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STEREOSELECTIVE SYNTHESIS OF CIS OR TRANS N-PHENYL 2-PHENYL DECAHYDROQUINOLIN-4 ONES BY CATALYZED HETERO-DIELS-ALDER REACTION.

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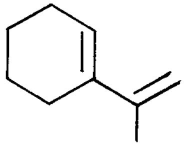
Summary : Cis or trans N-phenyl 2-phenyl decahydroquinolin-4 ones can be synthesized highly selectively.

The use of silyloxydienes has largely increased the synthetic potentiality of the Diels-Alder process. Recently, the Diels-Alder reaction between the silyl enol ether of acetyl cyclohexene 1 and α-enones has been examined (1). However despite the intense activity in the hetero-Diels-Alder (2,3) field, there is no report, to our knowledge, on the reaction of 1 with imines. We shall focus the present study on the synthesis of decahydroquinolin-4 ones, using benzylidenenaniline 2 as hetero dienophile.



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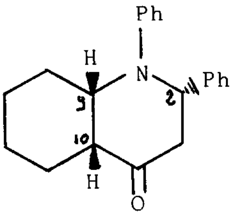
$PhCH=NPh$

2

No reaction took place without Lewis acid catalysis in different solvents either at room temperature or at reflux (toluene, methylene chloride, acetonitrile). When the reaction was run in CH_2Cl_2 in the presence of various Lewis acid using a slight excess of diene (1,2 eq), a mixture of diastereoisomeric cis decahydroquinolin-4 ones 3 and 4 besides small amounts of trans isomer 5 were obtained, after basic hydrolysis and treatment by $Et_3N/MeOH$ (treatment A).



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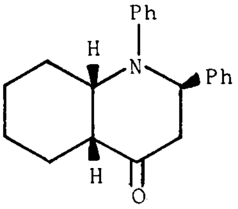

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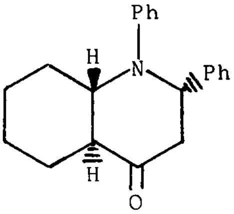

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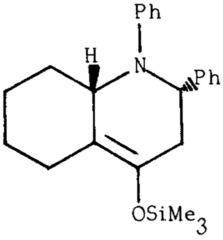
The structural assignments rely on IR (ν_{CO} = 1715 cm^{-1}) and ^1H NMR spectra (250 or 500 MHz) according to the values of H-2 coupling constants and H-9 W1/2 (H-9 and H-10 signals being assigned after Et_3N/MeOD treatment) (4).

When the reaction product in CH_2Cl_2 solution was treated by aqueous HCO_3Na and NEt_3 (treatment B), two enoxy-silanes 6 and 7 could be characterized by 250 MHz ^1H NMR. Mixtures of 6 and 7 treated by NEt_3-MeOH lead to 3 and 4 in similar ratios.



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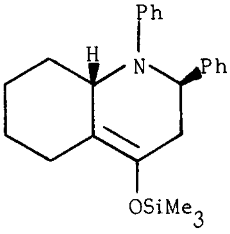

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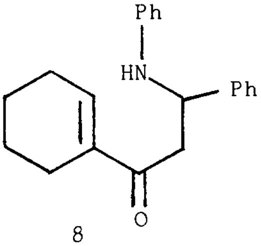
The 3/4 ratio depends on the nature of the Lewis acid and on the reaction time and temperature (see table).

When the reaction was performed with $TiCl_4$ (1 eq) for 40 mn and followed by aqueous HCO_3Na treatment, 5 was obtained next to a mixture of enoxy-silanes 6 and 7 in the ratio 5/6/7:25/2/73.

With $TiCl_4$ (3 eq) or $ZrCl_4$ (3 eq) respectively for 1 h or 2 h 40, the reaction gives, after treatment by aqueous HCO_3Na, only 5.

Furthermore, when the reaction was run with $BF_3.Et_2O$ (1 eq) followed by washing with water and MeOH treatment, 8 was isolated (70%). Treatment of 8 by 1 eq. $TiCl_4$ during 1h or 18h followed by water quenching gives respectively a mixture of 3, 4, 5 next to 8 or only 5.



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Substances 6 and 7 appear to be the primary products of the reaction process. Under kinetic control 6 and 7 are formed in a 70/30 ratio whatever the catalyst (entries 1, 3, 4, 7, 8) while under thermodynamic control 7 is highly predominant (entries 10, 11). Such a thermodynamic control could take place by Diels $\rightleftharpoons$ retro-Diels process : related examples have been recently published in a homo-Diels reaction (5). However, equilibration via a silyloxonium intermediate on the reaction pathway can also be invoked according to Danishefsky (6). Further experiments are under the way to strengthen one of these possibilities.

The kinetic protonation of these intermediates leads to cis ring fused bicyclic ketones 3 and 4. The formation of the trans ring fused compound 5, which takes place when $TiCl_4$ or $ZrCl_4$ are used as Lewis acids might result from protonation of the equilibrating zirconium or titanium - enolates : it is known (7) that silyl enol ethers are cleaved into titanium enolates by $TiCl_4$.

According to experimental conditions the stereoselective synthesis of cis or trans N-phenyl 2-phenyl decahydroquinolin-4 ones can be selectively performed.

Table

Reaction of 1 with 2 in CH_2Cl_2

Entry	Lewis acid (1 eq.)	t°C	time	treatment	3/4[(a)]	(Yield %[(b)])
1	$BF_3.Et_2O$	-78	5 mn	B	67/33[(c)]	(f)
2	$BF_3.Et_2O$	0	5 mn	A	55/45[(d)]	(f)
3	$BF_3.Et_2O$[(e)]	20	1 h 30	A	70/30[(d)]	72
4	$AlCl_3$	-10	3 h 30	A	70/30	(f)
5	$AlCl_3$	20	5 mn	A	55/45	(f)
6	$AlCl_3$	20	1 h 30	A	10/90	60
7	Et_2AlCl	20	1 h 30	A	70/30	41
8	$ZrCl_4$	-40	5 mn	A	70/30	(f)
9	$ZrCl_4$	20	1 h	B	40/60[(c)]	(f)
10	$ZrCl_4$	20	4 h 30	A	1/99	50
11	$TiCl_4$	20	5 mn	A	2/98	(f)

a) 3/4 ratio determined by ^1H NMR on the crude crystalline product. b) Yields determined on the crude crystalline product. c) 3/4 ratio deduced from 6/7 ratio. d) Traces of 8. e) 0.1 eq. $BF_3.Et_2O$. f) Next to adducts, starting materials were observed.

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4) All new compounds gave correct elemental analysis (C,H,N), IR and ^1H NMR spectra in agreement with the proposed structures. 3 : mp °C = 167,3 ; 4 : mp °C = 156,8 ; 5 : mp °C = 144,1 ; 8: mp °C = 142 after ethyl acetate/hexane recrystallization.

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