REGIOSPECIFIC SYNTHESIS OF N-ALKYL-4- AND 5-SUBSTITUTED IMIDAZOLES

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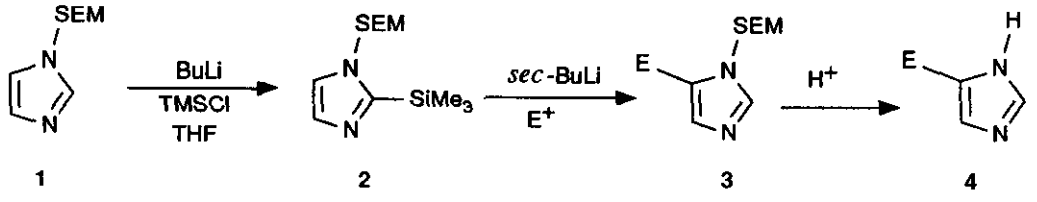
Abstract- A facile regiospecific synthesis of 4- and 5-substituted *N*-alkyl imidazoles has been developed from *N*-trimethylsilyloxyethyl-imidazole(s). The method combines directed metallation with alkyl triflate mediated imidazole quaternization and SEM group cleavage.

Imidazole is an important heterocycle because of its catalytic properties,[1] liganding abilities[2] and biological activities.[3] Although there are many methods for imidazole ring synthesis, there is still need for general and practical methods to prepare imidazole derivatives of a defined substitution pattern with regard to an *N*-substituent. In this communication we report a simple flexible method which allows the regiospecific synthesis of 4-substituted *N*-alkylimidazoles as well as the corresponding 5-substituted isomers. Lipshutz has developed an excellent method for preparing free N-H, 4(5)-substituted imidazoles[4] (**Scheme 1**). He has demonstrated that 1-trimethylsilylethyloxyimidazole (1-SEM-imidazole) is readily deprotonated in the 2-position and then blocked *in situ* with a trimethylsilyl group. Afterwards, the 5-position can be efficiently

Scheme 1



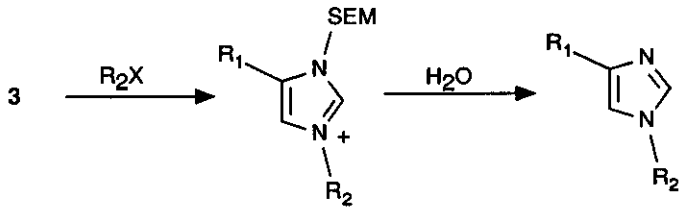
1 2 3 4

SEM= $CH_2OCH_2CH_2SiMe_3$

deprotonated in a directed metallation with *sec*-BuLi at low temperature and various electrophiles introduced, the trimethylsilyl group is removed upon simple aqueous work-up.[5] Removal of the SEM directing group then yields 4(5)-substituted imidazoles with the regiochemistry regarding the *N*-substituent being lost in the process. The simple *N*-alkylation of free N-H imidazoles generally[6] yields a mixture of regioisomers. We envisaged and have realized the expansion of the Lipshutz method to the facile, regiospecific synthesis of both 4-substituted *N*-alkylimidazoles and by slight extension, the corresponding 5-substituted regioisomers.

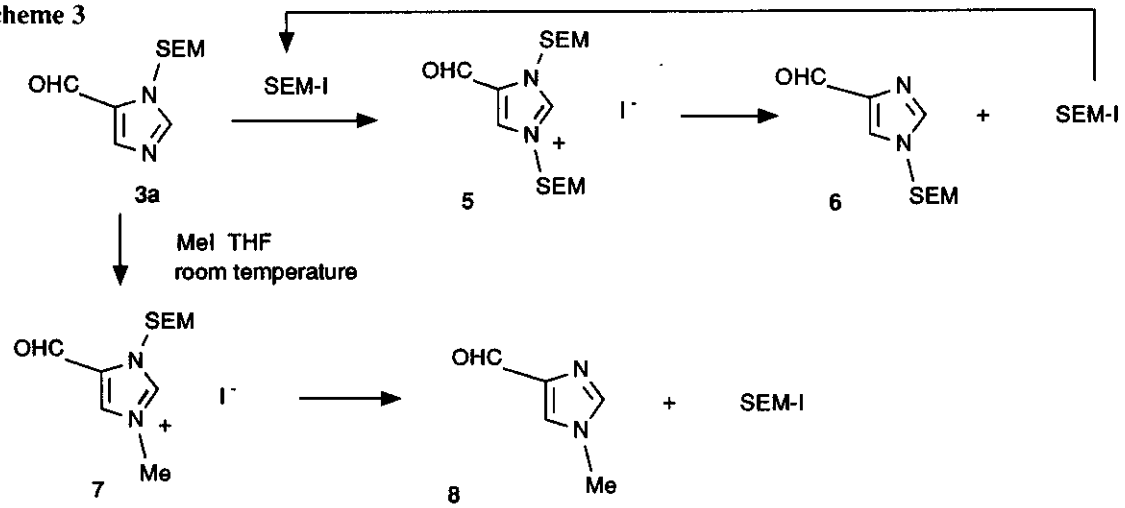
Our strategy (**Scheme 2**) was to alkylate the 5-substituted 1-SEM-imidazoles (**3**) on the distal, unsubstituted imidazole nitrogen to give an 1-SEM-3-alkylimidazolium species from which the SEM group could

Scheme 2



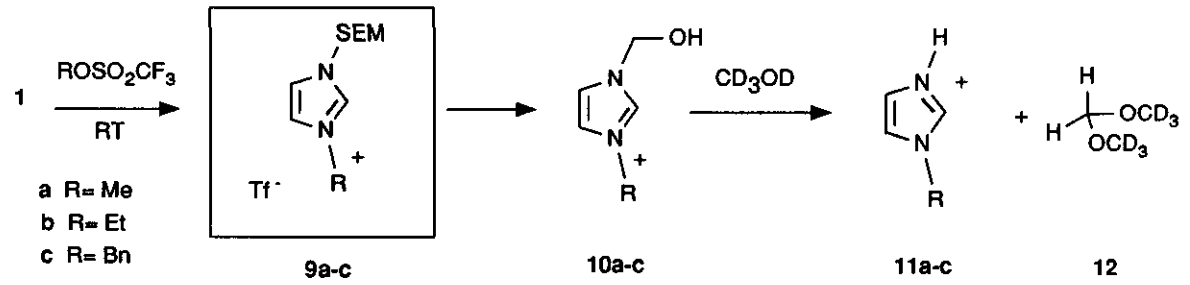
presumably be easily hydrolyzed to give 1-alkyl-4-substituted imidazoles. In a model study, treatment of **1** with methyl iodide gave the corresponding 1-SEM-3-methylimidazolium iodide[7] as an oil in good yield. This was then readily converted to 1-methylimidazole using the previously described conditions[4] (3N-HCl, EtOH reflux). To our surprise, when **3a** was treated with methyl iodide, instead of receiving the corresponding imidazolium salt, compound **(6)**[8] representing a formal migration of the SEM group was the major reaction product (isolated 45%) along with many minor uncharacterized products (**Scheme 3**). Apparently, in this case, iodide ion generated upon slow formation of the imidazolium species **(7)** undergoes internal return cleaving the SEM group to give the imidazole **(8)** and SEM-iodide. However, SEM-iodide then quaternizes **3a** more rapidly than methyl iodide. The bis-SEM imidazolium iodide **(5)** formed, then undergoes analogous internal return of iodide to regenerate SEM-iodide and **6** in a catalytic migration process. Compound **(6)** does not react significantly with methyl iodide under these conditions. Reasoning that a non-nucleophilic counterion in the

Scheme 3



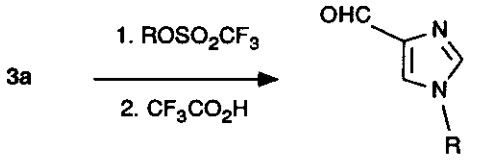
imidazolium species could circumvent the above problem, we turned to alkyl triflates as alkylating agents. In a model study **1** was treated with methyl and ethyl trifluoromethanesulfonate in toluene[9] or benzyl trifluoromethanesulfonate[10] in dichloromethane at 0°C. The species formed and their fates could be readily monitored by ^{1}H-nmr spectroscopy in CD_3OD.[11] The putative initially formed intermediates **(9a-c)** could not be observed. Thus the spectra revealed that silyl group cleavage had already occurred to give the 1-alkyl-3-hydroxymethyl-imidazolium species **(10a-c)**. These species then decay to the protonated 1-alkylimidazoles **(11a-c)** and formaldehyde dideuteromethylacetal in a very clean reaction (**Scheme 4**).[12] Based on these results **3a** was treated with methyl and ethyl trifluoromethanesulfonate in toluene or benzyltrifluoromethanesulfonate in dichloromethane at 0°C.[13] ^{1}H-nmr analysis of the imidazolium species generated showed at least the partial

Scheme 4



presence of the initially formed SEM-imidazolium species indicating a stabilizing effect of the aldehyde function in these cases. To obtain the imidazolealdehydes directly, the solvent was removed and the reaction

Scheme 5

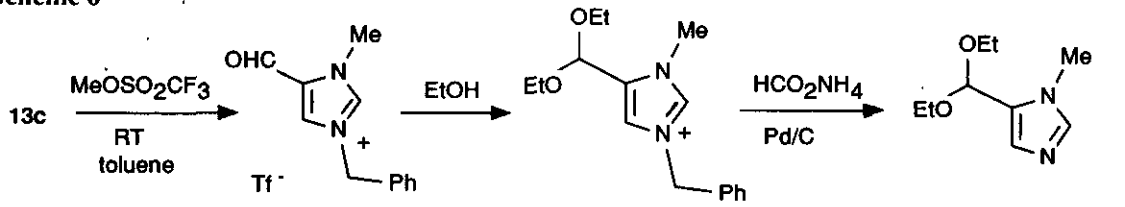


13a R= Me 90%
13b R= Et 85%
13c R= Bn 54%

products were treated with trifluoroacetic acid. In this fashion **13a**,[14] **13b**[15] and **13c**[16] were easily prepared and isolated in good yields after standard chromatography (**Scheme 5**).

The same alkylative transposition strategy can be employed to prepare 1-alkyl-5-substituted imidazoles from 1-alkyl-4-benzylimidazoles such as **13c**. Alkylation, of the unsubtituted distal imidazole nitrogen in such a compound gives a stable imidazolium species, which upon simple hydrogenolysis of the benzyl group leads to the related 1-alkyl-5-substituted imidazole. Thus, treatment of **13c** with methyl trifluoromethanesulfonate in toluene resulted in the precipitation of the putative imidazolium species (**14**) as an oil. Dissolving this species in ethanol led to the clean formation of the corresponding imidazolium diethyl acetal (**15**) which was

Scheme 6



characterized by ^{1}H-nmr analysis in $CDCl_3$.[17] This very facile acetal formation from an imidazolium species[18] is useful in that a separate protection step is avoided should this be necessary for further transformation (eg. a 2-position deprotonation/trapping sequence). The toluene solvent was decanted and ethanol added along with ammonium formate and 10% Pd/C. After brief heating at reflux the 1-methyl-5-formylimidazole diethyl acetal (**16**) was obtained in excellent yield (**Scheme 6**).[19]

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2. S. Knapp, J. Albaneze and H. J. Schugar, *J. Org. Chem.*, **1993**, *58*, 997 and references cited therein.
3. For a review of pilocarpine analog SAR see G. Shapiro and A. Enz, *Drugs of the Future*, **1992**, *17*, 489.
4. B. H. Lipshutz, B. Huff and W. Hagen, *Tetrahedron Lett.*, **1988**, *29*, 3411.
5. P. Jutzi and W. Sakriss, *Chem. Ber.*, **1973**, *106*, 2815.
6. In the absence of unusual steric parameters (see B. H. Lipshutz and M. C. Morey, *J. Org. Chem.*, **1983**, *48*, 3745) the alkylation of 4(5)-substituted imidazoles generally gives a regioisomeric mixture somewhat favoring the 1-alkyl-4-substituted isomers. Acylation proceeds with greater regioselectivity allowing, after alkylative quaternization and hydrolysis, the regioselective synthesis of 1-alkyl-5-substituted imidazoles: E. F. Godefroi and J. H. F. M. Mentjens, *Recl. Trav. Chim. Pays-Bas.*, **1974**, *93*, 56.
7. ^{1}H-nmr (200 MHz, $CDCl_3$) δ= 10.16 (s, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 5.73 (s, 2H), 4.16 (s, 3H), 3.72 (t, 2H, *J*= 8.6Hz), 0.97 (t, 2H, *J*= 8.6Hz), 0.3 (s, 9H).
8. **3a:** ^{1}H-nmr (360 MHz, $CDCl_3$) δ= 9.72 (s, 1H), 7.90 (s, 5H), 7.85 (s, 1H), 5.73 (s, 2H), 3.62 (t, 2H, *J*= 8.4Hz), 0.95 (t, 2H, *J*= 8.4Hz), 0.01 (s, 9H). **6:** ^{1}H-nmr (360 MHz, $CDCl_3$) δ= 9.91 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 5.34 (s, 2H), 3.53 (t, 2H, *J*= 8.4Hz), 0.94 (t, 2H, *J*= 8.4Hz), 0.01 (s, 9H). FAB-ms M^++1 =227.
9. Methyl and ethyl trifluoromethanesulfonate were purchased from Fluka AG.
10. Benzyl trifluoromethanesulfonate: a. R. U. Lemieux and T. Kondo, *Carbohydrate Research*, **1974**, *35*, C4. b. B. L. Booth, R. N. Haszeldine, and K. Laali, *J. Chem. Soc. Perkin Trans. I*, **1980**, 2887. Benzyl trifluoromethanesulfonate prepared according to reference 10a could be used *in situ* for the preparation of **11c**, **13c** while the method of reference 10b was found unsatisfactory for this purpose.
11. **10a:** ^{1}H-nmr (360 MHz, $CDCl_3$) δ= 8.93 (s, 1H), 7.62 (s, 1H), 7.57 (s, 1H), 5.54 (s, 2H), 3.96 (s, 3H). ^{1}H-nmr 24 hours later, **11a + 12:** ^{1}H-nmr (360MHz, $CDCl_3$) δ= 8.82(s, 1H), 7.56 (s, 1H), 7.52 (s, 1H), 4.51 (s, 2H, $CH_2(OCD_3)_2$), 3.93 (s, 3H).
12. To prepare the methyl and ethyl derivatives a 10% excess of alkyl trifluoromethanesulfonate was added to a solution of **1** or **3a** in toluene at 0 ^{0}C. The imidazolium species precipitated from the solution as an oil. The solvent was removed by decantation, the oil was dried under high vacuum and directly investigated by nmr or subjected to hydrolysis.
13. To prepare the benzyl derivatives, the benzyl trifluoromethanesulfonate[10a] was preformed *in situ* by adding a solution of benzyl alcohol and diisopropylethylamine in CH_2Cl_2 to a solution of trifluoromethanesulfonic anhydride in CH_2Cl_2 under argon at -78 ^{0}C. After 30 min imidazole (**1**) or (**3a**) was added in CH_2Cl_2. After stirring for 2 hours, the solvent was evaporated under reduced pressure and directly investigated by nmr or subjected to hydrolysis.
14. P. K. Martin, H. R. Matthews, H. Rapoport and G. Thyagarajan, *J. Org. Chem.*, **1968**, *33*, 3758.
15. This compound has been reported without spectral data: M. M. Herrador, J. Saénz de Buruaga and M. D. Suarez, *J. Med. Chem.*, **1985**, *28*, 146. **13b:** ^{1}H-nmr (360 MHz, $CDCl_3$) δ= 9.88 (s, 1H), 7.66 (s, 1H), 7.58 (s, 1H), 4.04 (q, 2H, *J*= 7.5Hz), 1.52 (t, 3H, *J*= 7.5Hz). EI-ms M^+=124.
16. L. A. Reiter, *J. Org. Chem.*, **1987**, *52*, 2714.
17. **15:** ^{1}H-nmr (200 MHz, $CDCl_3$) δ= 9.26 (s, 1H), 7.40 (s, 5H), 7.18 (s, 1H), 5.55 (s,1H), 5.34 (s, 2H), 3.92 (s, 3H), 3.60 (m, 4H), 1.20 (t, 6H, *J*= 7.5Hz).
18. Similar behaviour was observed when the imidazolium species, formed by treatment of **3a** with an alkyl trifluoromethanesulfonate, were dissolved in alcohol.
19. **16:** ^{1}H-nmr (200 MHz, $CDCl_3$) δ= 7.42 (s, 1H), 7.05 (s, 1H), 5.50 (s, 1H), 3.69 (s, 3H), 3.57 (m, 4H), 1.23 (t, 6H, *J*= 7.5Hz) .

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