Tetrahedron Letters No. 33, pp 3507 - 3508, 1972. Pergamon Press. Printed in Great Britain.

THE REGIO-SPECIFIC METALATION OF HETEROCYCLIC COMPOUNDS

Gareth M. Davies and Patricia S. Davies

Imperial Chemical Industries Limited, Pharmaceuticals Division,

Alderley Park, Macclesfield SK10 4TG.

(Received in UK 11 July 1972; accepted for publication 17 July 1972)

Although the metalation of organic compounds by organolithium derivatives is a versatile technique extensively used in the synthesis of organic compounds[1], many apparently well-conceived syntheses have been frustrated by the difficulty of achieving metalation at a specific position. Halogen containing compounds for example, frequently undergo both halogen-metal and proton-metal exchange. We wish to report that lithium di-isopropylamide is a highly selective metalating agent of exceptional potential for circumventing this difficulty. In all the examples studied it has efficiently led to exclusive proton-metal exchange, even when the substrate contained reactive halogen substituents. The specificity of the reagent may be attributed to its weak nucleophilic character and its reactivity to its strong basicity. An additional factor favouring the exclusive proton-metal exchange in halogen containing substrates may be the unfavourable energy change which would result from the exchange of a carbon-bromine bond for a nitrogen-bromine bond:

$$\text{R-Br} + \text{LiN}({}^{i}\text{Pr})_2 \rightleftarrows \text{R-Li} + \text{BrN}({}^{i}\text{Pr})_2$$

The reactions tabulated below were carried out under an inert atmosphere in either ether or tetrahydrofuran at -70°C. Lithium di-isopropylamide was generated from n-butyl-lithium in hexane and di-isopropylamine. The lithiated intermediates were reacted with either trimethyl silyl chloride or with D_2O and the products analysed by GLC. Examination of the nmr spectra of the crude products unambiguously revealed the position of metalation in each case.

COMPOUND METALATED	FINAL PRODUCT	REMARKS
2-Bromothiophene	2-Bromo-5-trimethylsilylthiophene	Metalation with n-butyl-lithium led to halogen exchange[2].
2,5-Dibromothiophene	2,5-Dibromo-3-trimethylsilyl-thiophene	Metalation with n-butyl-lithium gave halogen-metal exchange[2].

3-Nitrothiophene	3-Nitro-2-trimethylsilylthiophene	3-Nitrothiophene was incompletely metalated with phenyl-lithium[3]; n-butyl-lithium gave a highly coloured solution which did not lead to an identifiable product after treatment with trimethylsilyl chloride[3].
3-Thenoic Acid	2-Trimethylsilyl-3-thenoic acid	Hexamethylphosphoramide was used as co-solvent.
3-Bromofuran	3-Bromo-2-trimethylsilylfuran	3-Bromofuran underwent halogen-metal exchange with n-butyl-lithium[4]; phenyl-lithium gave a mixture of 2- and 3-lithio derivatives[3].
2,3-Dibromofuran	2,3 Dibromo-5-trimethylsilylfuran	2,3-Dibromofuran gave 2-lithio-3-bromofuran with n-butyl-lithium[4].
2-(3-Bromofur-2-yl)-1,3-dioxolane	2-(3-Bromo-5-deuterofur-2-yl)-1,3-dioxolane	n-butyl-lithium led to the 3-lithio derivative[5].

The synthetic potential of metalated compounds bearing halogen substituents, which are used either as easily removed blocking groups or as substituents for subsequent modification, is clearly enormous. Furthermore, using the reagent we have metalated compounds in the presence of a carbanion acceptor thereby reducing the incidence of side-reactions, and it is likely that this procedure can be extended to the metalation of compounds bearing unprotected functional groups.

Current work extending the application of the reagent will be reported in a later communication.

Acknowledgements: We thank Mr. B. Crooks and Miss S.L. Stevenson for GLC analyses and Mr. B. Wright for the interpretation of the nmr spectra. We also thank Dr. P.N. Edwards for helpful discussions.

References:

1. J.M. Mallan and R.L. Bebb, Chem. Rev. 1969, **69**, 693.
2. S. Gronowitz, Advances in Heterocyclic chemistry, 1963, **1**, 1.
3. Unpublished results.
4. R. Sornay, J-Marie Meunier, and P. Fournari, Bull. Soc. Chim. France, 1971, 990.
5. S. Gronowitz and U. Michael, Arkiv Kemi, 1971, **32** 283.