H >> C_5-H > C_4-H. When the C-2 position is blocked, directed deprotonation at C-5 has led to useful reactions, providing imidazole nucleoside analogs.[6] Lipshutz, *et al.* have reported the selective C-5 lithiation of imidazolylphenyl sulfide **2** with n-BuLi (-78 °C) affording carboxaldehyde **3**.[7] Recently Potier has described a

related C-5 deprotonation and stannylation.[8] Our studies reveal the exclusive and preparatively useful C-4 lithiation of phenylsulfone **1**. Documentation of this remarkable regioselectivity in carbanion reactions from **1** was unambiguously obtained by X-ray crystallographic analysis (Figure 1) of the C-4 iodide **4**.[9]

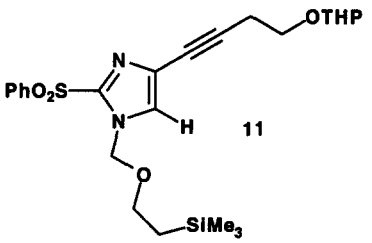
Table 1: Reactions of C-4 Carbanions of 1

Entry	Electrophile[a]	Yield[b]	Product
1		89%	 **5**
2	DMF	95%	 **6**
3		60%	 **7**
4		70%	 **8**[c]
5		75%	 **9**
6		80%	 **10**

a) Ketones (entries 5 and 6) were added at 0 °C whereas the other electrophilic agents were combined with our C-4 carbanion at -78 °C. b) Yields are based on isolated, purified product. c) Diastereoselective chelation-controlled addition gives **8** as the major product (70:30 ratio). These diastereomers are separated and individually characterized upon conversion to the diols (see compound **13**).

Oxidative preparation of 1-[2'-(trimethylsilyl)ethoxymethyl]-2-phenylsulfonylimidazole (**1**) from the known sulfide **2**[7] with MCPBA (2.1 equivs; MeOH; 22 °C) in the presence of Na_2HPO_4 buffer (5 equivs.) afforded a 90% yield. Subsequent treatment of **1** with LDA (1.1 equiv., THF) at -78 °C for one hour followed by cannulation into a solution of N-iodosuccinimide (THF at -78 °C) provided a single iodide **4** in 82% yield.[10] Similarly, the 4-lithio carbanion of **1** reacts with various electrophiles in good to excellent yields (Table 1, entries 1-4). Initial condensations of the lithium reagent with ketones gave poor yields (30-40%). However, formation of the C-4 Grignard reagent via halogen exchange of **4** with *tert*-BuMgBr[11] (1 equiv., CH_2Cl_2 at 0 °C) gave the desired tertiary alcohols **9** and **10** in good yields (entries 5 and 6).[12]

The 4-iodo-imidazole **4** is an excellent substrate for Sonogashira couplings[13] with terminal acetylenes. Catalysis with $PdCl_2(PPh_3)_2$ in the presence of CuI (excess Et_3N, CH_3CN, 70-80 °C, 3 h) afforded alkynes **11** (95%) and **12** (88%), as two representative examples of this strategy. The C-2 sulfonyl group may play an important role in delivering the high yields in our reactions as compared with the observations and results in other recent reports.[2a]



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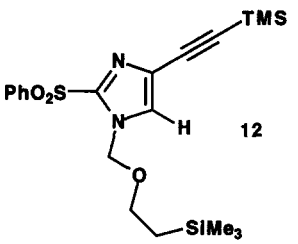
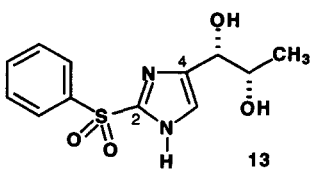
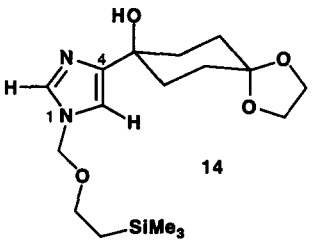


12

An important feature of the imidazole **1** is the ease and flexibility for deprotection and further elaboration. The SEM protecting group of our C-4 substituted imidazoles may be removed under mildly acidic conditions. For example, treatment of **8** with PPTs (1 equiv., MeOH, 24 h) at room temperature provided the diol **13**, as a single imidazole isomer. Stronger acids (alcoholic HCl) result in rapid N-deprotection, and basic conditions using *tetra*-n-butylammonium fluoride (TBAF) in THF (22 °C) are also very effective. Alternatively, the 2-phenylsulfonyl unit is removed in >85% yields with excess 2% Na(Hg) in dry MeOH (22 °C) in the presence of Na_2HPO_4. The SEM group is not effected, and no competing reductions of the benzylic alcohols are observed as illustrated in formation of **14**.



13



14

In summary, synthetic methodology is presented for the regioselective deprotonation and substitution of the imidazole nucleus at the 4- position. Sequential deprotections at the 1-(N) and 2- positions unmask reactive sites allowing for a flexible scheme amenable for development of a general imidazole library.

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9. Complete X-ray diffraction data for the single crystal analysis of **4** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. We gratefully thank Professor Henry Rapoport for his assistance in facilitating this diffraction study.
10. a) Our continuing studies will examine the significance of the base for deprotonation. Iodination of **1** with n-BuLi (THF, -78 °C; then NIS) gave a mixture (70:30 ratio) of the 4-iodo and 5-iodo isomers, respectively. These products were conveniently separated by flash (silica gel) chromatography and identified by their proton NMR spectra. 4-iodo imidazole **4**: ^{1}H NMR (300 MHz, $CDCl_3$): 8.0 (m, 2H), 7.60 (m, 2H), 7.54 (m, 3H), 7.23 (s, 1H), 5.66 (s, 2H), 3.45 (m, 2H), 0.83 (m, 2H), 0.05 (s, 9H). 5-iodo imidazole isomer: ^{1}H NMR (300 MHz, $CDCl_3$): 8.03 (m, 2H), 7.62 (m, 2H), 7.54 (m, 3H), 7.23 (s, 1H), 5.75 (s, 2H), ,3.52 (m, 2H), 0.80 (m, 2H), 0.05 (s, 9H). b) For related ^{1}H NMR information to distinguish C-4 and C-5 isomers: Matthews, D.P.; Whitten, J.P.; McCarthy, J.R. *J. Heterocyclic Chem.* **1987**, *24*, 689.
11. Turner, R.M.; Lindell, S.D.; Ley, S.V. *J. Org. Chem.* **1991**, 5739.
12. Proton NMR data (300 MHz, $CDCl_3$) for selected products:

    Compound **1**: δ 8.06 (m, 2H), 7.60 (m, 1H), 7.53 (m, 2H), 7.16 (d, 2H), 5.70 (s, 2H), 3.44 (m, 2H), 0.81 (m, 2H), -0.05 (s, 9H).

    Compound **5** (Table 1): δ 8.6 (d, 2H), 8.02 (m, 2H), 7.66 (m, 1H), 7.56 (m, 2H), 7.32 (d, 2H), 6.76 (s, 1H), 5.90 (br s, 1H), 5.75 (AB quartet, 2H), 4.12 (m, 1H), 3.66 (m, 2H), 0.90 (m, 2H), 0.05 (s, 9H).

    Compound **6** (Table 1): δ 9.84 (s, 1H), 8.09 (m, 2H), 7.78 (s, 1H), 7.67 (m, 1H), 7.56 (m, 2H), 6.18 (s, 2H), 3.53 (m, 2H), 0.80 (m, 2H), -0.05 (s, 9H).

    Compound **7** (Table 1): δ 8.02 (m, 2H), 7.60 (m, 1H), 7.52 (m, 2H), 6.90 (s, 1H), 5.66 (s, 2H), 3.51 (m, 2H), 2.60 (t, 2H), 1.68 (m, 6H), 1.53 (m, 2H), 1.18 (m, 4H), 0.88 (m, 1H), 0.82 (m, 2H).

    Compound **9** (Table 1): δ 8.0 (m, 2H), 7.59 (m, 1H), 7.50 (m, 2H), 7.02 (s, 1H), 5.62 (s, 2H), 3.93 (m, 4H), 3.41 (m, 2H), 2.58 (br s, 1H), 1.96 (m, 4H), 0.78 (m, 2H), 0.05 (s, 9H).

    Compound **12**: δ 8.04 (m, 2H), 7.62 (m, 1H), 7.52 (m, 2H), 7.39 (s, 1H), 5.64 (s, 1H), 3.41 (m, 2H), 0.80 (m, 2H), 0.19 (s, 9H), -0.03 (s, 9H).

    Compound **14**: δ 7.50 (d, 1H, J = 1.2 Hz), 6.88 (d, 1H, J = 1.2 Hz), 5.20 (s, 2H), 3.93 (m, 4H), 3.45 (m, 2H), 2.02 (m, 4H), 0.88 (m, 2H), 0.05 (s, 9H).
13. a) Cliff, M.; Pyne, S.G. *J. Org. Chem.* **1997**, *62*, 1023. b) Sonogashira, K. In *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 3*, p. 521.

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