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TRAPPING THE INTERMEDIATE INVOLVED IN THE INTRAMOLECULAR CYCLISATION OF CYCLOPROPYL KETONES. A CONVENIENT PREPARATION OF OPEN-CHAIN γ-HYDROXY KETONES.

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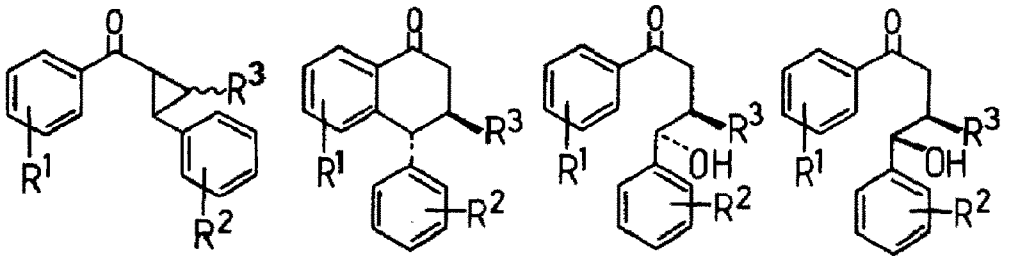
The concerted mechanism for the stannic chloride catalysed cyclisation of aryl cyclopropyl ketones is disproved by trapping the intermediate. The reaction provides a facile route to γ-hydroxyketones.

Rigid cyclopropyl ketones were converted to benzodecalones by Stork[1] using Lewis acid catalysis. The non-rigid analogues were found by Grieco[2] to undergo similar reactions. Both authors concluded that cyclopropane cleavage occurred with aryl participation in a concerted mechanism. We have shown[3] that Lewis acids also catalyse the intramolecular cyclisation of aryl cyclopropyl ketones e.g. (1b) to 1-aryl tetralones (2b) and have applied this reaction successfully[4] to the synthesis of the known[5] podophyllotoxin precursor (21). However, the side-products - the γ-hydroxybutanones (3) and (4) - were occasionally formed[3] under the conditions ($SnCl_4$, CH_2Cl_2 or C_6H_6, room temp.). This result seriously limited the synthetic potential of this cyclisation route to 1-aryltetralones and also in the light of Stork's[1] and Grieco's[2] conclusion, made the mechanism unclear.

We now find that when $SnCl_4$ is used with nitromethane as solvent[6] the carbinols (3) and



(1) (2) (3) (4)

	R^1	R^2	R^3		R^1	R^2	R^3
a	H	H	H	g	3-OMe	4-OMe	CO_2Et
b	3-OMe	4-OMe	H	h	3,4-$(OMe)_2$	3,4-$(OMe)_2$	CO_2Et
c	4-OMe	4-OMe	H	i	3,4-$(OMe)_2$	3,4-OCH_2O-	CO_2Et
d	4-OMe	3,4-$(OMe)_2$	H	j	3,4-OCH_2O-	3,4-$(OMe)_2$	CO_2Et
e	3,4-$(OMe)_2$	3,4-$(OMe)_2$	H	k	3,4-OCH_2O-	3,4-OCH_2O-	CO_2Et
f	3,4-$(OMe)_2$	3,4-OCH_2O-	H	l	3,4-OCH_2O-	3,4,5-$(OMe)_3$	CO_2Et

TABLE

Stannic Chloride Catalysed Reactions

Entry	Reactant	Conditions[a]		Product (yield, %)[c]		Ratio[d]		
		Temperature (°C)	Time[b]	(2)	(3) + (4)	(3)	:	(4)
1	(1a)	room temp.	30 min.	-	90			
2	"	0°	6 h	-	90			
3	(1b)	0°	5 min	90	trace			
4	"	- 15° → - 20°	20 min	37	50			
5	(1c)	- 15° → - 20°	20 min	-	71			
6	(1d)	room temp./PhH	10 h	-	70			
7	"	- 15° → - 20°	20 min		57[e]			
8	(1e)	room temp./PhH	10 h	15	60			
9	"	0°	35 min	60	30			
10	"	- 15° → - 20°	20 min	55	25			
11	(1f)	room temp./PhH	47 h	35	36			
12	(1g)	room temp.	2 h	90	-			
13	"	0°	5 min	-	90	58	:	42
14	(1h)	room temp./CH_2Cl_2	50 h	27	16			
15	"	room temp.	45 h	90	-			
16	"	0°	50 min	-	85	53	:	47
17	(1i)	room temp.	70 h	80	-			
18	"	room temp.	30 h	(3) : (4) ≃ 1:1[f]				
19	"	0°	75 min	-	85	34	:	66
20	(1j)	room temp.	70 h	62[g]	-			
21	"	0°	50 min	-	88	50	:	50
22	(1k)	room temp.	120 h	70	-			
23	"	room temp.	45 h	58	27			
24	"	0°	75 min.	-	83	40	:	60
25	(1l)	room temp.	120 h	50	39			
26	"	0°	3 h	-	trace			
27	(3f)	room temp.	12 d	55[e]				

[a] All reactions, unless otherwise stated, were carried out in nitromethane. [b] followed by t.l.c. [c] isolated yield. [d] ratio sensitive to work-up, determined by n.m.r. [e] reactant also recovered. [f] not isolated. [g] 1-(3',4'-methylenedioxy), 3-ethoxycarbonyl-6,7-dimethoxy naphalene also isolated (29%).

(4) are obtained exclusively by quenching at low temperature (see entries 2, 5, 7, 13, 16, 19, 21, 24 in Table). The reaction is general and compatable with a wide range of functionality including R^3 = CO_2Et. Since the cyclopropyl ketones (1) are prepared in one step[3,4] from chalcones[7] this result constitutes a short, facile and high yield route to the carbinols (3) and (4) and opens a new approach to 1,4-diarylbutane lignans[8] and 1-arylnaphthalene lignans.[9]

When the reaction times and temperature are increased complete conversion to the tetralones (2)[10] is observed (see entries 3, 12, 15, 17, 20, 22). Cyclisation of (1) is general providing R^1 is activating (see entries 1, 2), although the rate of reaction is noticeably reduced by the ethoxycarbonyl group (compare entries 3 and 4 with 13).[11]

Trapping the intermediate as the carbinols (3) and (4) disproves a concerted mechanism for the conversion of (1) to (2) in all cases, including the most reactive substrates (1b, entry 4) and (1e, entry 9). This result was confirmed by interrupting the cyclisation reactions (see entries 18 and 23) and by the conversion of the combined carbinols (3f) and (4f) to the tetralone (2f) (entry 27). This is the first time that an intermediate from cationic cyclopropane cleavage has been intercepted in the presence of a neighbouring activated aryl group. The cyclisation of (1) to (2) which can be considered a 5-*Endo* cyclisation[12] is non-concerted probably for stereoelectronic reasons. In contrast, both systems investigated by Stork[1] and Grieco[2] involved *Exo*-cyclisation.

Concerning the nature of the intermediate, we suggest a 2,5-diaryl oxacyclopent-1-enyl cation (5)[13] since it is both a well established precursor of γ-hydroxyketones and it accounts for the anomously long life of the intermediate undergoing cyclisation (compare entries 22 and 24).

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6. Both CH_2Cl_2 and C_6H_6 were also used at 0^o but results were less satisfactory. Reactions were heterogeneous and the rates were slower.

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8. R. Stevenson in 'Chemistry of Lignans' Ed. C.B.S. Rao, Andhra Univ. Press, 1978, p. 65.

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10. In all cases when $R^3 = CO_2Et$, the *trans*-isomer only is formed.

11. The relative rates of tetralone formation (compare, for example, entries 1 with 3, 6 with 8, 15 with 20) are consistent with the effects of substituents on the rates of electrophilic substitution, see C. Baddeley, G. Holt, N.H.P. Smith and F.A. Whittaker, Nature, 1951, 168, 368; D.A. Evans, P.A. Cain, and R.Y. Wong, J. Amer. Chem. Soc., 1977, 99, 7083; Z. Horii, M. Tsujiuchi and T. Momose, Tetrahedron Letters, 1969, 1079; idem., J.C.S. Chem. Comm., 1968, 653.

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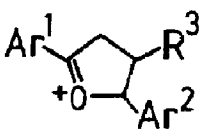
13. The intermediacy of cation (5)  and analogues has been

(5)

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