Pergamon

Tetrahedron Letters, Vol. 37, No. 24, pp. 4281-4282, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00817-9

Changing Course with an Additive: A Striking Example of the Effect of TMSCl on Lithium Amide Reactivity.

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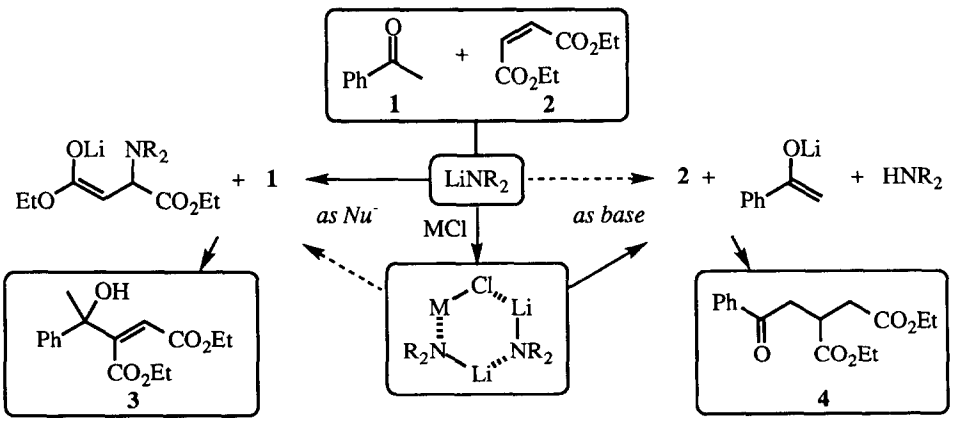
Abstract: *When a solution of diethyl maleate and acetophenone is added to a cooled (-78°C) solution of a lithium amide the maleate derivative 3 is given in good yield. Pre-treatment of the lithium amide with TMSCl alters the course of this reaction dramatically. With half an equivalent of this additive the Michael adduct 4 is given in 62% yield while employing three equivalents leads to the silyl enol ether 5 in >85% yield.*

Illustrations of the influence of additives on the reactions of lithium amide bases abound in the contemporary literature. Lithium chloride and trimethylsilyl chloride, for example, have been shown to improve *E/Z* selectivity in the enolisation of acyclic ketones and to enhance enantioselectivity in the desymmetrisation of mesomeric ketones by homochiral lithium amide bases.[1,2] The rôle of these additives has been subject to much scrutiny and it is believed that they enhance the kinetic basicity of the reagent through the formation of $MCl:(LiNR_2)_n$ aggregates.[3] Surprisingly, the influence of TMSCl and LiCl on other reactions involving lithium amides has received scant attention.[4]

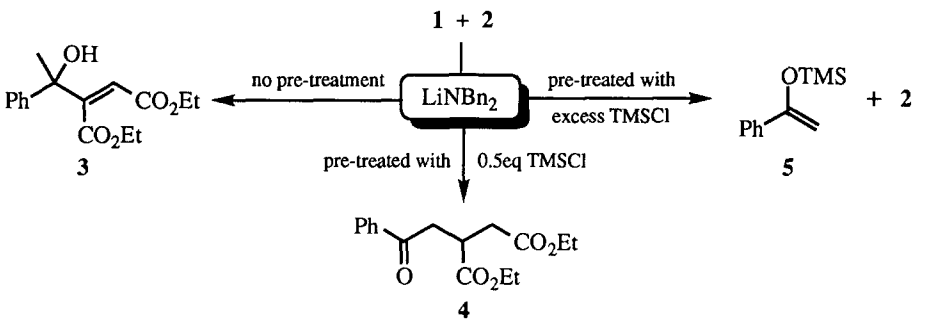


Scheme 1

We were intrigued as to their effect on our Michael initiated - condensation elimination sequence towards maleate derivatives *viz.* **1** + **2** --> **3**.[5] For if pre-treatment gave a reagent with enhanced basicity then the course of this reaction should be altered in favour of the adduct **4** (Scheme 1). Initial attempts to

realise that objective using LiCl met with limited success. Employing lithium dibenzylamide or lithium tetramethylpiperidide in the presence of added LiCl afforded ~15% of the ketone **4** together with ~45% of the MICE adduct **3**. Similar results were obtained when the 'LiCl:$LiNBn_2$' complex was formed from $Bn_2NH.HCl$ and two equivalents of butyl lithium.[6]

When this reaction was performed with lithium dibenzylamide that had been pre-treated with half an equivalent of trimethylsilyl chloride however, the ketone **4** was furnished in 62% yield and only traces of the maleate **3** (~10%) were observed. Moreover, when $LiNBn_2$ was pre-treated with 3 equivalents of TMSCl the major product was the silyl enol ether **5** (>85%, Scheme 2). These results suggest that deprotonation first leads to the lithium enolate and that this is trapped most efficiently by *external* electrophiles (*i.e.* those not associated with the aggregate complex). They also demonstrate a clear distinction between the TMSCl and LiCl effect on lithium amide reactivity.[7]



Scheme 2

Finally, we have shown that this behaviour extends to other lithium amide bases such as LDA and LiTMP. In the latter case the yield of **4** was greatest (55%) when one equivalent of TMSCl was employed, suggesting that in THF this reagent preferentially forms a 1:1 complex with trimethylsilyl chloride.[3] We are currently examining further aspects of this chemistry and are actively exploring applications in synthesis.

Acknowledgements The authors wish to thank The University of Southampton and The Nuffield Foundation for financial support.

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(*Received in UK* 15 *April* 1996; *accepted* 26 *April* 1996)