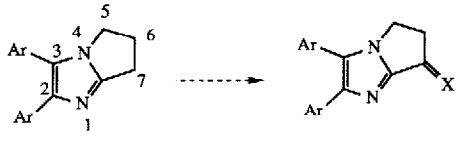
Tetrahedron Letters,Vol.30,No.48,pp 6599-6602,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

C-7 FUNCTIONALIZATION OF 6,7-DIHYDRO[5H]PYRROLO[1,2-a]IMIDAZOLES: ACTIVATION VIA QUATERNIZATION WITH MEMCl.

Timothy F. Gallagher* and Jerry L. Adams
Department of Medicinal Chemistry, Smith Kline & French Laboratories
P.O. Box 1539, King of Prussia, PA 19406-0939, USA

Abstract: Several 6,7-dihydro[5H]pyrrolo[1,2-a]imidazoles were activated toward functionalization at C-7 by conversion to quaternary imidazolium salts. The MEMCl derived quaternary salts upon treatment with base reacted with both aldehydes and alkyl halides. The MEM group was removed under mild conditions by heating the functionalized adducts in a variety of solvents.

As part of a program to define structure-activity relationships in a series of antiinflammatory 2,3-diaryl-6,7-dihydro[5H]pyrrolo[1,2-a]imidazoles,[1] we became interested in preparing a variety of C-7 functionalized analogs. Futhermore, we wanted to be able to prepare these derivatives directly from non-functionalized pyrroloimidazoles to avoid a total synthesis for each analog. A review of the literature indicated that no generally applicable method existed.[2]

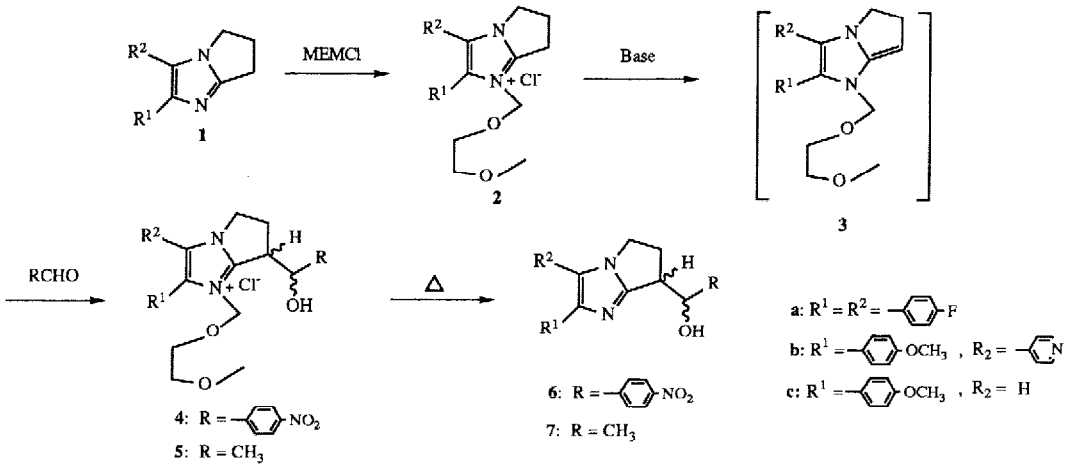


X = O; H,OH; F,F; CH_3,CH_3

All attempts to derivatize C-7 by first treating these molecules with a strong base, followed by quenching with the appropriate electrophile, were unsuccessful due to lack of anion formation.[3] Several attempts to oxidize C-7 directly were also unsuccessful.[4] In order to facilitate deprotonation at C-7, we reasoned that quaternization of the imidazole moiety should greatly enhance the acidity of the protons at this position facilitating formation of an anhydrobase.[5] While this strategy has been utilized in various heterocyclic systems,[6] it has not been fully exploited due to the difficulty of subsequent dequaternization.[7]

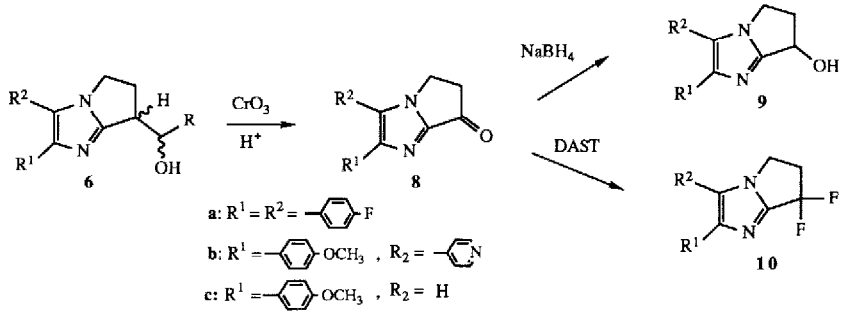
Our initial work involved quaternization with allyl bromide.[8] Treatment of **1a** with allyl bromide at reflux yielded a stable quaternary imidazolium compound, however, dequaternization required heating the intermediate to 250 °C under reduced pressure. We next examined MEMCl, reasoning that the aminal-like quaternary salts would prove more labile. Treatment of **1a** with MEMCl led to the quaternary imidazole **2a** from which the MEM group could be thermally removed at 100 °C or less in an inert solvent.[9]

As expected, quaternization increased the acidity of the protons at C-7 facilitating condensation with aldehydes either at ambient temperature with DBU as the base or in refluxing ethanol with triethylamine as the base. For example, reaction of **2a** with p-nitrobenzaldehyde in refluxing ethanol in the presence of triethylamine for 48 h gave the dequaternized condensation product **6a** in 42% overall yield.[10] Similar treatment of **2b** (24 h reflux) afforded a mixture of the quaternized and dequaternized condensation products **4b** and **6b**, respectively.[11] Conversion of remaining **4b** to **6b** was accomplished by heating the mixture in DMF for 1h at 100 °C to afford **6b** in an overall yield of 54%.[12]

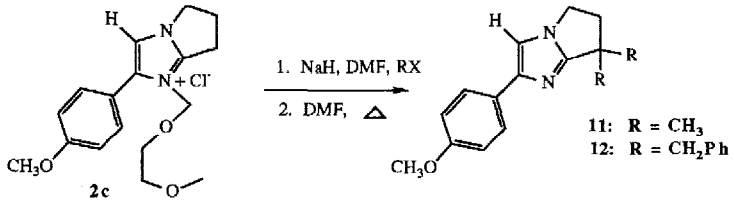


Reaction of the 3-H analog **2c** under the above conditions led to a complex mixture of **2c**, **4c** & **6c** along with a small amount of **1c**. However, treatment of **2c** at ambient temperature with p-nitrobenzaldehyde in CH_2Cl_2 containing DBU as the base gave the quaternized condensation product **4c** in high yield.[13] Dequaternization was effected by heating in DMF for 2 h at 100 °C. Condensation and dequaternization were equally effective when acetaldehyde was used in place of p-nitrobenzaldehyde (**2c** → **7c**).

Compounds **6a**,**b** & **c** were all converted to their corresponding 7-keto derivatives (**8a**, **b** & **c**, respectively) by oxidation with Jones reagent in acetone[14] in approximately 40% yield. Reduction of the ketones with sodium borohydride in dichloromethane / methanol gave the 7-hydroxy derivatives **9a, b** & **c**. Treatment of **8b** with DAST afforded the 7,7-difluoro analog **10b**.

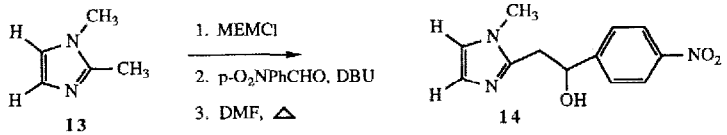


Quaternization also permitted alkylation at C-7 under relatively mild conditions. For example, treatment of **2c** with 2 equivalents of sodium hydride in the presence of excess methyl iodide or benzyl bromide (DMF, ambient temperature) afforded the dialkyl derivatives **11** and **12**, respectively. Again, dequaternization was achieved by heating in DMF.



2c

The concept of activating the α-position of C-2 alkyl substituted imidazoles via quaternization with MEMCl may be useful in other imidazole systems. For example, in the case of the simple disubstituted imidazole, 1,2-dimethylimidazole (**13**), treatment with MEMCl gave a stable quaternary imidazolium compound, which condensed with p-nitrobenzaldehyde in DBU / dichloromethane to give, after heating in DMF, the dequaternized condensation product **14**. However, attempts to adapt this methodology to other nitrogen-containing heterocycles, namely, 2-methylpyridine, 2-methylquinoline and 2-methylbenzoxazole were unsuccessful. In the case of 2-methylquinoline and 2-methylbenzoxazole stable quaternary salts could not be isolated. In the case of 2-methylpyridine, the quaternary salt and the anhydrobase could be formed but no condensation product was isolated. The instability of the MEM salts of these heterocycles suggests that selective activation of imidazoles is possible in systems containing other potentially reactive heterocyclic moieties.



13 14

References and Notes

[1]P. E. Bender and N. Hanna, "Pyrrolo[1,2-a]imidazoles and pyrrolo[1,2-a]pyridine derivatives and their use as 5-lipoxygenase pathway inhibitors", U. S. Patent 4,719,218, **1988**.

[2]The only example we found involved a t-butoxide catalysed condensation of a highly activated 5-nitro pyrroloimidazole with benzaldehyde; see: D. W. Henry and D. R. Hoff, U. S. Patent 3,472,864, **1969**.

[3](a) Treatment with organolithium bases at temperatures from -78 °C to ambient did not result in deprotonation (D_2O quench) or led to decomposition. (b) Difficulty in deprotonating 2-alkyl imidazoles when the substitution pattern is other than methyl is precedented. For example see: J. V. Hay, D. E. Porlock and J. F. Wolfe, *J. Org. Chem.* **1978**, 38, 4379.

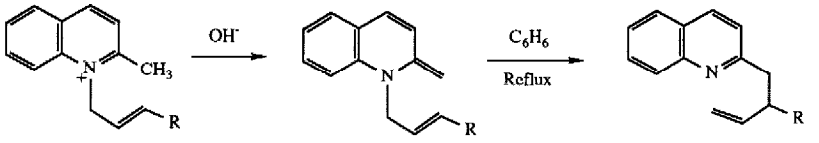
[4]Oxidation with chromium trioxide led to cleavage of the pyrrolo ring; selenium dioxide and N-bromosuccinimide afforded only starting material.

[5]To our knowledge, no examples of stable imidazole anhydrobases have been reported although they have been proposed as intermediates in condensation reactions involving imidazoles. See: M. R. Grimmett in "Comprehensive Heterocyclic Chemistry", vol. 5, A. R. Katritzky, ed., Pergamon Press, Oxford, **1984**, p. 430.

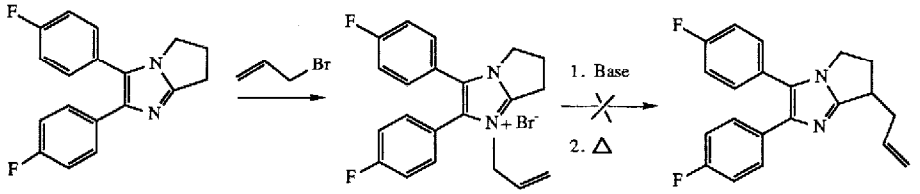
[6]For examples of the use of quaternization to accelerate aldehyde condensation reactions and alkylations see: (a) W. H. Mills and R. Raper, *J. Chem. Soc.* **1925**, 127, 2466. (b) W. Lampe and J. Smolinska, *Bull. Acad. Polon. Sci.* **1957**, 5, 835; *Chem. Abst.* **1958**, 52, 6319.

[7]B. K. M. Chan, N. H. Chang and M. R. Grimmet, *Aust. J. Chem.* **1977**, 30, 2005.

[8]Our rationale for utilizing allyl bromide to achieve C-7 functionalization was to create a quaternary salt which upon treatment with base would form an anhydrobase capable of undergoing a 3,3-sigmatropic rearrangement. Such a strategy has been successfully employed with 2-methylquinoline (R. K. Hill and G. R. Newkome, *Tetrahedron Lett.* **1968**, 5059).



Adaptation of this methodology to our system failed. Presumably the anhydrobase was not stable enough to undergo Claisen rearrangement.



[9]Although MEMCl quaternization was easily reversed by heating, the quaternary salt was stable to conditions used to deprotect MEM ethers (e.g. $TiCl_4$ / CH_2Cl_2 or HCl / ethanol).

[10]Formula **6a** actually represents two separable diastereomers. The experimental procedure for the preparation of **6a** is as follows: MEMCl (3 ml, 24 mmol) was added dropwise to a solution of **1a** (1.5 g, 5.1 mmol) in CH_2Cl_2 (10 ml). After stirring for 0.5 h at ambient temperature, hexane was added to precipitate the adduct. The solvent was decanted and the residue was triturated twice with ether and dissolved in ethanol (15 ml). To this solution was added triethylamine (2.1 ml, 15 mmol) followed by p-nitrobenzaldehyde (1.5 g, 9.9 mmol). The reaction mixture was heated at reflux for 48 h, at which point TLC (9:1 chloroform / methanol) showed the formation of two closely-migrating products. Upon cooling to ambient temperature a yellow precipitate formed. The solid was collected and washed with ethanol and ether; yield 0.55 g (24 %). TLC indicated that the yellow solid was composed almost entirely of the faster-migrating product; ^{1}H NMR ($CDCl_3$) δ 2.28 (m, 1H, 6-H), 2.57 (m, 1H, 6'-H), 3.7 (m, 3H, 5-H and 7-H), 5.59 (s, 1H, $O_2NPhC\underline{H}ROH$), 6.8 - 8.3 (12H, Ar$\underline{H}$). The mother liquor was concentrated and the residue was dissolved in CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and filtered. The filtrate was concentrated and the residue was triturated with ether to afford a light yellow solid which consisted primarily of the slower-migrating diastereomer; yield 0.4 g (18 %), ^{1}H NMR ($CDCl_3$) δ 2.40 (m, 2H, 6-H), 3.51 (q, 1-H, H-7), 3.82 (m, 2H, H-5), 4.93 (d, 1H, $O_2NPhC\underline{H}ROH$), 6.9 - 8.3 (12H, Ar$\underline{H}$).

[11]Compound **1b,** which contains a pyridine moiety in addition to the imidazole function, forms a stable bis-quaternary imidazolium salt upon treatment with MEMCl. Under the reaction conditions employed, however, dequaternization of the pyridine and the imidazole salts occurs.

[12]Again, **6b** represents two diastereomers; the slower-migrating compound (TLC - 9:1 chloroform / methanol) precipitates from ethanol.

[13]The procedure used to prepare **4c** is as follows: DBU (2.9 ml, 19 mmol) was added to a solution of **2c** (5.0 g, 15 mmol, prepared in the same manner as **2a**) and p-nitrobenzaldehyde (4.8 g, 4.4 mmol) in CH_2Cl_2 (25 ml) at ambient temperature. After stirring for 0.5 h, a precipitate formed. The solid was collected and washed sparingly with CH_2Cl_2 and copiously with ether to afford **4c** (mixture of diastereomers) as a white solid; yield 6.5 g (89 %), ^{1}H NMR ($CDCL_3$) δ 2.44 (m, 2H, 6-H), 3.0 - 3.5 (4H, $OC\underline{H}_2C\underline{H}_2O$), 3.28 (s, 3H, $CH_2OC\underline{H}_3$), 3.73 (s, 3H, $PhOCH_3$), 4.66 (m, 3H, 5-H and 7-H), 5.58 (s, 1H, $O_2NPhC\underline{H}ROH$), 5.64 (AB, 2H, $NC\underline{H}_2O$), 6.8 - 8.2 (9H, Ar$\underline{H}$).

[14]For a discussion of the probable mechanism of this cleavage reaction, see: H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Inc., Menlo Park, CA, **1972**, p. 283.

(Received in USA 15 August 1989)