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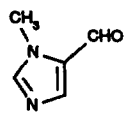
# SYNTHESIS OF 2,5-DILITHIO-1-METHYLIMIDAZOLE

Gideon Shapiro* and Martin Marzi

Preclinical Research, Sandoz Pharma Ltd., CH-4002 Basel, Switzerland

**Summary:** C5 to C2 position migrations of 2-trialkylsilyl and thiophenyl groups have been observed upon lithiation at the C5-position of corresponding C2-substituted 1-methylimidazoles. Double bromine-lithium exchange of 1-methyl-2,5-dibromoimidazole (5) affords a facile, quantitative and unequivocal synthesis of 2,5-dilithio-1-methyl-imidazole (4). Reaction of 4 with one equivalent of DMF occurs selectively at the C5 position to give 1-methylimidazole-5-carboxaldehyde (1).

In the course of our synthesis of (+)-pilosinine[1] we became interested in alternative routes for the important starting material, 1-methyl-imidazole-5-carboxaldehyde (1). Classically, 1 is prepared by a five step procedure starting from sarcosine methylester.[2] More recently the practical conversion of 5-bromo-1-methyl-imidazole (2) to 1 in two steps via Grignard reaction has been described.[3] There are however, drawbacks to both methods.[4]

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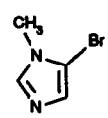


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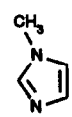


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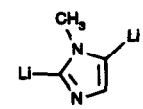
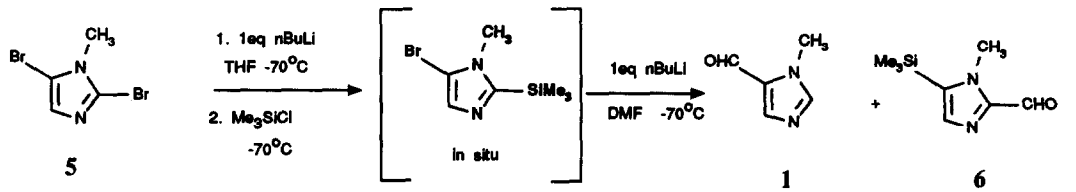



4

For a practical and economic synthesis of 1 we considered 3 an attractive starting material. Facile deprotonation of imidazoles in the 2-position with n-BuLi followed by introduction of various electrophiles is well established.[5] Furthermore, dilithiation of 3 via deprotonation with two or more equivalents of nBuLi had been reported by three groups.[6] One group in particular has reported a very detailed analysis of reaction conditions: solvent, temperature (room temperature or reflux), TMEDA additive and amount of nBuLi on the yield of 4 based on deuterium incorporation upon $D_2O$ quenching of the reaction mixture.[6b] Ether and hexane were better solvents than THF, and TMEDA enhanced the rate of double deprotonation which could be driven to near completion by the use of excess nBuLi.[6b] Unfortunately, the trapping of 4 prepared as such, requires the use of excess electrophiles,[7] has other drawbacks later called attention to[8] and was, in our hands, unsuitable even for the preparation of 1-methylimidazole-5-carboxylic acid.[7]

We decided to investigate the use of lithium-halogen exchange chemistry for the preparation of 1. An extensive lithium halogen exchange study of 1-methyl-polyhalogenated-imidazoles showing the varying reactivities of the 2, 4, and 5 positions served as our inspiration.[9] In particular it had been demonstrated that the 2-bromine of 1-methyl-2,5-dibromoimidazole (5)[10] was exchanged selectively upon treatment with nBuLi with 2 being obtained quantitatively upon aqueous quench. We conceived the following strategy for preparing 1: use

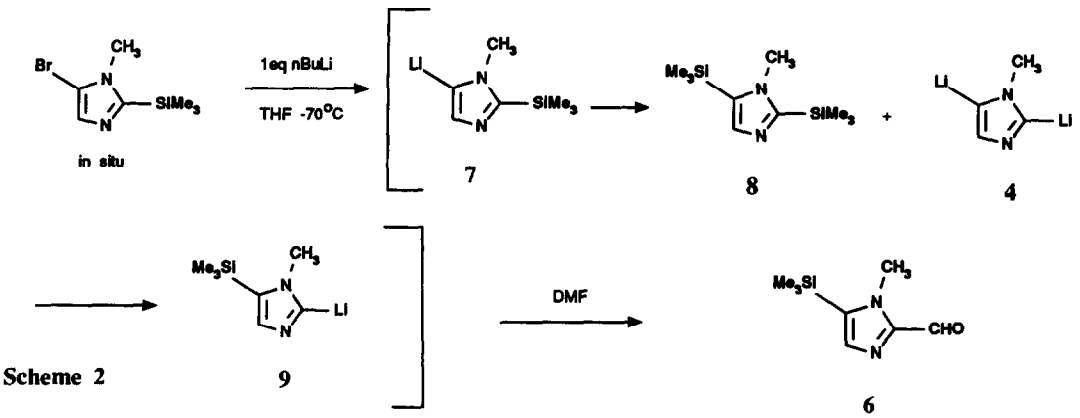
one equivalent of BuLi to perform a 2-position lithium-halogen exchange on **5**, transiently protect *in situ* with the labile[6ab] trimethylsilyl(TMS) function, use a second equivalent of BuLi to metallate the 5-position, quench with DMF and workup with removal of the TMS group. After conducting the experiment described above, a mixture of the desired **1** and 1-methyl-5-trimethylsilyl-2-formyl-imidazole (**6**) was obtained (**Scheme 1**) in ca. 40:60 ratio (50% yield after chromatography).[11] The formation of **6** can be explained as depicted in **Scheme 2**. After the second lithium-halogen exchange the intermediate 1-methyl-2-trimethylsilyl-5-lithio-imidazole (**7**) disproportionates to give disilyl species **8** and the dilithio species **4**; further disproportionation of **4** with **8** yields 1-methyl-2-lithio-5-trimethylsilyl-imidazole (**9**) which reacts with DMF to give **6**. In hindsight this




5 1 6

**Scheme 1**

rearrangement should not be so surprising since analogous 2 to 5 position proton shifts have been reported for alkali metal-halogen exchange reactions of 1-methylimidazoles conducted in THF.[5,9,12] Nevertheless, 4-unsubstituted-5-lithio imidazoles bearing a trialkylsilyl ($SiMe_3$,$SiEt_3$, $SiMe_2tBu$) or SPh group in the 2-position have been trapped successfully in THF with electrophiles in cases where a directing group is present in the 1-position ($SO_2NMe_2$, $CH_2OR$).[13] To our greater surprise we found that the more hindered t-butyldimethylsilyl group also migrates readily at -70°C to the 5-position (**Scheme 3**).[14] To study the potential

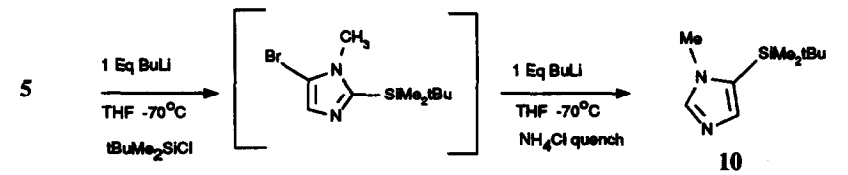



**Scheme 2**

migration of sulfur we prepared 1-methyl-2-thiophenyl-5-bromo-imidazole (**11**).[15] Upon treatment of **11** with nBuLi in THF at-70°C and warming to 0°C clean butylation at the 5-position with no rearrangement was observed.[16] We then prepared 1-methyl-2-thiophenyl-imidazole (**12**) and treated it with nBuLi in THF at 0°C. After 1.5 hours partial migration of the SPh group to the 5-position was observed (**Scheme 4**).[17]

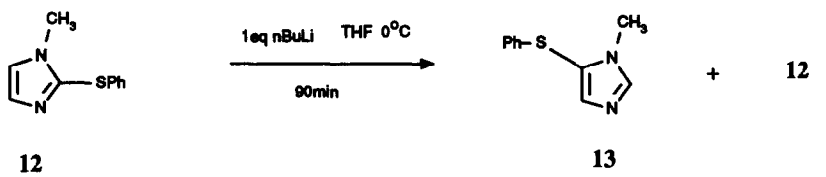
The above results indicated (**Scheme 2**) that an exchange reaction to give the intermediate dilithium

species 4 is fast even at -70°C. This being the case we reasoned that it should be possible to directly form 4 by double lithium-halogen exchange using two equivalents of nBuLi.[18] Indeed, treatment of 5 directly with two equivalents of BuLi in THF at -70°C resulted in the rapid precipitation of a colorless amorphous solid from solution.[19] The precipitate was first formed upon addition of the second equivalent of nBuLi and indicated that the true dilithioimidazole 4 is a highly insoluble species. Since it has been shown that lithium bromide dramatically enhances the solubility of enolates in THF,[20] we investigated its effect on the solubility of 4. When the double exchange was carried out in the presence of two equivalents of lithium bromide in THF at



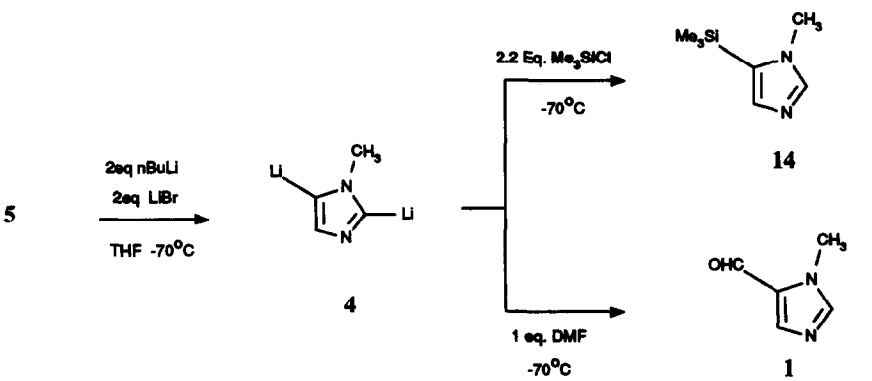

Scheme 3

-70°C, a homogeneous yellow solution of 4 was obtained. Addition of $Me_3SiCl$ (2.2 Eq.) to the reaction mixture at -70°C followed by aqueous ammonium chloride workup gave 14 in 88% yield after chromatography (Scheme 5). Furthermore, it proved possible to introduce an electrophile selectively at the 5-position of 4. Addition of 1.0 equivalents of DMF to the above solution of 4 at -70°C followed by aqueous workup -70°C and chromatography gave a 48% average yield of 1[21] with 3 being the major side product.




Scheme 4

In summary an imidazole silicon to carbon "dance reaction"[22] has been observed and a facile unequivocal preparation of the often questionably formulated 2,5-dilithio-1-methylimidazole achieved.




Scheme 5

## REFERENCES AND NOTES


1. Shapiro, G. and Chengzhi, C. *Tetrahedron Lett.* **1992**, *33*, 2447.
2. Link H. and Bernauer K. *Helv. Chim Acta* **1972**, *55*, 1053. using methyl 1-methyl-5-imidazole-carboxylate prepared via Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 644.
3. El Borai, M.; Moustafa, A. H, Anwar,M. and Ghatttas, A. G. *Croat. Chem. Acta* **1981**, *54*, 211.
4. The first preparation[2] is somewhat lengthy and expensive and the second[3] suffers from a moderate yield and the formation of multicomponent mixtures in the preparation of 2 from N-methylimidazole 3 via NBS bromination. A more selective bromination to 3 using 2,4,4,6-tetrabromocyclohexanedione has been reported: Calo, V.; Ciminale, F.; Lopez, L.; Naso, F. and Todesco, P. E. *J. Chem. Soc. Perkin Trans. I*, **1972**, 2567.
5. For a review of imidazole metallation chemistry see Iddon, B. *Heterocycles* **1985**, *23*, 417.
6. a. Jutzi, P. and Sakriss, W. *Chem. Ber.* **1973**, *106*, 2815. b. Carpenter, A. J.; Chadwick, D. J. and Ngochindo R: I. *J. Chem. Res.* (S), **1983**, 196. and *J. Chem. Res.* (M), **1983**, 1913-1941. c. Katritzky, A. R., Slawinski, J. J. and Brunner, F. *J. Chem. Soc. Perkin Trans. I*, **1989**, 1139.
7. Trapping 4 with the electrophiles $Ph_2CO$, MeSSMe, or TMSCl reportedly gave moderate yields of 2,5-disubstituted 1-methylimidazoles while the results with $CO_2$ and $ClCO_2Me$ were poor. The poor results with $CO_2$ (9% after conversion to the dimethyl ester) contrast strongly with the 63% yield of 1-methylimidazole-5-carboxylic acid claimed by another group[6c] after deprotonation with 2Eq BuLi-TMEDA in THF, $CO_2$ trap and acid catalyzed 2-position decarboxylation. The latter result could not be reproduced in the laboratory of Dr. E. Pombo (Sandoz Pharma Ltd.).
8. Chadwick, D. J. and Ngochindo, R. I. *J. Chem. Soc. Perkin Trans. I*, **1984**, 481 in which the more facile preparation of a 2,5-dilithioimidazole when a 1-dimethylsulfamoyl stabilizing group is present is reported.
9. El Borai, M.; Moustafa, A. H, Anwar,M. and Abdel Hay, F. I. *Pol. J. Chem.*, **1981**, *55*, 1659.
10. Compound 5 is available in two steps from 3 (1.BuLi/$Br_2$,80% 2.NBS 50%).[9]
11. The stability of 6 first to workup and then to stronger hydrolysis conditions (2N HCl) clearly pointed to a rearrangement of the $SiMe_3$ group from the 2-position. Water alone is sufficient to cleave the 2-trimethylsilyl substituent on a 1-methylimidazole.[6a] (6) $^1$H-NMR (200MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.3 (s, 1H), 4.05 (s, 3H), 0.38 (s, 9H).
12. Tertov, B. A. and Morkovnik A. S. *Chem. Heterocyclic Compounds*, **1975**, *11*, 343.
13. a. Lipschutz, B., Huff, B. and Hagen, W. *Tetrahedron Lett.* **1988**, *29*, 3411. b. Carpenter, A. J. and Chadwick, D. J *Tetrahedron* **1986**, *42*, 2351 c. Ngochindo R. I. *J. Chem. Soc. Perkin Trans. I*, **1990**, 1645. d. Breslow et al. *J. Am. Chem. Soc.* **1978**, *100*, 3918. reported metallation of 1-methoxy-methyl-2-thiophenylimidazole with nBuLi resulted in sulfur-imidazole and sulfur-phenyl cleavage whereas using LDA the corresponding 5-lithioimidazole was formed and was stable.
14. Metal halogen exchange was performed on 5 and 1.0 Eq of t-butyldimethylsilyl chloride was added; another equivalent of BuLi was added and the reaction mixture quenched ($NH_4Cl$) after 15min at -70°C. Chromatography of the product mixture gave a 55% yield of 10 which is to our knowledge a new compound, mp 73-75°C, $^1$H-NMR (360MHz, $CDCl_3$) δ 7.5 (s, 1H), 7.14 (s, 1H), 3.68 (s, 3H), 0.88 (s, 9H), 0.26 (s, 6H).,
15. Compound 11 was prepared by treatment of 5 with 1.0 eq. of BuLi in THF followed by sulfenylation with $PhSO_2SPh$ (80%). $^1$H-NMR (200MHz, $CDCl_3$) δ 7.15-7.33 (m, 6H), 3.6 (s, 3H)
16. 5-butyl-2-thiophenyl-1-methyl imidazole was isolated in 65% yield. $^1$H-NMR (360MHz, $CDCl_3$): δ 7.08-7.26 (m, 6H), 6.96 (s, 1H), 3.5 (s, 3H), 2.52-2.56 (3 line multiplet, 2H), 1.59-1.69 (quintet, 2H, J=8.0 Hz), 1.38-1.48 (sextet, 2H, J=8.0 Hz), 0.96 (t, 3H, J=8.0 Hz).
17. The major isolated products were 12 and 13 in ca. 1:1 ratio. 13: $^1$H-NMR (360MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.40 (s, 1H), 7.22-7.27 (m, 2H), 7.12-7.16 (m, 1H), 7.03-7.06 (m, 2H), 3.53 (s, 3H).
18. Multiple bromine-lithium exchange reactions have been described for 1-benzyl-tribromoimidazole, Iddon, B. and Khan, N. *J. Chem. Soc. Perkin Trans. I*, **1987**, 1453.
19. Attempts to obtain a crystalline form of 4 in collaboration with Professor D. Seebach (ETH Zurich) for eventual X-ray analysis were unsuccessful.
20. Seebach, D. *Angew. Chem.* **1988**, *100*, 1685.
21. The procedure to give 1 could be carried out easily on a 10mmol scale but purification on a larger scale was complicated by the LiBr . For the practical synthesis of 1 on a kg scale the patent procedure: Koehler, H.; Dockner, T. and Karn, H. *European Patent Application* **306868** starting from imidazole--4(5)-carboxylic acid available in kg quantity(BASF) to give methyl-1-methylimidazole-5-carboxylate followed by reduction-oxidation[2] is to be recommended. This procedure has been carried out by Dr. L. LaVecchia (Sandoz Pharma Ltd.)
22. For a halogen "dance reaction" in lithiated thiophenes see: Sauter, F., Froelich, H. and Kalt, W. *Synthesis*, **1989**, 771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