Tetrahedron Letters No. 47, pp 4095 - 4098, 1974. Pergamon Press. Printed in Great Britain.

REDUCTION OF NON-ENOLIZABLE KETONES BY LITHIUM AMIDES

E.P. Woo and K.T. Mak

Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong

(Received in Japan 2 September 1974; received in UK for publication 14 October 1974)

Hydride transfer reactions involving carbon-hydrogen bonds, as represented by the equation below, have been known for many years. Typical examples of this type are: the Meerwein-Ponndorf-Verley reduction[1] (Y-Z = -O-Al), reactions of

certain Grignard reagents with sterically hindered ketones[2] (Y-Z = -C-MgX), reactions of triethylaluminium with ketones[3] (Y-Z = $-CH_2Al$). However, analogous reaction involving metal amides (Y-Z = -N-M) has not yet been reported, despite the fact that alkoxides and amides, ketones and imines, have many properties in common. In connection with other work in our laboratory, we have undertaken such an investigation and wish to report our results herein. The amides studied were prepared from N-benzylaniline, N-ethylaniline, N-methylaniline and diisopropylamine by treatment with phenyllithium, and benzophenone was chosen as the substrate to avoid complications arising from enolization.

Addition of benzophenone to an etheral solution of an amide brought about the immediate development of an intense violet colour[4], which slowly faded to pale pink upon stirring or heating, with concurrent precipitation of the lithium salt of benzhydrol. Gas chromatographic analysis, after acid workup, revealed that reduction had occurred in each experiment, though to varying extent. Also there appears little correlation between reactivity and basicity of the amides: diisopropylamide, the most basic, and N-benzylanilide, the least basic, are of comparable reactivity (see Table).

Table

Reduction of Benzophenone by Lithium Amides

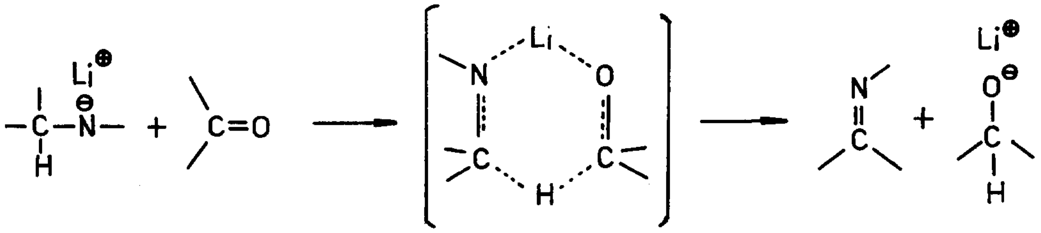
Amide	Amide:Ketone	Temp(°C)	Time	Product Ratio[a] Ketone	Product Ratio[a] Alcohol
$PhCH_2$-N-Ph	1 : 1	24-26	1 hr	50	50
	4 : 1	24-26	1 hr	48.5	51.5
	1 : 1	reflux	3 hr	8.7	91.3
	1.5: 1	reflux	3 hr	6	94
Et-N-Ph[b]	1 : 1	24-26	1 hr	84.8	15.2
	4 : 1	24-26	1 hr	62	38
	5 : 1	24-26	1 hr	63	37
CH_3-N-Ph	1 : 1	24-26	2 hr	89	11
	4 : 1	24-26	2 hr	86	14
	1 : 1	reflux	5 hr	9	91
$(isoPr)_2N$	1 : 1	24-26	2 hr	30	70
	2.5: 1	24-26	2 hr	26	74
	2.5: 1	reflux	3 hr	3	97
	2 : 1	reflux	3 hr	8	92

---

[a] Recovery of materials, with the exception of the experiments using N-ethylanilide, was over 80% in each case. Product ratios were based on recovered materials.

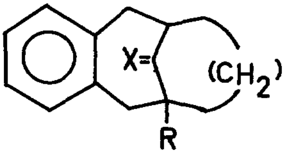
[b] The presence of condensation product (see text) complicated material balance.

The above observations are in accord with a mechanism, similar to that of the Meerwein-Ponndorf-Verley reduction, wherein the amide and benzophenone form an intensely coloured complex which slowly decomposes to the final products via a cyclic transition state. The rate of reaction is therefore dependent on the stability of the complex and that of the azomethine (or imine) to be generated. Since N-benzylanilide yields N-benzalanilide, the comparatively most stable azomethine, it should be the most reactive among the four amides.

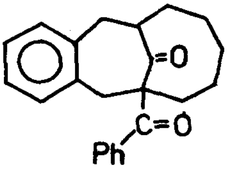


Supports for the proposed mechanism are readily available from detailed analyses of the reaction products of two of the amides. In the case of N-benzylanilide, N-benzalaniline and benzhydrol were found in equimolar amounts proving the stoichiometry of the reaction. In all the experiments involving N-ethylanilide, -phenylcinnamaldehyde was isolated as the sodium bisulfite adduct in as much as 53% yield. The obtention of -phenylcinnamaldehyde, seen as the condensation product of benzophenone and the anion of N-ethylideneaniline, affords an one-step alternative to the synthesis developed by Wittig and coworkers[5].

In order to ascertain that hydride transfer from amides to non-enolizable ketones is a general phenomenon, we treated a series of bicyclic ketones with lithium diisopropylamide. The ketones[6] (1a, 2a, and 3a), prepared in 70-75% yield by decarboxylation of their bridgehead carboxylic acids (1b, 2b, and 3b) in refluxing triglyme (4, 6, and 8 hr respectively), may be regarded as enolizable by virtue of the mode of their generation. Mixing ketone 1a with the amide led to an instantanous reaction giving an insoluble white solid. Addition of benzoyl chloride afforded the 1,3-diketone, 4. On the other hand, there was no precipitation in the reactions of ketones 2a and 3a, and quenching with benzoyl chloride gave the benzoates of 2c and 3c. Quenching with water in place of benzoyl chloride gave 2c and 3c in good yields.



1 n=3 a X=O, R=H.
2 n=2 b X=O. R=COOH.
3 n=1 c X=H,OH, R=H.



A couple of aspects of the above experiments deserve further comments. First, in the reaction of 2a, or 3a, only one epimeric alcohol was isolated, which is identical to the one obtained by reduction with lithium tris-t-butoxy-aluminium hydride. Second, the demarcation between the behaviours of 1a and 2a, sharply reflecting the difference in enolizability, suggests that this reaction constitutes a possibly better criterion for enolizability than thermal decarboxylation. Wiseman and coworkers[7] have related the stability of bicyclic structures incorporating bridgehead double bonds to that of trans-cycloalkenes, and have shown that those corresponding to trans-cyclooctene are stable while those corresponding to trans-cycloheptene are not. Accordingly the smooth abstraction of the bridgehead proton from 1a and the failure in 2a may be expected because the resulting enolate of the former relates to trans-cyclooctene, and that of the latter to trans-cycloheptene. Thus the amide reaction offers a simple test for the stability of these bridgehead olefins without the actual undertaking of their syntheses.

We wish to thank the Chinese University of Hong Kong for financial support.

Notes and References

(1) A.L. Wilds, Organic Reactions, 2, 178 (1944).

(2) See for example F.C. Whitmore and R.S. George, J.Am.Chem.Soc., 64, 1239 (1942).

(3) G.E. Coates, M.L.H. Green, P. Powell, and K. Wade, "Principles of Organometallic Chemistry", Methuen & Co. Ltd., 1971, p 108.

(4) Colour development was not observed with lithium diisopropylamide in this way. However, reverse addition without stirring gave the same colour which faded with diffusion.

(5) G. Wittig and A. Hesse, Organic Syntheses, 50, 66 (1970).

(6) All new compounds reported gave the correct elemental analyses and exhibited the expected spectral characteristics.

(7) J.R. Wiseman and W.A. Pletcher, J.Am.Chem.Soc., 92, 956 (1970); J.R. Wiseman and J.A. Chong, ibid, 91, 7775 (1969).