

## A VERY EFFICIENT PREPARATION OF 1,2-DIKETONES

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Summary : Treatment of  $\alpha$ -thiomethylketones with  $\text{CuCl}_2\text{-CuO}$  in aqueous acetone affords the corresponding 1,2-dicarbonyl compounds.

We have previously shown<sup>1</sup> that condensation of benzyne on 1,2-diketone monoketal enolates led to the formation of benzocyclobutenols in good to excellent yields. These compounds are of potential interest in the synthesis of polycyclic derivatives<sup>2</sup> as well as in medicinal chemistry.<sup>3</sup>

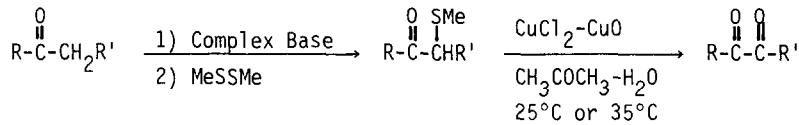
Large scale preparation of these alcohols are only limited by the large scale obtention of 1,2-diketone monoketals. The simplest way in obtaining these starting substrates lies in starting from the corresponding monoketones.

There are a number of reports dealing with the formation of 1,2-diketones monoketals.<sup>4</sup> However such methods are somewhat limited by the expensiveness and/or the toxicity of the reagents used. So we decided to turn towards a two step synthesis including the preparation of 1,2-diketones followed by monoketalisation.

The main difficulty with this strategy was the preparation of 1,2-diketones. Though numerous synthesis of such derivatives are described<sup>5</sup> they are far from being without inconvenience (see for ex.<sup>6</sup>).

Our attention was attracted by an interesting report of Gassman and coll.<sup>7</sup> showing that oxidation of the methine carbon in the 3 position of the 3-methylthioxindoles with N-chlorosuccinimide followed by hydrolysis of the chlorinated intermediate, provides a simple route to isatins. Indeed we previously showed<sup>8</sup> that methylthioketones can be easily obtained by  $\alpha$ -methylthiolation of ketones using the very unexpensive Complex Bases.<sup>9</sup> On the other hand it is well known<sup>10</sup> that  $\alpha$ -chloroketones can be obtained from simple ketones using  $\text{CuCl}_2$  as chlorinating agent. Finally copper salts are very efficient reagents in the hydrolysis of

thioderivatives of carbonyl compounds.<sup>11</sup> These observations led us to think of that under appropriate conditions, 1,2-diketones could be obtained in one pot starting from  $\alpha$ -methylthio ketones. This hypothesis was completely verified and 1,2-diketones were easily obtained by the two steps reaction given in the Scheme.



It is noteworthy that oxidation of the methylthio ketone was very fast even at room temperature. The diketones were obtained in good to very good yields (see Table).

Curiously the ten membered ring led to the desired product accompanied by a rather large amount of the corresponding monomethylthio enol ether. For the present time we have no explanation for this anomalous behaviour.

From some unreported experiments it appears that no oxidation took place in the presence of CuO alone, and that CuCl<sub>2</sub> cannot be used in catalytic amount. Moreover even under stoichiometric conditions, CuCl<sub>2</sub> alone led to a complex mixture of products.

Investigations are currently conducted in our laboratory in order to establish the actual mechanism of these oxidations and to extend their application field.

#### General procedure :

A mixture of the  $\alpha$ -methylthioketone (25 mmol), copper(II) chloride (50 mmol), copper(II) oxide (100 mmol) and aqueous 1 % acetone (100 ml) is stirred at the temperature and for the time indicated in the Table. (Disappearance of the ketone is monitored by G.L.C. or T.L.C.). The precipitate is filtered off and the filtrate is concentrated under reduced pressure. Ether is added to the residue and the resulting precipitate is filtered off. The filtrate is chromatographed or distilled to give the corresponding 1,2-dicarbonyl compound.

#### Acknowledgement :

M.C.C. acknowledges INSERM for financial support.

TABLE : Two-step conversion of ketones to 1,2-dicarbonyl compounds

Starting ketone	$\alpha$ -methylthioketone		Reaction temperature	1,2-dicarbonyl compound	
	n	Yield (%)	°C ; time, h	Yield (%)	
	n = 2	1 <sup>a</sup>	1 <sup>a</sup> (87)	35 ; 0.5	1 <sup>b</sup> <sup>c,d</sup> (60)
	n = 3	2 <sup>a</sup>	2 <sup>a</sup> (87)	35 ; 0.5	2 <sup>b</sup> <sup>e</sup> (80)
	n = 4	3 <sup>a</sup>	3 <sup>a</sup> (87)	35 ; 1	3 <sup>b</sup> <sup>e</sup> (70)
	n = 5	4 <sup>a</sup>	4 <sup>a</sup> (87)	35 ; 0.5	4 <sup>b</sup> <sup>e</sup> (87)
	n = 6	5 <sup>a</sup>	5 <sup>a</sup> (77)	35 ; 1	5 <sup>b</sup> <sup>c,d</sup> (43)
	n = 7	6 <sup>a</sup>	6 <sup>a</sup> (90)	25 ; 0.25	6 <sup>b</sup> <sup>c,f</sup> (45)
	n = 8	7 <sup>a</sup>	7 <sup>a</sup> (87)	25 ; 2	7 <sup>b</sup> <sup>c</sup> (80)
	n = 9	8 <sup>a</sup>	8 <sup>a</sup> (95)	35 ; 4	8 <sup>b</sup> <sup>c</sup> (80)
		9 <sup>a</sup>	9 <sup>a</sup> (87)	35 ; 0.5	9 <sup>b</sup> <sup>g</sup> (63)

a) Prepared as previously described<sup>8</sup>

b) Synthesized by the same method as for 1a-4a

c) Identified by IR and  $^1\text{H}$  NMR spectra and by melting point of its dioxime  $^{12}$

d) No attempt was made to optimize yields

e) Identified by comparison with authentic samples<sup>13</sup>

f) Formation of corresponding monomethylthioenol ether in 50 % yield characterized by IR and  $^1\text{H}$  NMR spectra

g) Isolated as phenylglyoxal monohydrate<sup>14</sup>.

REFERENCES

- 1) Carré, M.C. ; Grégoire, B. ; Caubère, P., *J. Org. Chem.* 1984, 49, 2050.
- 2) Kametani, T. ; Nemoto, H., *Tetrahedron* 1981, 37, 3 ; Kametani, T. ; Honda, T. ; Matsumoto, H. ; Fukumoto, K., *J. Chem. Soc., Perkin Trans. 1*, 1981, 1383 ; Kametani, T. ; Honda, T. ; Shiratori, Y. ; Matsumoto, H. ; Fukumoto, K., *Ibid.* 1981, 1386 ; Franck, R.W. ; John, T.V. ; Olejniczak, K. ; Blount, J.F., *J. Am. Chem. Soc.* 1982, 104, 1106 ; Stevens, R.V. ; Bisacchi, G.S., *J. Org. Chem.* 1982, 47, 2393 ; Stevens, R.V. ; Bisacchi, G.S., *Ibid.* 1982, 47, 2396.
- 3) Carré, M.C. ; Caubère, P. ; Trockle, G. ; Jacque, M., *Eur. J. Med. Chem.* 1977, 12, 577 ; Trockle, G. ; Catau, G. ; Barberi, C. ; Jacque, M. ; Carré, M.C. ; Caubère, P., *Life Sci.* 1981, 28, 23 ; Carré, M.C. ; Youlassani, A. ; Caubère, P. ; Saint-Aubin-Floch, A. ; Blanc, M. ; Advenier, C., *J. Med. Chem.* 1984, 27, 792.
- 4) Nagao, Y. ; Kaneko, K. ; Fujita, E., *Tetrahedron Lett.* 1978, 19, 4115 ; Nagao, Y. ; Kaneko, K. ; Kawabata, K. ; Fujita, E., *Tetrahedron Lett.* 1978, 19, 5021.
- 5) Trost, B.M. ; Massiot, G.S., *J. Am. Chem. Soc.* 1977, 99, 4405 ; Rabjohn, N., *Org. React.* 1977, 24, 261 ; Rao, D.V. ; Stuber, F.A. ; Ulrich, H., *J. Org. Chem.* 1979, 44, 456.
- 6) Tsunetsugu, J. ; Sugahara, M. ; Heima, K. ; Ogawa, Y. ; Kasugi, M. ; Sato, M. ; Ebine, S., *J. Chem. Soc. Perkin Trans. I* 1983, 1983.
- 7) Gassman, P.G. ; Cue, B.W. Jr. ; Luh, T.Y., *J. Org. Chem.* 1977, 42, 1344.
- 8) Carré, M.C. ; Ndebeka, G. ; Riondel, A. ; Bourgasser, P. ; Caubère, P., *Tetrahedron Lett.* 1984, 25, 1551.
- 9) Caubère, P., *Acc. Chem. Res.* 1974, 7, 301 ; *Top. Curr. Chem.* 1978, 73, 50 ; *Crown Ethers and Phase Transfer Catalysis in Polymer Science*, Mathias, L.J. and Carraher, C.E., Plenum Publishing Corporation, 1984, 139.
- 10) Kosower, E.M. ; Cole, W.J. ; Wu, G.S. ; Cardy, D.E. ; Meisters, G., *J. Org. Chem.* 1963, 28, 630.
- 11) Gröbel, B.T. ; Seebach, D., *Synthesis*, 1977, 357 and ref. cited therein.
- 12) Cumper, C.W.N. ; Leton, G.B. ; Vogel, A.I., *J. Chem. Soc.* 1965, 2067.
- 13) Hach, C.C. ; Banks, C.V. ; Diehl, H. "Organic Syntheses", Wiley : New York, 1963 ; *Collect. Vol. IV*, p. 229 ; Vandermaar, R.W. ; Voter, R.C. ; Banks, C.V., *J. Org. Chem.* 1949, 14, 836 ; Bauer, D.P. ; Macomber, R.S., *J. Org. Chem.* 1975, 40, 1990.
- 14) Vogel's "Textbook of Practical Organic Chemistry", 4th ed., Longman London and New York, 1978, p. 440.

(Received in France 4 April 1985)