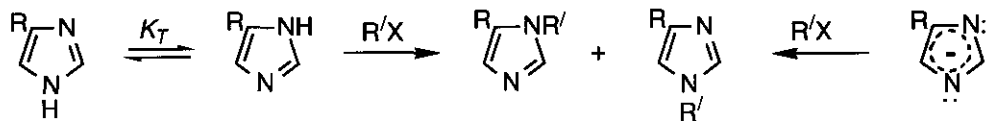
ALKYLATION OF 4(5)-SUBSTITUTED IMIDAZOLES

Paul Benjes and Ross Grimmett *

Chemistry Department, University of Otago, P.O. Box 56, Dunedin, New Zealand

Abstract – 4(5)-Substituted imidazoles were alkylated under "neutral" and alkaline conditions to give mixtures of isomers in ratios which depended on the reaction conditions, and the nature of the substituent and alkylating agents.

It has been known for many years that 4(5)-substituted imidazoles (**1a**, **1b**) usually give mixtures of isomeric products when treated with alkylating agents.[1]



(**1a**) (**1b**) (**2**) (**3**) (**4**)

For this reason it is frequently difficult to prepare pure samples of 1-alkyl-4- and 1-alkyl-5-substituted imidazoles. Product ratios are known to vary from substrate to substrate, with reaction conditions, solvent, and alkylating agent all exerting influence on the direction of alkylation. Of the azole ring systems, systematic researches into the regiochemistry of *N*-alkylation have been performed for 5-substituted tetrazoles,[2] and unsymmetrically substituted pyrazoles[3] and triazoles.[4] Few efforts, however, have been made to study the process systematically in imidazoles, and the wide variety of results quoted in the literature mirror the myriad

approaches to the alkylation reactions. Recently, Begtrup[5] has attempted, with some success, to provide a systematic approach to the preparation of *N*-alkylated and *N*-acylated azoles based on preconversion of the azole into an anionic salt, and subsequent alkylation under carefully selected conditions in a separate step.

This current study, while not concerned with the development of efficient methods for regiospecific alkylation, endeavours to provide some further understanding of the processes which direct the reactions. Accordingly, reaction conditions have been chosen with a view to comparing our results with those of earlier workers. Thus, methylation in "basic medium" utilises aqueous sodium hydroxide with dimethyl sulfate, historically a common set of conditions, but often synthetically inferior to heterogeneous[6] and two step[5] (anion salt isolation) alkylation procedures. Methylation of the imidazole free bases under "neutral" conditions has been standardised as a simple refluxing of the azole with dimethyl sulfate in ethanol. Product ratios were determined by ^{1}H nmr analysis of the crude product mixture which has been found to give a higher degree of accuracy and reproducibility than historical methods which were based on gravimetric analysis of products of recrystallisation or distillation.

A wide range of 4-substituted imidazoles have been prepared by reported methods. Each of the *N*-unsubstituted imidazoles was methylated, ethylated and benzylated in "neutral" and basic conditions,[7] the product mixture analysed, and the *N*-alkyl isomers chromatographically isolated. The regiochemistry of alkylation was rigorously determined by ^{1}H and ^{13}C nmr. A selection of the methylation results is shown in the Table.

A number of factors can be shown to affect the product ratios. It is generally accepted that the free base is methylated by an S_E2' process while the imidazole anion (**4**) obeys S_E2cB kinetics.[8] The ratios of 1,5- : 1,4- products (**2**:**3**) determined from reaction in basic medium seem to depend entirely on polar and steric factors. Electron-withdrawing groups in the 4(5)-position render the more remote nitrogen the least deactivated to electrophilic attack. Correlation of the results obtained is

Table. Ratios of N-Methyl Isomers (2:3).

4(5)-R	Me_2SO_4 / $NaOH_{(aq)}$	Me_2SO_4 / EtOH
CH_3	1.4 : 1	1.2 : 1
CH_2OH	1.2 : 1	1 : 1.6
CHO	1 : 1	1 : 3.6
C_6H_5	7.3 : 1 [A]	4.0 : 1
Cl	3.0 : 1	1 : 17
Br	2.6 : 1	1 : 11.5
I	1.4 : 1	1 : 4.9
NO_2	8.6 : 1	1 : 50

[A] Me_2SO_4 / EtONa / EtOH.

much better with σ_I or σ_m than with σ_p substituent constants, indicating that the major effect of the substituent is inductive. As previously observed in the alkylation of 3(5)-substituted pyrazoles,[3] and tetrazoles,[2] steric effects play a very significant role in the overall regiochemistry of alkylation. An increased preference for the less-hindered nitrogen is demonstrated as both the size of the substituent and the size of the incoming electrophile increases. In "neutral" conditions matters are more complex. Certainly steric effects can be seen, but the expected electronic effects are frequently overcome by a dominant tautomeric effect when the substituent is an electron-withdrawing group. A few K_T values had been published previously.[9] Some of these were re-determined and a number of others determined for this study using the procedure which compares the basic pK_a values of the tautomeric 4(5)-substituted imidazole and its two *N*-methylated isomers as "fixed models".[8] Values obtained (4(5)-R, K_T (**1a**/**1b**) : NO_2, >400 [8]; Cl, 90; Br, 47; I, 19; CH_3, 1.1) demonstrate that the dominant tautomer is **1a** when the substituent is electron-withdrawing, and even though this is the less-reactive tautomer in an S_E2' reaction it still controls the product ratio, leading to high proportions of 1-alkyl-5-R-imidazole (**2**) in the product mixture. It should be noted that our experimental evidence reflects kinetic control of isomer ratios in both media under the conditions used. No isomerisation of the products (**2**, **3**) was observed.

The full results of this study, which include other alkylation regimes (diazomethane, phase transfer catalysis etc), a wider range of substrates, detailed Hammett and charge density correlations, and nmr studies will be published later.

REFERENCES AND NOTES

1) K. Schofield, M.R. Grimmett, and B.R.T. Keene, 'Heteroaromatic Nitrogen Compounds, The Azoles', Cambridge, 1976, p. 74; M.R. Grimmett, 'Advances in Heterocyclic Chemistry : Advances in Imidazole Chemistry', Vol. 27, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, Inc., New York, 1980, pp. 292-296; P. Benjes and M.R. Grimmett, 'Advances in Detailed Reaction Mechanisms Vol. 3 : N-Alkylation of Nitrogen Azoles', in Press.

2) R.J. Spear, Aust. J. Chem., 1984, **37**, 2453.

3) M.R. Grimmett, K.H.R. Lim, and R.T. Weavers, Aust. J. Chem., 1979, **32**, 2203.

4) S. Kubota and M. Uda, Chem. Pharm. Bull., 1975, **23**, 955; M. Uda, Y. Hisazumi, K. Sato, and S. Kubota, Chem. Pharm. Bull., 1976, **24**, 3103.

5) M. Begtrup and P. Larsen, Acta Chem. Scand., 1990, **44**, 1050.

6) R.J. Gallo, M. Makosza, H.J.-M. Dou, and P. Hassanaly, Adv. Heterocycl. Chem., 1984, **36**, 175.

7) "Basic" alkylation : the substrate was dissolved in 10% aqueous sodium hydroxide, the alkyating agent added, and the reaction mixture stirred at room temperature for 2 hours. "Neutral" alkylation : the substrate was dissolved in ethanol, the alkylating agent added, and the reaction mixture heated under reflux for 2 hours.

8) A. Grimison, J.H. Ridd, and B.V. Smith, J. Chem. Soc., 1960, 1352 and 1357.

9) J. Elguero, C. Marzin, and A.R. Katritzky, 'The Tautomerism of Heterocycles', Adv. Heterocycl. Chem. Suppl. 1, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, Inc., New York, 1976, p. 279.

Received, 1st October, 1993