Synthesis of Perhydroquinolinones Bearing an Angular Methyl Group *via* Lewis Acid Catalyzed Hetero-Diels-Alder Cyclization

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(Received April 28, 1997; CL-970314)

The first results utilizing the sterically demanding diene **1** in hetero Diels-Alder reactions are reported. The effect of commonly used Lewis acids and the substitution pattern of various imines on the mechanism of the reaction with the diene **1** is discussed.

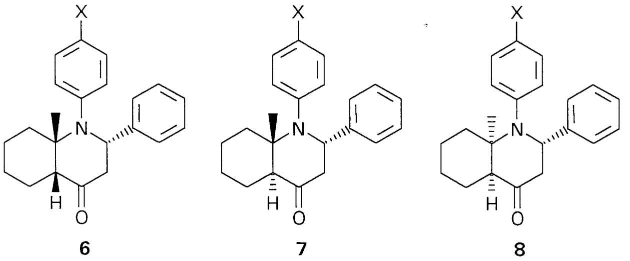
The application of Lewis acid catalyzed Diels-Alder reactions using carbonyl and imino functionalities as dienophiles proved to be a very useful methodology in heterocyclic synthesis.[1] Due to their potential biological activity a lot of research projects were focused on the formation of nitrogen containing heterocycles *via* this strategy in recent time.[2-8]

In this paper we are presenting a new application of the diene **1**[9] acting as a useful building block for the construction of fused heterocyclic ring systems bearing an angular methyl group as a characteristic feature. Various imines **2** proved to react with this sterically hindered silyl enol ether under Lewis acid catalysis to form cyclic products **3** and **4**. However, depending on the nature of the substituent X and the Lewis acid applied, substantial amounts of the open chain product **5** have been isolated as a by-product, obviously resulting from a nucleophilic addition of **1** to the imine.

Subsequent conversion into the corresponding ketones **6** - **8** was usually performed using basic and protic conditions (MeOH/NEt_3) without separation of the silyl enol ethers **3** and **4**, respectively.

Analysis of the reaction mixtures was carried out after removal of the TMS-group and the obtained ketones were purified by flash column chromatography. Structural assignment was carried out by 2D-NMR analysis and confirmed by X-ray diffraction. The influence of electron-withdrawing and -donating substituents at the imine **2** on both the mechanism and the *exo*/*endo* selectivity of the reaction with the diene **1** is summarized in Table 1.

In the case of the imine **2a** the best results were obtained using $TiCl_4$ as Lewis acid in CH_2Cl_2 (entry 1). Complete *endo* selectivity was observed and the isomers **6a** and **7a** were isolated in good yield. $SnCl_4$ (entries 2 and 3) showed somewhat weaker catalytic activity, however, the *endo* selectivity was not influenced. ZnI_2 favored the competing addition reaction to **5a** (entries 4 and 5) which became the single product in a very slow reaction when the solvent was changed to the strong donor THF (entry 6).



6 7 8

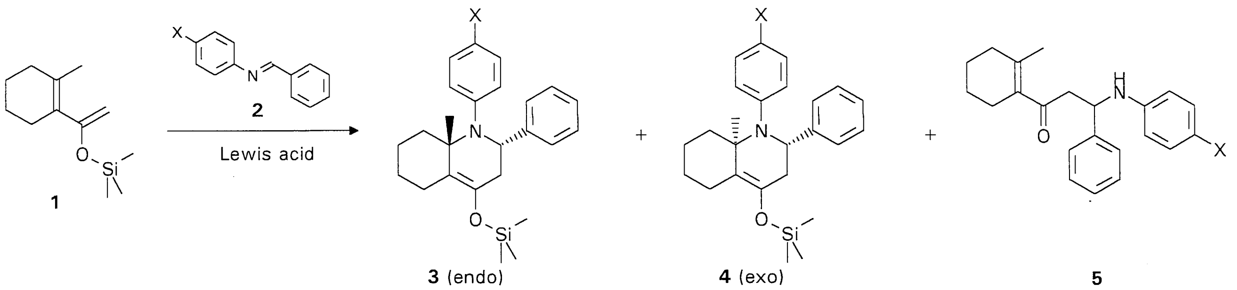
Scheme 2.

As expected, an electron withdrawing *N*-substituent activated the imine **2b** ($X=NO_2$) by increasing the polarity but it also reversed the effect of the strong Lewis acid $TiCl_4$ and the weaker Lewis acid ZnI_2 (entries 7-9). Calculations for the Lewis acid - imine complexes on *ab initio* level indicated that a large p_z-orbital coefficient at the imine carbon is essential for a successful Diels-Alder cyclization.[10] Due to weak interaction with $TiCl_4$ the increase is not sufficient, but polarization of the C=N bond seems still strong enough to allow a nucleophilic addition of **1**.

Introduction of an electron donating *N*-substituent in the case of **2c** ($X=OCH_3$) led to a significant decrease of the *endo* selectivity and the *exo*-product **8c** could be isolated (entries 10 and 11). As expected, the general reactivity of the imine in the reaction with the diene was decreased.

The obtained mixtures of the *cis*- and *trans*-isomers **6** and **7** were subsequently treated with NaOMe in dry MeOH yielding the thermodynamically favored *trans*-isomers **7** in high to quantitative yields.

A typical experimental procedure is as follows: The



3 (endo) 4 (exo) 5

Scheme 1.

Table 1. **Reaction of diene 1 with imines 2a-e under various conditions**

entry	imine[a]	Lewis acid	time [h]	temp. [°C]	solvent	**5**	product **6 + 7**	ratio **8**	rec. **2**	overall yield[b] [%]
1	**2a**	$TiCl_4$	1	20	CH_2Cl_2	0	100	0	0	74
2	**2a**	$SnCl_4$	1	20	CH_2Cl_2	0	60	0	40	
3	**2a**	$SnCl_4$	20	20	CH_2Cl_2	0	100	0	0	65
4	**2a**	ZnI_2	2	20	CH_2Cl_2	6	80	0	12	
5	**2a**	ZnI_2	7	20	CH_2Cl_2	12	82	0	6	
6	**2a**	ZnI_2	2	20	THF	17	0	0	83	
7	**2b**	$TiCl_4$	1	20	CH_2Cl_2	traces	0	0	~100	
8	**2b**	$TiCl_4$	2	-20	CH_2Cl_2	100	0	0	0	41
9	**2b**	ZnI_2	22	20	CH_2Cl_2	30	70	0	0	91
10	**2c**	$TiCl_4$	2	20	CH_2Cl_2	0	65	35	0	75
11	**2c**	$SnCl_4$	20	20	CH_2Cl_2	0	84	8	8	

[a] **2a**: X=H; **2b**: X=NO_2; **2c**: X=OCH_3; [b] Overall yield represents the yield of all isolated reaction products and is based on imine (only given in case of complete conversion).

Lewis acid (1 equiv.) was added to a solution of the imine **2** (1 equiv.) in dry CH_2Cl_2 under a nitrogen atmosphere. After the mixture had been stirred for 30 minutes, diene **1** (2 equiv.) in dry CH_2Cl_2 was added and the stirring continued for the time and at the temperature given in Table 1. The reaction mixture was poured on sat. $NaHCO_3$ solution, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was removed and the residue (enol ethers **3** and **4**) was treated overnight with a 1:1 mixture of dry NEt_3 and MeOH. After the volatiles had been evaporated the crude ketones **6** - **8** were purified by flash column chromatography on basic SiO_2 (light petroleum / ethyl acetate). All compounds were characterized by ^1H- and ^{13}C-NMR and gave satisfactory elemental analysis.

We thank Dr. Franz Renz for his assistance of calculating the Lewis acid - imine complexes on *ab initio* level. Structural elucidation performed by Dr. Kurt Mereiter and Dr. Horst Völlenkle is gratefully acknowledged.

References and Notes

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