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ON THE SYNTHESIS OF α-DI-(METHYLMERCAPTO)-METHYLENE DERIVATIVES OF SYMMETRICAL KETONES

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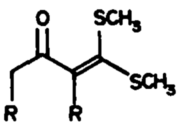
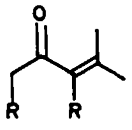
Abstract—The generation of synthetic intermediates α-di-(methylmercapto)-methylene ketones **1** has been optimized. Selection of the best base/solvent system for quantitative formation of **1** is justified.

Corey and Chen reported the use of the lithium salt of 4-methyl-2,6-di-t-butylphenol (LDP) in ether, for the preparation of α-di-(methylmercapto)-methylene ketones (**1**) which are useful intermediates in the synthesis of enones (**2**) and β-trisubstituted ketones (**3**).[1]



1



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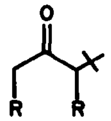

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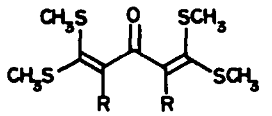

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The preparation of derivatives of **1** related to cyclohexanone and 4-t-butylcyclohexanone is reported. When the procedure described by Corey was followed (entries 1 and 2, Table 1) considerable amounts of **4** were obtained together with the desired derivatives of **1**.

RESULTS AND DISCUSSION

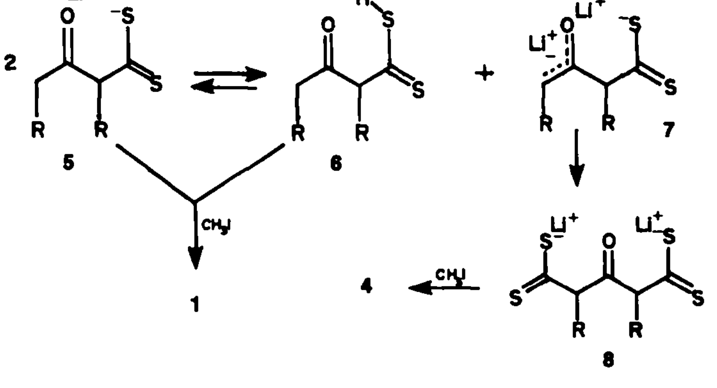
Intermediates like these had already been described before Corey's work, although they had only been isolated in low yields and under conditions which do not guarantee the specificity of the reaction.[2] The conditions established by Corey made it impossible to minimise the formation of **4**, even when LDP/ketone ratios less than two were used (entry 3, Table 1). In spite of the deficiency of base, acceptable conversions were obtained.

These results may be a consequence of the acid-base equilibrium of the intermediate (**5**) or its tautomeric forms, for only one base equivalent is required. This is summarised in Scheme 1.

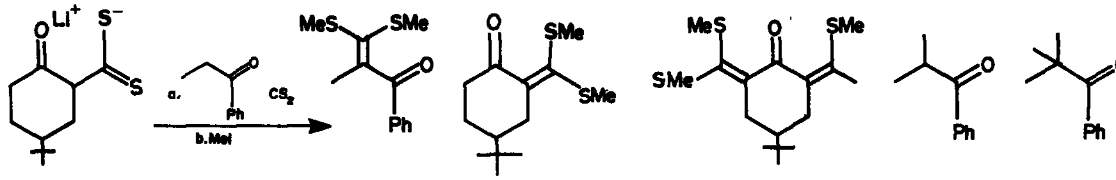
The intermediate species **7**, with an excess of CS_2, can form the bis-dithiosalt **8**, which by treatment with methyl iodide would give rise to **4**. **5** and **6** are nucleophilic species which on methylation give **1**.

In order to confirm this hypothesis, propiophenone and CS_2 were treated with intermediate **7**, which had been obtained from 4-t-butylcyclohexanone and 0.25 equiv of lithiumdiisopropylamide (LDA) and 1 equiv of CS_2 in THF. Treatment of the mixture with excess methyl iodide afforded **10**, **11** and traces of **12** together with the methylation and dimethylation products of propiophenone (Scheme 2).

The addition product of LDA to CS_2 was not observed under these conditions. According to this, intermediate **9** acted as base in the reaction in which it was formed. The use of LDA in this and following experiments (entries 4–7, Table 1) was more suitable for practical purposes than that of LDP owing to the greater reactivity of the former and easier separation of the by-products. In any case, experiment 4—Table 1 showed that the results



Scheme 1.



9 10 7% 11 55% 12 <2% 27% 11%

Scheme 2.

obtained do not vary considerably from one system to the other.

Since the formation of 4 seemed to depend on the stability of intermediate 7, an attempt was made to make the latter more unstable by increasing the solvating capacity of the solvent (HMPT > THF > Et_2O). Thus, with the LDA system, when the solvent used was THF the ratio 1:4 was greatly modified (entry 5, Table 1) and the conversion was very good. Under these same conditions, the use of HMPT prevented the formation of 4 even though the conversion was lower due to the fact that CS_2 reacted with HMPT and LDA (entry 6, Table 1). However if an excess of base and CS_2 was used with LDA and HMPT, the conversion was similar to that of entry 5. The absence of 4 was again confirmed (entry 7, Table 1).

By changing the nature of the base (NaH vs LDA) and consequently that of the metallic cation, considerable amounts of 4 were formed (entries 8 and 9, Table 1). However, if the excess of base was reduced by the addition of stoichiometric quantities of water (these conditions are compatible with the subsequent methylation using an excess of the reactive), the formation of 4 did not take place in HMPT (entry 10, Table 1). Therefore in this solvent, intermediate 7 was not formed. However, excess of NaH with 1 in the presence of CS_2 and MeI gave rise to 4 (entry 9).

When the reaction was carried out in THF under similar conditions (entry 11, Table 1), the formation of 4 in large quantities was observed. This was probably due to the different hardness of ion Na^+ vs Li^+ which caused a critical displacement of the solvating capacity towards HMPT.

According to this, the system LDA/HMPT (entries 6 and 7, Table 1) as well as the conditions established in entry 10, solved the problem of disubstitution in the synthesis of α-di-(methylmercapto)-methylene derivatives of ketones. Likewise other conditions (e.g. entry 5, Table 1) can be applied provided the separation of 1 and 4 can be satisfactorily achieved.

EXPERIMENTAL

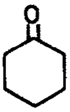
The IR spectra were recorded on a Perkin–Elmer 257 spectrophotometer. The NMR spectra were run on a Varian T-60A spectrometer using TMS as internal standard and the values are expressed in the δ scale. The mass spectra were obtained with a Varian MAT-711 mass spectrometer.

Table 1. Experimental conditions and results observed in the formation of 1 and 4 derivatives of cyclohexanone and 4-t-butylcyclohexanone

No.	Ketone	Base/solvent	B/K/CS	1/4[a]	% Conversion[b]	Other Products[c]
1[d]	4-t-Bu-cyclohexanone	LDP/Et_2O	2 /1/5.3	60/40	98	e
2[d]	Cyclohexanone	LDP/Et_2O	2 /1/5.3	73/27	97	e
3[d]	"	LDP/Et_2O	1 /1/5.3	66/34	81	e
4	4-t-Bu-cyclohexanone	LDA/Et_2O	2 /1/5.3	75/25	78	48%[f]
5	"	LDA/THF	1 /1/1.2	96/4	92	-
6	"	LDA/HMPT	1 /1/1.2	100/-	82	4%[g] 12%[f]
7	"	LDA/HMPT	2 /1/5.3	100/-	93	3%[g] 31%[f]
8	"	NaH/THF	1.6/1/1.6	23/76	91	-
9	"	NaH/HMPT	2 /1/1.2	67/33	78	-
10[h]	"	NaH/HMPT	3.8/1/3.8	100/-	92	9%[g]
11[h]	"	NaH/THF	3 /1/3.0	15/85	98	-

(a) Analysis by ^{1}HNMR. (b) Evaluated by GLC, L: 2m;ϕ:1/8 inc. Programmed temperature: 120°-220° at 10°/min. in a Hewlett-Packard 5750 instrument. Compound 4 is not eluted using these and other GLC conditions. (c) In none of these reactions, were detected products of α-methylation. (d) The experimental conditions established by Corey (1) were followed. (e) 4-methyl-2,6-di-t-buthylphenol was recovered. (f) i-Pr_2N-CS-SCH_3. (g) Me_2N-CS-SCH_3. f) and g) were easily separated by chromatography on silica gel using CH_2Cl_2 as solvent. Were identified by comparison with pure samples. (h) Addition of CH_3I is carried out after removing the excess of base.

Table 2. Spectroscopic characteristics of 1 and 4 derivatives of cyclohexanone and 4-t-butylcyclohexanone

Ketone	derivative	IR (ν_{CO}) cm^{-1}	EM $M^{+\cdot}$ (%)	^{1}HNMR*
	1	1685	202 (46.5)	1.82 (m, 4H) 2.30 (m, 2H) 2.32 (s, 3H) 2.35 (s, 3H) 2.85 (m, 2H).
	4	1665	306 (11.5)	1.73 (m, 2H, J:6Hz.) 2.37 (s, 12H) 2.80 (t, 4H, J:6Hz.).
	1	1660	258 (65.4)	0.93 (2, 9H) 1.2-2.47 (m, 6H) 2.23 (s, 3H) 2.30 (s, 3H) 3.20 (m, 1H).
	4	1665	362 (34.5)	1,00 (s, 9H) 1.13-2.47 (m, 3H) 2.30 (s, 6H) 2.33 (s, 6H) 3.03 (dd, 2H, J=4Hz, 16Hz).

(*) δ (ppm) CCl_4

α-Di-(methylmercapto)-methylene ketones

General procedure. A soln of 0.01 mol ketone in 5 ml solvent was added to 30 ml of the base soln (LDA or NaH; for number of moles see Table 1), at room temp. (For entries 4,5—Table 1—temps kept below −20°). After 16 hr (4 hr for entries 4 and 7—Table 1—) CS_2 was added in the quantities specified in Table 1. MeI was then added and the mixture was stirred for 8 hr at 25°. The mixture was then diluted with water and diethyl ether. The organic layer was separated and washed with HCl (5%), H_2O, dried over $MgSO_4$ and concentrated.

The crude mixtures were applied to tlc plates and eluted with CH_2Cl_2 to give a main fraction consisting of a mixture of 1 and 4. These were analysed by ^{1}HNMR upon S-CH_3 signals, which were differentiated by the addition of Eu(fod)$_3$.

Pure samples of 1 and 4 were obtained by preparative tlc (silica gel) using CH_2Cl_2 in consecutive elutions. The spectroscopic data of these products are summarised in Table 2.

REFERENCES

[1] E. J. Corey and R. H. K. Chen, *Tetrahedron Letters* 3817 (1973).
[2] A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.* 1938 (1959); *Ibid.* 2182 (1962); *Ibid.* 2187 (1962); *Ibid.* 2194 (1962); I. Shahak and Y. Sasson, *Tetrahedron Letters* 4207 (1973); S. M. S. Chauhan and H. Junjappa, *Tetrahedron* 32, 1779 (1976); *Ibid.* 32, 1911 (1976).