Tetrahedron Letters No.4, pp. 293-297, 1967. Pergamon Press Ltd. Printed in Great Britain.

A NOVEL REACTION OF 4-DICHLOROMETHYL-4-METHYL-2,5-CYCLOHEXADIEN-1-ONE

K. Nagarajan and A. Venkateswarlu

CIBA Research Centre, Goregaon, Bombay 63

(Received 21 November 1966)

A recent communication[1] describing the formation of diethyl p-tolylphosphate by the action of triethylphosphite on 4-methyl-4-tribromomethyl-2,5-cyclohexadien-1-one warrants a disclosure of our novel finding regarding the behaviour of 4-dichloromethyl-4-methyl-2, 5-cyclohexadien-1-one (I)[2] towards secondary bases. The dienone I forms the normal carbonyl derivatives with semicarbazide and p-bromo-and p-nitrophenylhydrazines[2]; likewise with hydroxylamine, the expected oxime is formed, which undergoes ring expansion when treated with sodium hydroxide to 4-methyltropone oxime[3]. The action of sodium methoxide on I leads to 2-hydroxy-5-methylbenzaldehyde in poor yield[4]. Anionic reagents like methylmagnesiumhalides add normally to the carbonyl group of I[2], whereas acetone dicarboxylic ester adds to I in the presence of alkoxide, in Michael fashion[5]. We wish to report here an interesting aromatisation reaction of I brought about by secondary amines.

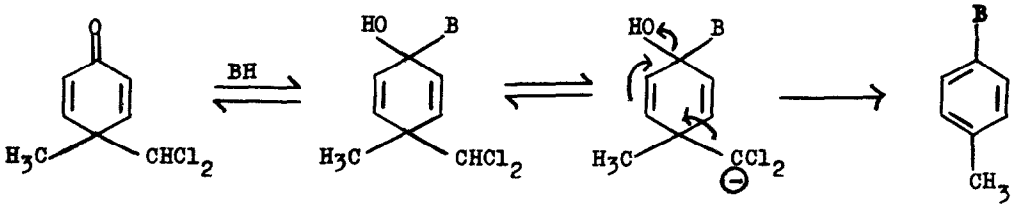
Upon treatment of I with 4 molar equivalents of morpholine at 90-100°C, a sudden exothermic reaction set in. After being heated for 2 hours, the mixture was treated with ether and morpholine hydrochloride (~ 2 equivalents) was filtered off. The filtrate was worked up conventionally to give as the basic

---

Contribution No. 85 from CIBA Research Centre, Bombay 63.

product a 90% yield of crude N-(p-tolyl) morpholine (II: B=morpholino). Crystallization from hexane afforded the analytically pure substance (51%), m.p. 50-53° (lit.[6], m.p. 51°). Pyrrolidine and the dienone I underwent a similar reaction to yield N-(p-tolyl)-pyrrolidine, characterized as the picrate, m.p. 110-111° (lit.[7], m.p. 111°); N-methylpiperazine and piperidine did not react with I easily and the mixture was heated on the water bath for 5 hours. N-(p-Tolyl)piperidine thus obtained was converted to the hydrochloride and identified with a sample obtained by cycloalkylation of p-toluidine with pentamethylenedibromide[8]. N-(p-Tolyl)-N'-methylpiperazine was likewise identical with a sample prepared by catalytic reductive methylation of N-p-tolylpiperazine. The accompanying table summarises the data on these products.

The reaction probably occurs through the following mechanism, the dichloromethyl group leaving as dichlorocarbene.



I II

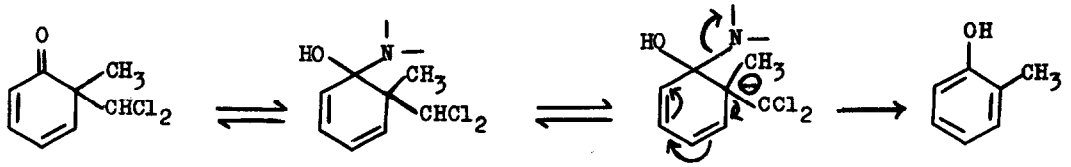
Subsequent reaction of the carbene with morpholine would result in the formation of morpholine hydrochloride. The fate of the carbene carbon atom was not ascertained. It ended up probably as N-formylmorpholine and was lost as formic acid in the acid treatment for separation of the basic products of the reaction.

The IR spectrum of a cold solution of I and morpholine in $CHCl_3$ showed over a period of time, no decrease in the intensity of the carbonyl peak at 1660 cm^{-1}, nor a new one to correspond to a saturated carbonyl. This would imply that there is negligible addition of the secondary amine to the double band adjacent to the carbonyl and also that the attack at the carbonyl carbon needs elevated temperatures. Diethylamine with a greater steric demand would be expected to react with I by the mechanism shown less readily than the cyclic

bases. In fact even after 20 hrs. reflux of I with a four-fold excess of diethylamine, 80% of the dienone was recovered unchanged; the expected base was also formed to the extent of 19% (90% based on the dienone reacted) and characterized as the picrate, m.p. 109-111° (lit.[9], m.p. 110°).

Our ideas on the course of the reaction and the results obtained prompted us to study two other reactions. Firstly it was hoped that reaction of p-cresol with chloroform and morpholine would lead to N-(p-tolyl) morpholine straightaway, but this was not realized. Secondly it was considered likely that the poor yields of I from the action of chloroform and alkali on p-cresol may be due to the operation of a reaction of the type we had encountered for I with secondary amines. I would then be transformed back to p-cresol and thence irreversibly to 2-hydroxy-5-methylbenzaldehyde, the 'normal' product of the Riemer-Tiemann reaction. However after being heated with a 5 molar excess of NaOH in aqueous dioxane at 80-90° for 4 hrs., I was recovered in 80% yield and only a trace of p-cresol was detectable in the phenolic products of the reaction. It seems therefore that in the initial step of the mechanistic sequence depicted (addition of OH^- to the carbonyl group), the equilibrium must lie far in favour of the dienone.

In order to amplify our study, the behaviour of the allied 6-dichloromethyl-6-methyl-2, 4-cyclohexadien-1-one(III)[1] towards secondary bases was also studied. From the reaction of III with N-methyl-piperazine at 70° for 5 hrs., very little basic material was got, while the neutral product was resinous. Treatment of III with 4 molar equivalents of morpholine at room temperature for 8 days led to 34% recovery of III. There was again very little basic product, but o-cresol was isolable as the phenolic product in 60% yield. The result would be best explained by the mechanism postulated below.



III IV

In the last step, instead of hydroxide ion being lost, the ejection of morpholine and loss of dichlorocarbene could lead to o-cresol. This difference between I and III may be due to either IV having the departing group in the preferred geometry or to the propensity of such groups to leave from IV as would lead to a product having lesser ortho interactions.

Acknowledgment : Our thanks are due to Dr. T.R. Govindachari for his interest in this work and to Dr. S.Selvavinayakam and associates for analytical and spectral data.

REFERENCES

1. B. Miller, J.Amer.Chem.Soc., 88, 1841 (1966).

2. K.V. Auwers and G.Keil, Ber., 35, 4207 (1902); 36, 1861 (1903).

3. J.Schreiber, M.Pessaro, W.Leimgruber and A.Eschenmoser, Helv.Chim Acta, 41, 2103 (1958).

4. J.Leitch, J.Org.chem., 27, 1081 (1962).

5. H.Stetter and J.Mayer., Chem.Ber., 92, 2664 (1959).

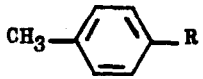
6. L.H.Cretcher and W.H. Pittenger, J.Amer.Chem.Soc., 47, 163 (1925).

7. Yu. K.Yur'ev and G.A.Minkina, J.Gen.Chem. (U.S.S.R.), 7, 2945 (1937).

8. R.Huisgen and J.Sauer, Chem.Ber., 91, 1453 (1958).

9. H.A. Fahim and A.M. Fleifel, J.Chem.Soc., 1951, 2761.

TABLE



R	Yield %		m.p.°C	Molecular formula	Analysis					
					Calcd %			Found %		
	Crude	Purified			C	H	N	C	H	N
N-morpholino	90	51	50–53	$C_{11}H_{15}NO$	74.54	8.53	7.90	74.80	8.76	8.07
N-pyrrolidino	87	33 (picrate)	110–111	$C_{17}H_{18}N_4O_7$	52.30	4.65	14.35	52.67	4.9	14.29
N-piperidino	69	55 HCl	208–211	$C_{12}H_{18}ClN\ \frac{1}{2}H_2O$	65.30	8.67	6.34	66.01	8.43	6.98
N-(N'-methyl)-piperazino	-	90	72–73	$C_{12}H_{18}N_2$	75.74	9.54	14.72	75.82	9.25	14.81
N-diethyl-amino	19	9 (picrate)	109–111	$C_{17}H_{20}N_4O_7$	52.04	5.14	14.28	52.17	5.30	14.59