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Synthesis of (+,-) 3,4-Disubstituted 3,4-Dihydro-2*H*-thiopyrans via a Diastereoselective Hetero Diels-Alder Reaction

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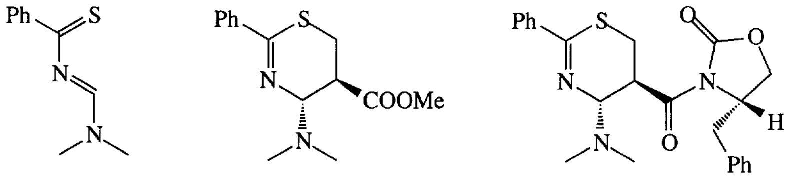
Abstract: .The behaviour of endo selective diene **4** in kinetically controlled hetero Diels-Alder cycloadditions is in marked contrast with that of its exo selective aza analogue **1**.

The hetero Diels-Alder reaction represents, without contest, one of the most powerful way for the regio- and stereoselective construction of six-membered heterocyclic compounds and, in our laboratory, there has been long-standing interest in this methodology for the purpose of elaborating various substituted 1,3-thiazine derivatives (e.g., **2**)[1]. Recently, an asymmetric route to this class of heterocycles has been developed using the $MgBr_2$-catalysed addition of diene **1** to chiral (4*S*)-3-(2-propenoyl)-4-(phenylmethyl)-2-oxazolidinone, which gave the dihydro-1,3-thiazine **3** with virtually 100% diastereoselectivity[2].



1 **2** **3**

Scheme 1

Besides the potential synthetic utility of the above cycloaddition products we were intrigued by the general trend of diene **1** to give exo cycloaddition products independently of the activation mode (thermal, high pressure[3], Lewis acid at low temperature under presumed kinetic control) and the nature of the dienophile partner[4]. In order to learn more about the reasons that lead to the establishment of such an exo selectivity we found highly desirable to search for the structural features that could possibly influence the mode of approach of both reactant partners. Within this context we became much interested in studying the reaction of 4-dimethylamino-2-phenyl-1-thiabuta-1,3-diene **4** (an analogue of **1** where the nitrogen has been replaced by a carbon), the synthesis of which could be easily accomplished by addition of dimethylamine in excess onto a solution of a 3-phenyl-1,2-dithiolylium salt in ethanol[5]. In a first set of experiments cycloaddition reaction of diene **4** with methyl acrylate **5a** and N-enoyloxazolidinone **5b** was investigated (Scheme 2) at several different temperatures in both catalysed and uncatalysed conditions and some selected results are reported in the Table[6].

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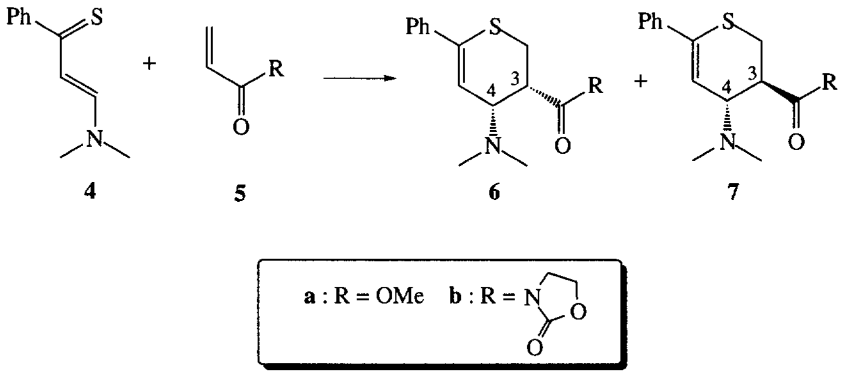


Scheme 2

Table : Hetero Diels-Alder reaction of diene **4** with dienophiles **5a** and **5b**

Entry	Dienophile	Experimental Conditions [a,b]			Endo/exo
		Lewis acid	temp.(°C)	time (h)	**6/7**
1	**5a**	no	-30	1.5	91/9 (100/0)[d]
2	**5a**	no	20	1.5	85/15
3	**5a**	no	80	3	0/100[e]
4	**5a**	Et_2AlCl[c]	-78 to -60	3	85/15
5	**5b**	no	-30	1.5	92/8
6	**5b**	no	18	10 min	28/72
7	**5b**	no	18	3	10/90 (0/100)[d]
8	**5b**	$MgBr_2$	0	1.5	7/93
9	**5b**	$MgBr_2$	-30	1.5	33/66
10	**5b**	$MgBr_2$	-78 to -60	1.5	54/46

[a]All reactions were performed in CH_2Cl_2 unless stated otherwise; Molar ratio diene-dienophile 1:1.5; Diene concentration: 0.05M.[b]Chemical yields are almost quantitative. [c]reaction performed in toluene. [d]after purification by flash-chromatography [e]About 20% of the thiopyran resulting from the loss of dimethylamine was formed under these conditions.

As the first three entries in the Table indicate, two important issues, in connection with the behaviour of diene **1**, are noteworthy.

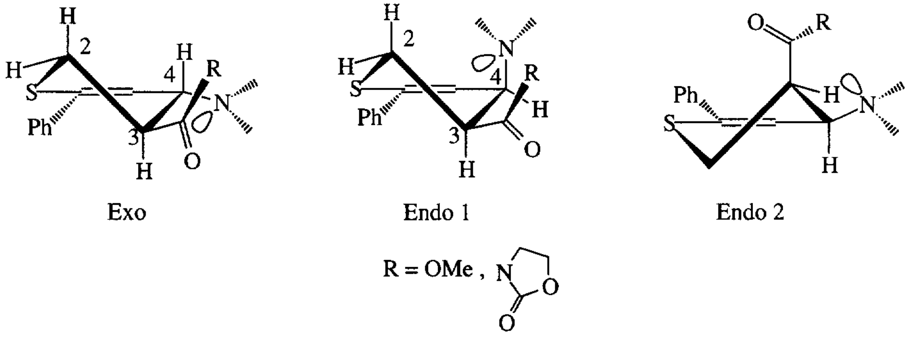
- First of all, diene **4** is significantly more reactive toward methylacrylate than the parent diene **1**. The reaction was thus complete within 1.5 hour at -30°C producing adducts **6a/7a** in almost quantitative yield whereas diene **1** needed longer reaction time and elevated temperature to cycloadd[7].

- Second, it should be noted that *the observed selectivity in the [4+2] cycloaddition of diene 4 is opposite to that of diene 1*, endo (cis) adduct **6a** being predominantly formed at room temperature or below. However, raising the reaction temperature resulted in the isolation of the single exo (trans) diastereomer **7a** along with about 20% of a thiopyran by-product resulting from the loss of dimethylamine.

Similar observations could be made from the cycloaddition reaction of **4** to N-enoyloxazolidinone **5b** as the dienophile (entries 5 to 7). A remarkable difference with the preceding addition to **5a** is the facility with which endo adduct **6b** undergoes equilibration into its more stable exo diastereomer[8] **7b**. This occurs rapidly at room temperature whereas heating was necessary in case of adduct **6a**. The fact that this equilibration is the result of a sequential retro Diels-Alder - Diels-Alder process was clearly demonstrated by the results of the following competitive experiment. Thus, mixing the 92/8 mixture of **6b/7b**, shown in entry 5 of the Table, with a sevenfold excess of methylacrylate in CH_2Cl_2 at 20°C for 1.5h resulted in the production of a new mixture consisting of **6b/7b** (22/78, 32%) and **6a/7a** (85/15, 62%).

The cycloaddition reaction of diene **4** to dienophiles **5** could also be effected at very low temperature in the presence of Lewis acids. As far as methylacrylate is concerned, the diastereomeric ratio **6a/7a** remained unchanged (85/15) if compared to the uncatalysed reaction performed at room temperature (entries 2 and 4). In contrast, the $MgBr_2$-catalysed reaction of **4** to N-enoyloxazolidinone **5b**, was unselective at -78°C. However, raising the reaction temperature resulted in a pronounced increase in the formation of the exo adduct as previously observed for the uncatalysed process (entries 8 to 10). In fact, not only the temperature but also the Lewis acid allow the reaction to occur under thermodynamic control. This was demonstrated by allowing a 92/8 mixture of **6b/7b** to stand at 0°C in CH_2Cl_2 for 1.5h in the presence of one equivalent of $MgBr_2$. A 54/46 mixture was recovered whereas the initial ratio remained constant in the absence of the Lewis acid.

Distinction between the endo and exo adducts, which could be separated by standard silica gel flash-chromatography, was readily accomplished by inspection of their NMR spectra[9]. The coupling constants for the endo adducts **6a** and **7a** reveal that the "endo 1" conformation is largely predominant over the "endo 2" conformation in chloroform solution[10] (Scheme 3). This is also the preferred conformation in the solid state as revealed by an X-ray structure[11] obtained for the endo adduct **6a**.



Scheme 3

In conclusion, our study has demonstrated that cycloaddition reaction of diene **4** with dienophiles **5** affords, with good selectivity, the kinetically controlled endo adducts or their more stable exo diastereomers depending on the experimental conditions[12]. However the most important conclusion to be drawn from the results so far obtained is the critical role played by the nitrogen in diene **1** which clearly influences the mode of cycloaddition toward the exclusive formation of exo adducts . Further studies are planed to delineate the origin of this "nitrogen effect" and also to develop an asymmetric version of the above cycloaddition reaction.

References and notes

1 Pradère, J.P.; Tonnard, F.; Abouelfida, A.; Cellerin, C.; Andriamanamihaja, M.; Jousseaume, B.; Toupet, L.; Guénot, P. *Bull. Soc. Chim. Fr.*, **1993**, *130*, 610-619 and references cited therein.

2 Marchand, A.; Mauger, D.; Guingant, A.; Pradère, J.P. *Tetrahedron: Asymmetry*, **1995**, *6*, 853-856.

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4 For recent examples of exo-selective Diels-Alder cycloadditions featuring 2-azadienes, see Morel, G.; Marchand, E.; Pradère, J.P.; Toupet, L.; Sinbandhit, S. *Tetrahedron*, **1996**, *52*, 10095-10112 and references cited therein.

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6 Early studies concerning the cycloaddition reaction of 4-dimethylamino-2-aryl-1-thiabutadiene to a variety of dienophiles in benzene solution at reflux, concluded to the exclusive formation of exo adducts. Pradère, J.P.; N'Guessan, T.; Quiniou, H.; Tonnard, F. *Tetrahedron*, **1975**, *31*, 3059-3064.

7 At the PM3 level the calculated HOMO energies for dienes **1** and **4** are -9.05ev and -8.50ev , respectively.

8 Semi-empirical calculations (PM3 hamiltonian) have been carried out on the heat of formation of adducts endo **6a**, **6b** and exo **7a**,**7b**. The computational results show that exo adducts **7a** and **7b** are more stable than endo adducts **6a** and **6b** by 6.36 and 13.68 kJ/mol, respectively.

9 Some selected physical data:

6a: yellow solid, mp 83-84°C (ethylacetate) ; IR (KBr): 1734, 1342, 691cm^{-1} ; ^{1}H NMR (400 MHz,$CDCl_3$, δ): 2,37 (s, 6H), 2,90 (ddd, *J* = 3.4Hz, 5,0Hz, 13,1Hz, 1H), 3.0 (dd, *J* = 3.4Hz, 13.1Hz, 1H), 3.36 (dd, *J* = 13.1Hz, *J* = 13.1Hz, 1H), 3.76 (s, 3H), 3.76 (m, 1H), 6.16 (d, *J* = 6.0Hz, 1H), 7.34 and 7.50 (m, 5H) ; ^{13}C (100MHz, $CDCl_3$, δ): 24.3, 44.7, 46.0, 51.8, 58.3, 116.8, 126.7, 128.5, 137.6, 139.7, 173.4.

7a: yellow solid, mp 60-61°C (ether/petroleum ether) ; IR (KBr): 1740, 1347, 697cm^{-1} ; ^{1}H NMR (400 MHz,$CDCl_3$ δ): 2.36 (s, 6H), 2.99 (dd, *J* = 2.8Hz, 12.4Hz, 1H), 3.03 (ddd, *J* = 2.8, 9.3, 10.5Hz, 1H), 3.30 (dd, *J* = 10.5Hz, 12.4Hz, 1H), 3.75 (s, 3H), 3.82 (dd, *J* = 2.9Hz, 9.3Hz, 1H), 6.04 (d, *J* = 2.9Hz, 1H), 7.33 and 7.48 (m, 5H) ; ^{13}C (100MHz, $CDCl_3$, δ): 29.4, 41.0, 42.6, 52.4, 61.9, 118.4, 126.6, 128.6, 137.1, 139.4, 174.6.

6b: pale yellow solid (due to its instability, this compound was always polluted by ca. 2-10% of **7b**) ; IR (KBr): 1770, 1693, 694cm^{-1} ; ^{1}H NMR (400 MHz,C_6D_6 δ): 2.21 (s, 6H), 2.79 (dd, *J* = 3.2Hz, 13.2Hz, 1H), 3.22 (m, 4H), 3.60 (dd, *J* = 13.2Hz, 13.2Hz), 1H), 4.17 (ddd, *J* = 3.2Hz, 6.9Hz, 13.2Hz, 1H), 4.36 (dd, *J* = 5.0Hz, 6.9Hz, 1H), 6.16 (d, *J* = 5Hz, 1H), 7.11 and 7.58 (m, 5H) ; ^{13}C (100MHz, $CDCl_3$, δ): 29.9, 40.3, 41.2, 43.1, 62.1, 62.2, 117.8, 126.7, 128.6, 131.9, 137.2, 139.5, 153.5, 174.5.

7b: pale yellow solid, mp 131-132 (ethylacetate/petroleum ether) ; IR (KBr): 1770, 1693, 694cm^{-1} ; ^{1}H NMR (400 MHz,$CDCl_3$ δ): 2.35 (s, 6H), 2.98 (dd, *J* = 2.8Hz, 12.7Hz, 1H), 3.25 (dd, *J* = 11.0Hz, 12.7Hz, 1H), 4.07 (m, 3H), 4.44 (ddd, *J* = 2.5Hz, 7.7Hz, 8.6Hz, 2H), 4.47 (ddd, *J* = 2.8Hz, 10.1Hz, 11.0Hz, 1H), 6.07 (d, *J* = 2.7Hz, 1H), 7.33 and 7.48 (m, 5H) ; ^{13}C (100MHz, $CDCl_3$, δ): 29.9, 40.3, 41.2, 43.1, 62.1, 62.2, 117.8, 126.7, 128.6, 131.9, 137.2, 139.5, 153.5, 174.5.

10 At the PM3 level "endo 1" conformation is more stable than "endo 2" conformation by 12.60 kJ/mol for **7a** .

11 Toupet, L. Université de Rennes. Details of the crystal structure of **6a** will be reported in a forthcoming full paper.

12 For some recent examples of hetero Diels-Alder reactions involving dienes bearing some structural similarities with diene **4**, see: a) Motoki, S.; Saito, T.; Karakasa, T.; Kato, H.; Matsushita, T.; Hayashibe, S. *J.Chem.Soc., Perkin Trans. 1*, **1991**, 2281-2283. b) Saito, T.; Karakasa, T.; Fuji, H.; Furuno, E.; Suda, H.; Kobayashi, K. *J.Chem.Soc., Perkin Trans. 1*, **1994**, 1359-1362. c) Saito, T.; Fujii, H.; Hayashibe, S.; Matsushita, T.; Kato, H.; Kobayashi, K. *J.Chem.Soc., Perkin Trans. 1*, **1996**, 1897-1903. d) Barluenga, J.; Tomás, M.; Ballesterós, A.; Lopez, L.A. *Tetrahedron Lett.*, **1989**, *30*, 6923-6926. e) Barluenga, J.; Tomás, M.; Ballesterós, A.; Lopez, L.A. *J. Org. Chem.* **1991**, *56*, 5680-5684. f) Barnish, I.T.; Fishwick, C.W.G.; Hill, D.R.; Szantai, C. *Tetrahedron*, **1989**, *45*, 6771-6790 and 7879-7898. g) Barnish, I.T.; Fishwick, C.W.G.; Hill, D.R. *Tetrahedron Lett.*, **1991**, *32*, 405-408. h) Bell, A.S.; Fishwick, C.W.G.; Reed, J. *Tetrahedron Lett.*, **1996**, *37*, 123-126.

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