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INTRAMOLECULAR CYCLOADDITIONS WITH AZOMETHINE YLIDES FOR THE SYNTHESIS OF METACYCLOPHANES

W.Eberbach* [a], H.Fritz[b], I.Heinze[a], P.von Laer[a] and P.Link [a]

Institut für Organische Chemie und Biochemie der Universität
D-7800 Freiburg, West Germany [a]
Ciba-Geigy AG, CH-4002 Basel, Switzerland [b]

Abstract. On thermal treatment of the aziridines 5a - f intramolecular cycloaddition reactions of the intermediate azomethine ylides 6 result in the formation of the metacyclophanes 7 - 9. For 7a and 7b the conformational barriers are estimated to be approximately 20 and 12 kcal/mol, respectively.

The simultaneous formation of two new rings is certainly one of the major advantages of intramolecular 1,3-dipolar [1] and Diels-Alder cycloaddition reactions [2]. Whereas the direct addition process creates a five- and a six-membered ring system, respectively, the size of the second cycle is variable and depends on the chain between the reaction centers. Although in most cases the latter rings are of normal size, i.e. five-, six- or seven-membered, there are some examples demonstrating the use of this method also for the preparation of smaller [3] and, more frequently, of larger ring systems [4,5].

In this communication we report on the application of the method towards the synthesis of cyclophanes, a class of compounds with considerable theoretical [6] and pharmaceutical interest [7]. In particular, the preparation of metacyclophanes (type II) by intramolecular cycloaddition of azomethine ylide dipoles to electron deficient C=C-bonds is described. It was the special emphasis to explore this approach for large as well as for short bridges.

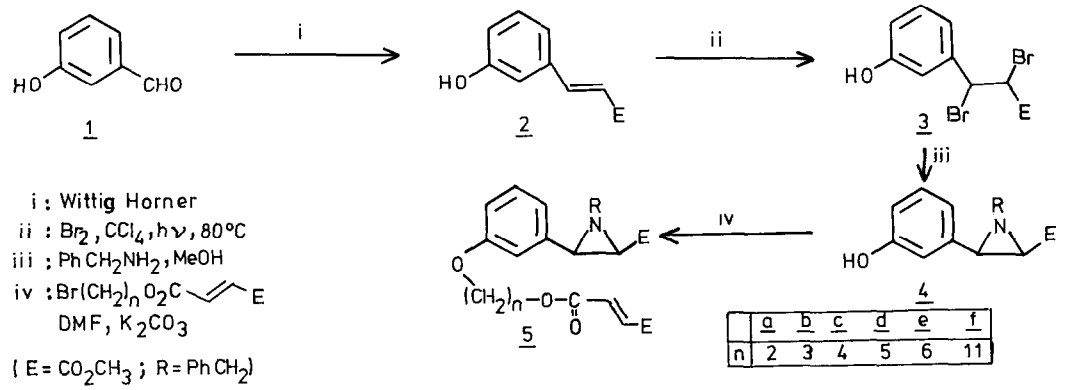
I II

Amongst the various known routes to azomethine ylides [8] we chose the thermally induced ring opening of appropriately substituted aziridines. Although this method has been applied for many bimolecular cycloadditions of azomethine ylides [1b] only three reports are published describing the intramolecular version [9].

The required ene-aziridines 5a-f were easily available according to the

reaction sequence delineated in Scheme 1. The formation of the aziridine 4 by the Cromwell procedure [10] led stereospecifically to the Z-configurated product (J = 7.5 Hz for the aziridine protons [11]).

Scheme 1



The results of our thermolytic experiments with 5a-f, summarized in Scheme 2 and in Table 1, indicate that the azomethine ylide intermediates are formed already in refluxing toluene. Not unexpectedly, the rate of the subsequent intramolecular cycloaddition depends strongly on the number of methylene groups of the chain: while the derivatives with n = 3 - 6 (5b-e) are converted to the corresponding metacyclophanes under very similar conditions, both 5a (n = 2) and 5f (n = 11) have to be heated either for prolonged periods or at higher temperatures. In the case of 5a even then only about 5% of the cyclic products 7a/8a (ratio 4 : 1) are formed. The main material is supposed to arise from bimolecular reactions of 6a (according to R_F values, ^{1}H-NMR- and MS data). Interestingly enough, the next higher homologue 5b is transformed under milder conditions almost quantitatively into a single product, namely the meta-bridged adduct 7b. In contrast to the results with 5a and 5c-f no indications were obtained for the formation of other diastereomers (e.g. 8b). Obviously there must exist a low energy transition state for the cycloaddition

Table 1. Intramolecular Cycloadducts of the Ene-Aziridines 5a - f

	Thermolysis Conditions [a]		Yield		Cycloadducts [d]			
	°C	min	% [b]	% [c]	7	8	9	x [e]
5a [f]	150	50		5	80	20	-	-
5b	111	120	95	80	100	-	-	-
5c	111	120	83	60	40	60	-	-
5d	111	120	84	53	65	35	-	-
5e	120	200		55	45	45	-	10
5f	130	240		44	23	55	8	14

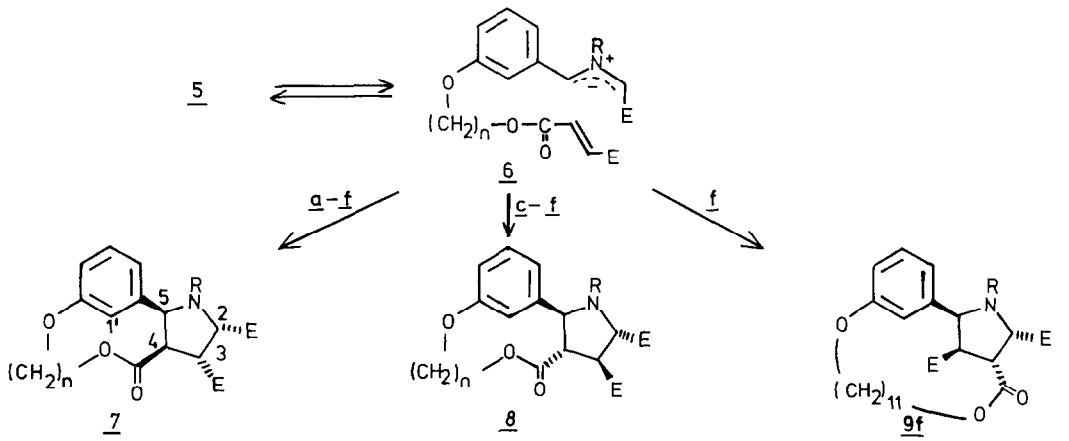
a) Ca. 10^{-2} M in toluene. b) ^{1}H-NMR analysis of the raw material. c) After TLC. d) Numbers in %, related to isolated products. e) Cycloadducts of unknown structure. f) See text.

process 6b ⟶ 7b (n = 3) with both enthalpic and entropic factors being specially favorable.

The work-up of the thermolysis mixtures was accomplished by thin layer- and/or flash chromatography. While compounds 7c, 8a, 8c, 7f, 8f and 9f were obtained together with varying quantities of the respective isomers (Table 1), the other cycloadducts have been isolated in crystalline form [12].

The structural and configurational assignments of the compounds 7/8/9 are based on extensive ^{1}H-NMR investigations including double resonance and NOE-experiments (for pertinent NMR data see Table 2). In the trans-fused series 8f to 8a a consistent upfield shift of the 4-H signals is observed indicating the increasing shielding effect of the aromatic ring ($\Delta\delta$ up to 1.19 ppm). As another result of the gradual distortion of the pyrrolidine ring with decreasing bridge length, the vicinal coupling constants of the 8-isomers are variable (Table 2). Due to the lack of such strain effects the corresponding values of the cyclophanes 7a-f do not change very much.

Scheme 2



The different conformational flexibility of the bridges in the metacyclophane derivatives a - f is nicely demonstrated by the temperature dependence of their ^{1}H-NMR spectra: whereas the spectra of the cycloadducts with n ≥ 4 (c-f) indicate a rapid conformational change even at -60°C, measurements at ambient temperature showed a considerable line broadening for 7b (n = 3), and the existence of two conformers (ratio ca. 3 : 2) in the case of 7a (n = 2), which is formally a [7]metacyclophane. A rough estimation [13] of the energy barriers, based on the change of the 5-H signals, gave $\Delta G^{\neq} \simeq 20$ kcal/mol ($T_c \simeq 100$°C in C_6D_5Br) for 7a and $\Delta G^{\neq} \simeq 12$ kcal/mol ($T_c \simeq 0$°C in $CDCl_3$) for 7b. Compared to the dynamic situation of the parent [7]metacyclophane ($\Delta G^{\neq} = 11.5$ kcal/mol, $T_c = -28$°C in $CDCl_3$) [14] the lower flexibility of the 7a bridge is explained by the particular substitution pattern, including a sp^2-center.

Table 2. Selected ^{1}H-NMR Data of the Compounds 7 - 9 ($CDCl_3$, 400 MHz)

	δ_{2-H}	δ_{3-H}	δ_{4-H}	δ_{5-H}	$\delta_{1'-H'}$	$\delta_{CO_2CH_3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
7a	4.07	3.6	4.09	5.00	7.64	3.70/3.57	7.0	11.0	11.0
7a' a)	b)	b)	3.91	4.64	6.80	3.77/3.62	b)	10.5	10.5
7b c)	4.11	3.86	4.10	4.80	7.07	3.71/3.60	7.0	10.5	10.5
7c	4.14	3.91	4.09	4.76	7.17	3.72/3.63	7.0	11.0	11.0
7d	4.11	3.94	4.09	4.72	7.07	3.72/3.63	7.0	11.0	11.0
7e c)	4.04	3.92	4.05	4.62	7.00	3.72/3.63	7.0	10.5	11.0
7f	4.09	4.0	4.0	4.63	7.09	3.72/3.67	6.0	b)	10.0
8a	b)	3.65	2.41	4.61	b)	3.68/ b)	4.5	10.0	10.0
8c	4.22	3.7	2.92	4.55	6.73	3.69/3.67	4.5	10.0	10.0
8d	4.12	3.66	3.27	4.49	6.97	3.72/3.71	2.5	6.0	8.5
8e	4.14	3.68	3.40	4.64	7.00	3.71/3.73	2.5	5.5	8.0
8f	4.11	3.66	3.60	4.45	6.99	3.73/3.69	2	4	7
9f	----	ca. 4.1 - 3.7 -------- b)				3.65/3.16	b)	b)	10.0

a) Minor conformer. b) Signals covered, partially or completely. c) 55°C.

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REFERENCES and NOTES

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12 Mp. (ether/pentane): 7a, 140-142°C; 7b, 165°C; 7d, 143-146°C; 8d, 95-97°C; 7e, 138-140°C; 8e, 105-107°C.

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