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Zinc-Promoted Reactions. 8. The Effect of Ring Strain in the Reduction of 1,2-Dibenzoylcycloalkanes

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Abstract: Ring cleavage was the main route in the Zn reduction of **1** in neat AcOH, while selective carbonyl reduction predominated in the presence of LiCl. The less strained **2** underwent only carbonyl reduction with Zn/AcOH. The Clemmensen reduction of both **1** and **2** resulted mainly in acyclic products. The unstrained **3** was fairly resistant towards reduction, and did not undergo ring cleavage.

Trans-1,2-dibenzoyl -cyclopropane and -cyclobutane were reported to smoothly undergo reductive ring cleavage by treatment with zinc in anhydrous solvents (AcOH and EtOH/$ZnCl_2$).[1-3] The mechanism of these reactions, in which the two carbonyls were preserved, was not elucidated.

The Zn-promoted reduction of *trans*-1,2-dibenzoylcyclobutane (**1**), *trans*-1,2-dibenzoylcyclopentane (**2**), and *trans*-1,2-dibenzoylcyclohexane (**3**) was then investigated under different reaction conditions, in order to evaluate the effect of ring strain and stereochemical factors affecting the reductive cleavage.

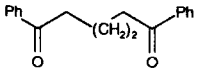
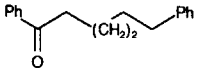
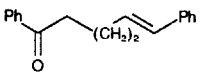
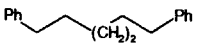
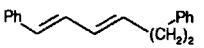
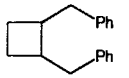
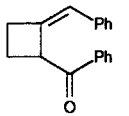
Results and Discussion

The Zn reductions of **1**, **2**, and **3** were studied in neat AcOH, in anhydrous AcOH/LiCl, and according to the Clemmensen procedure (7M HCl). The results are reported in Tables 1-3.

Preliminary experiments proved that in the Zn/EtOH/$ZnCl_2$ system, by contrast with the previous statement,[3] ring cleavage of **1** did not occur in absolute EtOH, a certain amount of H_2O being necessary to promote the reaction. This result suggests that the presence of HCl, clearly deriving from $ZnCl_2$ hydrolysis, is required by the cleavage in EtOH (See Experimental). As for the reduction of **1** in neat AcOH and in 7M HCl, ring cleavage accounted for more than 90% of the reaction, the main product being 1,6-diphenylhexane-1,6-dione (**4**) and 1,6-diphenylhexane (**7**), respectively. Noticeably, a considerable amount of 1,2-dibenzylcyclobutane (**9**) was obtained from **1** in anhydrous AcOH/LiCl.

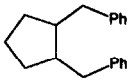
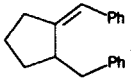
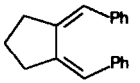
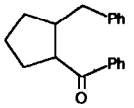
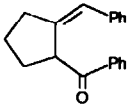
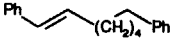
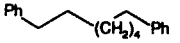
The reductions of cyclopentane and cyclohexane derivatives **2** and **3** were not as clean as those of **1**. In fact, in addition to those reported in Tables 2 and 3, other minor products were always present in the complex reaction mixtures. However, it was clear that no ring cleavage occurred in the reductions of **2** in AcOH, while

Table 1. Product Distribution in the Zn/Hg Reduction of 1.[a]

Products[b]		Reaction System		
		AcOH[c]	AcOH LiCl	7M HCl
	**4**	61 (63)	3	3
	**5**	14 (22)	10	12
	**6**	13 (9)	6	-
	**7**	3 (2)	29	66
	**8**	3 (-)	16	10
	**9**	3 (2)	34	6
	**10**	3 (2)	2	3

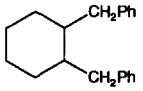
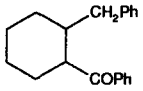
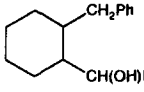
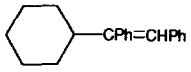
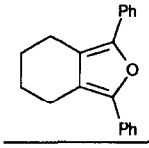
[a]Experimental conditions: 2h at refluxing temperature. Conversion: 100%. [b]Product distributions are in percentage. The stereochemistry of compounds **6**, **8** - **10** has not been established. [c]The data in parenthesis refer to a reaction with non amalgamated zinc, under the same experimental conditions.

Table 2. Main Products in the Zn/Hg Reduction of 2.[a]

Products[b]		Reaction System		
		AcOH	AcOH LiCl	7M HCl
	**11**	32	1	10
	**12**	30	9	-
	**13**	22	39	-
	**14**	-	13	-
	**15**	-	11	-
	**16**	-	-	20
	**17**	-	-	40

[a]Experimental conditions: 2h at refluxing temperature. Conversion: 100%. [b]Product distributions are in percentage. The stereochemistry of compounds **11** - **16** has not been established.

Table 3. Main Products in the Zn/Hg Reduction of 3.[a]

Product[b]		Reaction system				
		AcOH	AcOH LiCl	AcOH HCl_g	AcOH HCl_{aq}	7M HCl
	**18**	-	-	-	20	9
	**19**	17	22	21	16	15
	**20**	5	-	6	-	21
	**21**	13	-	12	23	-
	**22**[c]	2	-	6	31	10
Conversion		32	35	63	100	75

[a]Experimental conditions: 2h at refluxing temperature. [b]Product distributions are in percentage. The stereochemistry of compound **21** has not been established. [c]Isobenzofurane **22** is a side product of a non reductive pathway.

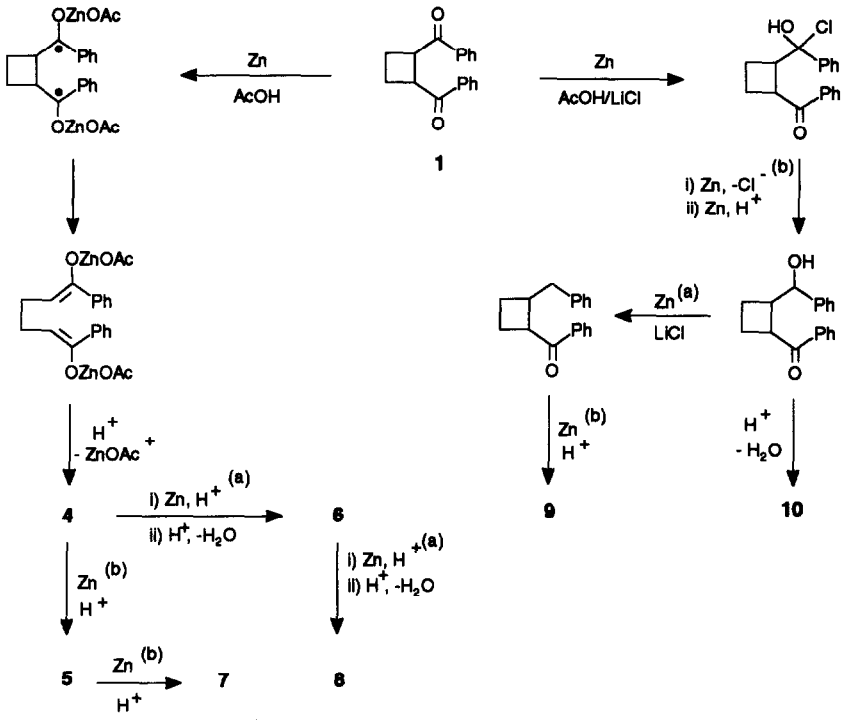
open chain products predominated in 7M HCl.

Cyclohexane derivative **3** was in turn fairly resistant towards reduction. Anyhow, only ring-intact products were observed under any of the selected conditions.

The above results can be discussed in terms of the general mechanism already proposed to explain zinc-promoted reductions of ketonic substrates.[4] According to the Scheme, the reduction of cyclobutane derivative **1** in neat AcOH may proceed through two distinct pathways, both involving single electron transfers (SETs) from the metal to the carbonyl oxygen. However, the pathway leading to open-chain products **4-8** requires that the first two SETs occur at the level of each of the carbonyl groups. Diradical species are essential for the cleavage of the strained cyclobutane ring in neat AcOH. This statement is supported by the different reactivity of benzoylcyclobutane: this monoketone, in fact, afforded only ring intact products under the same experimental conditions that determined ring opening in the case of **1** (See Experimental). The second pathway, instead, requires that differentiated SETs may occur from the metal to the two carbonyls, the monoradical species accounting for the formation of cyclobutane derivatives **9** and **10**. This pathway becomes very important in the reduction in anhydrous AcOH/LiCl, which resulted in considerable amounts of **9**. The role exerted by LiCl may be ascribed to the formation of a HCl mono adduct, as previously proposed for the Zn/AcOH/LiCl reduction of aryl ketones.[5]

The conclusions drawn from the Zn/AcOH reduction of **1** are not entirely valid for its Clemmensen reduction, which afforded mainly 1,6-diphenylhexane. The latter compound was formed through the reduction

Scheme. The Zn Reduction of 1 in AcOH and AcOH/LiCl.



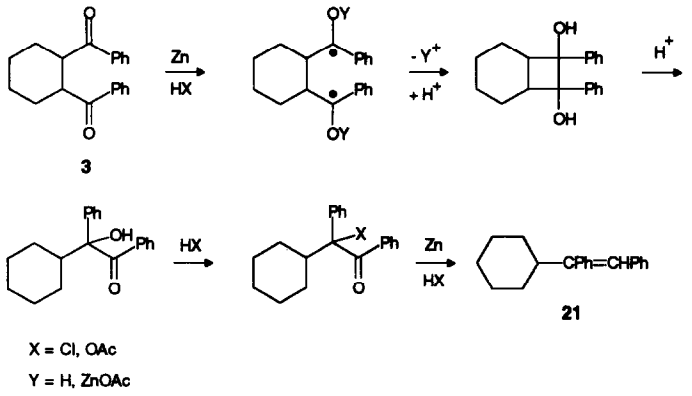
[a]Reaction pathways are in Ref. 5. [b]Reaction pathways are in Ref. 7.

of **4**, that was shown to be fairly resistant towards Zn/AcOH, but it was reduced, mainly to **7**, under the Clemmensen procedure. The same behaviour was founded with 1,4-diphenylbutane-1,4-dione (See Experimental). Indeed, under the more drastic condition (7M HCl), the cyclobutane ring opening might, at least partially, occur through another pathway not involving the diradical species of the Scheme. This view is supported by the finding that the Clemmensen reduction of benzoylcyclobutane afforded some open chain products (See Experimental).

The formation of 1,6-diphenyl-5-hexen-1-one (**6**), 1,6-diphenylhexa-1,3-diene (**8**), and 1-benzoyl-2-benzylidencyclobutane (**10**) can reasonably be due to acid-catalysed dehydration of the corresponding benzylic alcohols, intermediately formed.

By comparing the results obtained with **1**, **2**, and **3** it becomes evident that ring strain is a determinant factor for the reductive cleavage of the cycloalkane ring.[6] In the case of **3**, steric hindrance, in the absence of ring strain, may account for the low yield in the reduction. Indeed, an analogous effect was observed in the reduction of hindered ketones, such as benzopinacolone[7] and pivalophenone.[5]

However, the more interesting result with **3** was the yield of considerable amounts of 1-cyclohexyl-1,2-diphenylethene (**21**). The formation of this alkene, of unknown stereochemistry, involves both the rupture of a σ-bond joining one of the benzoyl substituents and the formation of a new σ-bond between the carbonyl carbons. A possible reaction scheme for the reductive rearrangement leading from **3** to **21** is the following:



The Zn/AcOH reduction of α-haloketones[8] and α-acetoxyketones[9] were already reported.

Experimental Section

The reactions were generally performed with amalgamated zinc. The procedure for the reductions was previously described.[7] GC analyses were carried out with a Carlo Erba HRGC 5300 Mega Series apparatus on 30 m x 0.25 mm i.d. x 0.33 μm SPB-35 column. GC/MS analyses were performed with a VG Quattro mass spectrometer on the same column. ^{1}H NMR spectra were recorded on a Bruker WP-80 spectrometer with $CDCl_3$ as the solvent.

Materials. Anhydrous AcOH was prepared by refluxing (4h) 99.8% AcOH (Merck) with Ac_2O (Merck). Stock solutions of approximately 0.3 M anhydrous HCl in AcOH were prepared by bubbling a HCl gas in the solvent. Compounds **1-4** benzoylcyclobutane and 1,4-diphenylbutane-1,4-dione were prepared according to the literature.[10-15]

Product Distribution Analysis. Identification of the products and their distribution in the crude reaction mixture were accomplished by GLC, NMR, and GC/MS analyses and, when available, by comparison with literature data (**4**,[13] **5**,[16] **6**,[17] **7**,[18] **13**,[19] **16**,[20] **17**,[18] **21**,[21] **22**,[12] 1,4-diphenylbutane,[18] 1,4-diphenyl-1-butene,[22] 1,4-diphenyl-2-butene,[23] 1,4-diphenyl-3-buten-1-one,[17] 2,5-diphenylfurane,[24] benzylidencyclobutane,[25] 1-phenyl-1-pentene,[26]). Mass spectra of the products are given as supplementary material.

Reduction of 1,2-Dibenzoylcyclobutane (1) with Zn/$ZnCl_2$ in EtOH. The reductions were performed using an approximately 1:3:10 molar ratio of substrate, $ZnCl_2$ and zinc. After 2 h at reflux temperature the results were the following: with absolute EtOH, the substrate was recovered unchanged; with EtOH 95 %: 4% **4**; with EtOH 90%: 8% **4**; with EtOH 60 %: 91% **4**, 2% **5**, 1% **6**.

Reduction of 1,4-Diphenylbutane-1,4-dione. The reduction performed with Zn/Hg in neat AcOH for 2h at reflux temperature gave a 22% conversion, the product distribution being: 14% 1,4-diphenyl-1-buten-4-

ol; 6% 1,4-diphenyl-3-buten-1-one; 1% 2,5-diphenylfurane. In the 7M HCl system the product distribution was: 47% 1,4-diphenylbutane; 6% 1,4-diphenyl-1-butene; 8% 1,4-diphenyl-2-butene; 39% 2,5-diphenylfurane.

Reduction of 1,6-Diphenylhexane-1,6-dione (4). The reduction was performed with amalgamated zinc in 7M HCl at the refluxing temperature for 2 h. The products were: 2% **5**, 90% **7**, 8% **8**.

Reduction of Benzoylcyclobutane. The reduction performed with Zn/Hg in neat AcOH for 2 h at reflux temperature gave a 25% conversion, the product distribution being: 24% benzylidenecyclobutane, 1% benzylcyclobutane. In the 7M HCl system the product distribution was: 45% benzylcyclobutane, 12% 1-phenyl-1-pentene, 14% dimer.

Acknowledgements

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References

1 Wenkert, E.; Yoder, J. E. *J. Org. Chem.* **1970**, *35*, 2986-2989.
2 Dekker, J.; Martins, F. J. C.; Kruger, J. A.; Goosen, A. J. *Tetrahedron Lett.* **1974**, 3721-3724.
3 Dekker, J.; Martins, F. J. C.; Kruger, J. A. *Tetrahedron Lett.* **1975**, 2489-2490.
4 Di Vona M. L.; Floris, B.; Luchetti, L.; Rosnati, V. *Tetrahedron Lett.* **1990**, 6081-6083.
5 Luchetti, L.; Rosnati, V. *J. Org. Chem.* **1991**, *56*, 6836-6839.
6 Unfortunately strain energy data on these compounds are not available, but they should not largely differ from those of cyclohexane and cyclopentane (1.4 and 7.3 kcal·mol^{-1}, respectively). Greenberg, A.; Liebman, J. F. in *Strained Organic Molecules*, Academic Press, New York, 1978, p. 66.
7 Di Vona M. L.; Rosnati, V. *J. Org. Chem.* **1991**, *56*, 4269-4273.
8 Martin, E. L. in *Organic Reactions*; John Wiley: New York, 1975, Vol. 1, Chapter 7, p. 162.
9 Rosenfeld, R. S.; Gallagher, T. F. *J. Am. Chem. Soc.* **1955**, *77*, 4367-4370; Rosenfeld, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5540-5542.
10 Kao, T. Y.; Fuson, R. C. *J. Am. Chem. Soc.* **1932**, *54*, 1120-1124.
11 Fuson, R. C.; Fleming, C. L.; Warfield, P. F.; Wolf, D. E. *J. Org. Chem.* **1945**, *10*, 121-127.
12 Fuson, R. C.; Speck, S. B.; Hatchard, W. R. *J. Org. Chem.* **1945**, *10*, 55-61.
13 Kossanyi, J.; Mogto, J. K. *Org. Mass Spectrom.* **1970**, *3*, 721-734.
14 Mariella, R. P.; Raube, R. R. *J. Am. Chem. Soc.* **1952**, *74*, 521-524.
15 Drewes, S. E.; Hogan, C. J.; Kaje, P. T.; Roos, G. H. P. *J. Chem. Soc. Perkin Trans. I* **1989**, 1585-1591.
16 Overberger, C. G.; Tashlick, I. *J. Am. Chem. Soc.*, **1959**, *81*, 217-221.
17 Fenselau, C. F.; Baum, A. A.; Cowan, D. O. *Org. Mass Spectrom.* **1970**, *4*, 229-235.
18 Evans, E. A.; Whalley, M. *J. Chem. Soc.* **1954**, 3642-3643.
19 Witschard, G.; Griffin, C. E. *J. Org. Chem.* **1964**, *29*, 2335-2340.
20 Sousa Pessoa de Amorim, M. T.; Bouster, C.; Vermande, P.; Veron, J. *J. Anal. Appl. Pyrolysis* **1981**, *3*, 19-34.
21 Hey, D. H.; Musgrave, O. C. *J. Chem. Soc.* **1949**, 3156-3164.
22 Hill, C. M.; Simmons, D. E.; Hill, M. E. *J. Am. Chem. Soc.* **1955**, *77*, 3889-3892.
23 Ley, H.; Dirking, H. *Chem. Ber.* **1934**, *67*, 1331-1338.
24 Skraup, S.; Guggenheimer, S. *Chem. Ber.* **1925**, *58*, 2488-2500.
25 Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* **1990**, 627-630.
26 Conant, J. B.; Blatt, A. H. *J. Am. Chem. Soc.* **1928**, *50*, 551-558.

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