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Hetero Diels-Alder Reaction between 2,3-Dimethyl-1,3-butadiene and Perfluorooctanonitrile under High Pressure

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Abstract

3,4-Dimethyl-6-perfluoroheptyl-2,5-dihydropyridine (**1**) is obtained by hetero Diels-Alder reaction between 2,3-dimethyl-1,3-butadiene and perfluorooctanonitrile at 50°C and pressures of 1 and 1500 bar, respectively. **1** gradually eliminates hydrogen to give 3,4-dimethyl-6-perfluoroheptylpyridine (**2**). The investigation of influence of high pressure on this reaction showed a significant increase of yields of both heterocyclic compounds at 1500 bar. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords
Diels-Alder reactions; Dienes; Nitriles; Pyridines

Introduction

Besides the cobalt(I) catalyzed heterocyclization of ethyne and nitriles, which is a subject of active research [1,2,3,4,5,6], the hetero Diels-Alder reaction between dienes and nitriles is an effective method for the production of 2-substituted pyridines, too. However, the normal electron demands for hetero Diels-Alder reactions, an electron rich diene and an electron deficient dienophile, limit this method to a small number of activated dienes and nitriles. Otherwise elevated temperatures are necessary for activation. So the requirement of extremely high reaction temperatures has been one of the features of Diels-Alder reactions with nitriles made them unattractive for a long time since 1935, when Dilthey [7] found the ability of nitriles to act as dienophiles for the first time. In the following years Janz and co-workers [8,9,10,11,12,13] and Marwell and Hwa [14] intensively investigated hetero Diels-Alder reactions of 1,3-dienes with several derivatives of oxalonitrile in the gas phase (200-500°C).

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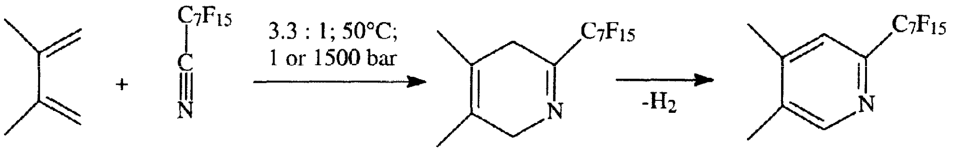
Hydrogen from the primary dihydropyridine product was eliminated under these extreme conditions, and the corresponding pyridines were obtained [15,16,17]. Good yields at lower temperatures were achieved only with the exceptionally reactive sulfonyl cyanides as dienophiles [18,19,20,21]. Except for the *p*-toluenesulfonyl cyanide [22] it could be shown recently, that methyl- [23] and ethylcyanoformate [24] as well as trichloroacetonitrile [25] can be used as dienophiles. Although the authors were able to detect the dihydropyridines as intermediates or primary products in some cases, the spontaneous aromatization converted them fast into the corresponding pyridines.

Results and Discussion

Our investigations focused on obtaining a pyridine and the primary product, the dihydropyridine, by hetero Diels-Alder reaction of a substituted 1,3-diene system with a nitrile under mild temperature conditions. Therefore substituents at the diene should not be appropriate leaving groups like siloxy and alkoxy groups which are activating the diene system very well but otherwise allow an easy elimination yielding aromatic pyridines. To make a reaction possible at low temperatures we wanted to counteract the loss of reactivity of the diene by use of high pressure. Diels-Alder reactions are known to have a large negative activation volume and have been shown to be favoured by the application of elevated pressures [26,27].

Among the other tested dienes and dienophiles the reaction of 2,3-dimethyl-1,3-butadiene and perfluorooctanonitrile showed the best results. In fact perfluorocarbon substituted nitriles have been reported in the literature [12,13] to be reactive dienophiles at temperatures above 350 °C in the gas phase because of the increasing electrophilic character of the cyano carbon [16].

The 3,4-dimethyl-6-perfluoroheptyl-2,5-dihydropyridine (**1**) as the expected hetero Diels-Alder cyclization product and the 3,4-dimethyl-6-perfluoroheptylpyridine (**2**) after the elimination of hydrogen from **1** were obtained as products of the reaction between 2,3-dimethyl-1,3-butadiene and perfluorooctanonitrile.



1 **2**

The reaction was carried out at 50°C and pressures of 1 and 1500 bar respectively with an 3.3 fold excess of the diene. Experimental results are listed in table 1.

After an initial phase of about four hours, during which only **1** was formed in low yields, the gradual elimination of hydrogen occurred to give **2**. Attempts to increase the yield of **1** by longer reaction times or a higher reaction temperature (80°C) showed a maximum of the available yield of about 30% after 29 hours at 50°C and 1500 bar. Further extension of the reaction time and a higher temperature caused a decrease of ratio between **1** and **2** and hence could not improve the yield of the 3,4-dimethyl-6-perfluoroheptyl-2,5-dihydropyridine (**1**).

Table 1
Selected data of the reaction between perfluorooctanonitrile and 2,3-dimethyl-1,3-butadiene; all yields based on perfluorooctanonitrile

t [h]	yield of **1** at 1 bar [%]	yield of **2** at 1 bar [%]	yield of **1** at 1500 bar [%]	yield of **2** at 1500 bar [%]
2.0	1.6	0.0	5.6	0.0
3.9	1.8	0.0	8.0	0.0
5.5	3.6	0.6	12.0	0.5
7.2	4.8	0.0		
21.5	14.1	1.7		
27.5	17.2	2.5		
29.0	14.6	4.2	29.1	7.8
44.1	21.3	3.4	28.6	8.5
67.0	23.7	4.4	31.3	13.3
97.5	27.0	10.2	26.4	20.8

The comparison of the sums of the yields of both reaction products at a pressure of 1 and 1500 bar respectively shows a significant increase at elevated pressure at any time we determined the yields (Figure 1). Thus high pressure accelerates the reaction rate, as it was discussed in the literature for nonhetero Diels-Alder reactions. Certainly, we could not find an influence of high pressure on the aromatization tendency.

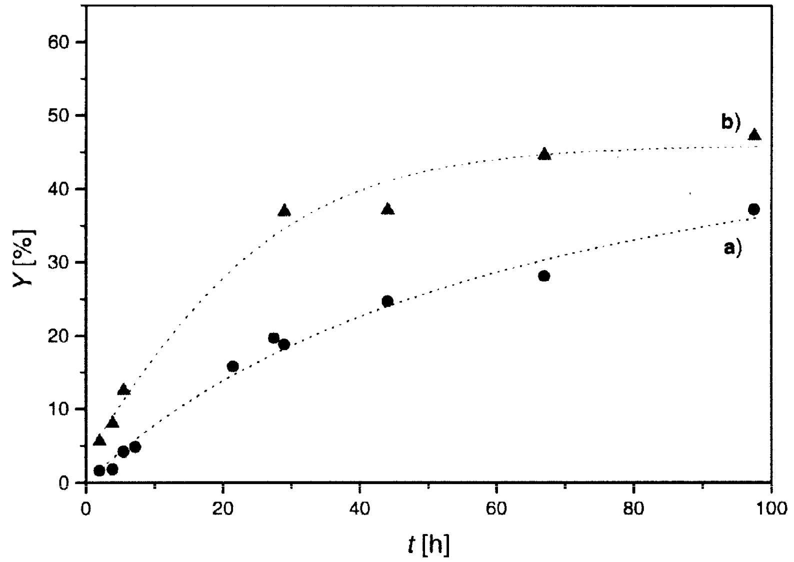


Figure 1
Combined yields Y of **1** and **2** as a function of time at 50°C and 1 bar (a) and 1500 bar (b) with an 3.3 fold excess of the diene

The structures of both compounds were determined by means of GC-MS, GC-IR and one and two-dimensional NMR techniques. Although the NMR spectra (^{1}H, ^{13}C, ^{13}C-DEPT) indicates the existence of the 3,4-dimethyl-6-perfluoroheptyl-2,5-dihydropyridine (^{13}C-DEPT: two CH_2 groups; COSY-2D: ^{13}C signals correlating to the corresponding ^{1}H signals), the IR spectrum, recorded in the gas phase in direct combination with GC, shows a band at 3460 cm^{-1} beeing characteristic for a ν(NH) mode. Certainly, the IR spectrum of the corresponding 3,4-dimethyl-6-perfluoroheptylpyridine does not show any band in that region. As a reason we assume a tautomerization in the gas phase into the probably more stable 1,2-dihydropyridine.

Attempts to isolate the pure 3,4-dimethyl-6-perfluoroheptyl-2,5-dihydropyridine (**1**) have not been successful because of the gradual aromatization to the 3,4-dimethyl-6-perfluoroheptylpyridine (**2**) in the solid state as well as in solution. We always obtained both compounds in various ratios, e. g. a mixture of solid **1** with a small amount of **2** was converted into **2** up to 98 % after 23 hours at 50°C. In *n*-heptane solution the aromatization proceeds much slower, only 40% of **2** were formed after two weeks at room temperature. However, we could identify the primary product to be compound **1** by comparison of the NMR data of the mixture of **1** and **2** with data of pure compound **2**. Although **1** is better soluble in $CDCl_3$, NMR spectra were recorded in benzene-d_6 because the conversion of **1** to **2** is much faster in $CDCl_3$ than in C_6D_6. This is in agreement with other literature reports concerning the behaviour of 1,4-dihydropyridines [28] and tetrahydropyridines [29].

Certainly, we could not find any trace of hydrogen in the reaction mixtures. However, we were able to detect a tetrahydropyridine by GC-MS, yielded by hydrogenation of dihydropyridine. While in the beginning of the hetero Diels-Alder reaction preferently **1** and only few **2** were formed, the progress of the reaction, particularly at 1500 bar, leads to a third compound (GC: additional peak between **1** and **2**) which was identified to be a tetrahydropyridine (m/z = 479). An estimation showed less than the stoichiometric amount of tetrahydropyridine. That means only a part of the hydrogen set free by the aromatization of dihydropyridine is used for the hydrogenation of this compound.

Conclusion

In summary to the best of our knowledge it was possible for the first time to characterize the free 2,5-dihydropyridine product of the hetero Diels-Alder reaction between a diene and a nitrile by NMR spectroscopy. Besides the recently published NMR data of 2,5-dihydropyridinium ylide complexes [30] our investigations show that the 2,5-dihydropyridines can be stable enough not only to be trapped but to be analyzed as free compounds before their oxidation. However, the 2,5-dihydropyridine seems to isomerize into the probably more stable 1,2-dihydropyridine in the gas phase.

Experimental

Both starting materials were obtained from commercial suppliers (perfluorooctanonitrile: 97% ABCR; 2,3-dimethyl-1,3-butadiene: ≥ 97% Fluka). 2,3-Dimethyl-1,3-butadiene was distilled under argon before use, perfluorooctanonitrile was used as received. Reactions were performed under an argon atmosphere in carefully dried glassware and teflon tubes.

NMR spectra were recorded in deuterobenzene on either a Bruker MSL 400 or an AMX-R 300 NMR instrument using the solvent as internal standard. Mass spectra were recorded on an AMD 402-3 (Intectra GmbH) spectrometer, GC-MS spectra on a system consisting of a Hewlett Packard HP 5890 II gas chromatograph and a HP 59827 A mass spectrometer. GC-IR spectra were recorded on a Hewlett Packard HP 5890 Series II gas chromatograph (column: HP5; 25 m) with an infrared detector HP 5965 B. Gas chromatograms were performed on a Hewlett Packard gas chromatograph HP 6890 Series (column: HP1; 25 m), for preparative GC we used a HP 5890 II gas chromatograph with a Multi Column System from Fa. Gerstel Mülheim/Germany (column: FFAP; 30 m).

Reaction of 2,3-dimethyl-1,3-butadiene and perfluorooctanonitrile

About 5 mmol of the nitrile and the diene (3.3 fold excess) were stirred for a few minutes without solvent. Then one part of the reaction mixture was filled into a teflon tube for the experiment at 1500 bar. The temperatures and pressures of both reaction solutions were held constant over the whole time ($T = 50°C \pm 1°C$; 1 bar and 1500 bar ± 10 bar, respectively).

For the high pressure experiments we used an equipment supplied by Nova Swiss which is similar to that described by van Eldik [31]. The products were analyzed by GC, GC-MS and GC-IR. For the purification of **2** the unchanged nitrile and the diene were distilled from the reaction mixtures in vacuum at room temperature. For the NMR measurements the products were further purified by preparative GC. The relation between **1** and **2** was estimated by both suitable methods GC as well as ^{1}H NMR spectroscopy.

*3,4-dimethyl-6-perfluoroheptyl-2,5-dihydropyridine (**1**):*

GC-MS: m/z = 477 (40%, M^+), 462 (15%, M^+-15), 458 (8%, M^+-19), 158 (28%, M^+-319), 108 (100%, M^+-369), 83 (22%), 67 (30%), 41 (12%); GC-IR: ν 655 (w), 737 (m), 780 (w), 800 (w), 1020 (w), 1147 (m), 1243 (s, CF), 1345 (w), 1432 (w), 1452 (w), 1602 (w), 1664 (w), 1703 (w), 2787 (w), 2842 (w), 2927 (w), 3000 (w), 3460 (w) cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 1.11 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.33 (t, J = 7.95 Hz, 2H, CH_2), 3.89 (t, 2H, CH_2) ppm; ^{13}C NMR (250 MHz, C_6D_6): δ 14.58 (CH_3), 17.17 (CH_3), 30.09 (CH_2), 56.21 (CH_2) ppm.

*3,4-dimethyl-6-perfluoroheptylpyridine (**2**):*

MS: m/z = 475 (12%, M^+), 456 (10%, M^+-19), 156 (100%, M^+-319), 106 (13%, M^+-369), 69

(8%), 39 (4%); GC-IR: ν 653 (w), 703 (w), 739 (m), 785 (w), 816 (w), 859 (w), 886 (w), 1007 (w), 1064 (w), 1147 (m), 1208 (s), 1243 (s, CF), 1345 (w), 1391 (w), 1456 (w), 1484 (w), 1598 (w), 2882 (w), 2938 (w), 3022 (w) cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 1.53 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 7.13 (s, 1H, CH), 8.13 (s, 1H, CH) ppm; ^{13}C NMR (250 MHz, C_6D_6): δ 15.63 (CH_3), 18.53 (CH_3), 122.15 (C), 122.91 (CH), 135.38 (C), 146.67 (C), 150.52 (CH) ppm.

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