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A REGIO- AND STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED PIPERIDONES

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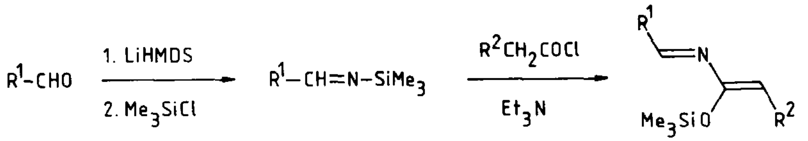
Abstract : The new activated 2-aza-1,3-dienes 1 are readily prepared by acylation of N-trimethylsilylimines 3. They react with electrophilic olefins to yield substituted piperidones 4 and 6 with high diastereoselectivity.

2-Aza-1,3-dienes bearing electron-releasing substituents at C-1 are excellent reagents for the synthesis of pyridones, tetrahydropyridones and pyrimidones[1,2]. Their reactions with electrophilic olefins are generally followed by spontaneous elimination of the substituent at C-1 and, as a result, stereochemical informations about the cycloaddition are lost. In a recent letter[2c], we described some preliminary work on the stereochemistry of cycloadditions involving a cyclic 2-aza-1,3-diene. We now report our preliminary observations on the stereochemistry of cycloaddition of acyclic 2-aza-1,3-dienes bearing no removable substituent at C-1.

Aldehydes 2 were readily converted[3] into the corresponding N-trimethylsilylimines 3 which were acylated in the presence of triethylamine to yield the new 2-aza-1,3-dienes 1 (Scheme 1). These were purified by distillation. They could be kept for several months at -78°C. The synthesis yielded only one stereoisomer[4].



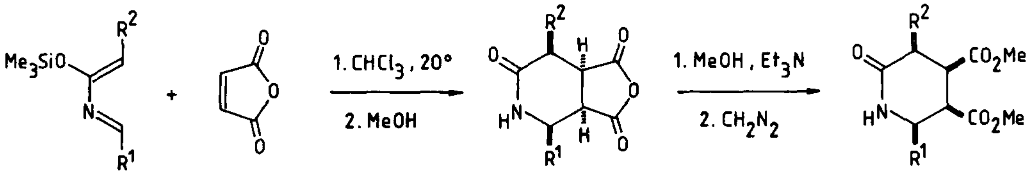
2a,b

3a R^1=Ph, 69%
3b R^1=tBu, crude

1a R^1=Ph, R^2=H, 72%
1b R^1=tBu, R^2=H, 80%
1c R^1=Ph, R^2=Me, 60%

Scheme 1

Dienes 1 reacted with maleic anhydride at room temperature to yield substituted piperidones 4 after methanolysis (Scheme 2). The values of coupling constants $^3J_{H_3H_4}$, $^3J_{H_4H_5}$ and $^3J_{H_5H_6}$ established the all-cis configuration of the adducts[5]. In the case of 4b, this was



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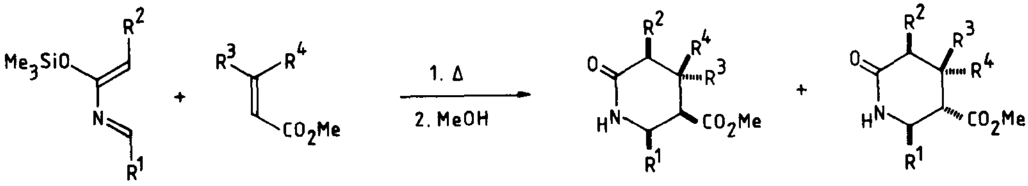
4a	R^1=Ph, R^2=H, 92%	5a	87%
4b	R^1=tBu, R^2=H, 90%	5b	90%
4c	R^1=Ph, R^2=Me, 84%	5c	89%

Scheme 2

confirmed by an X-ray cristallographic analysis[6]. Treatment of adducts 4 with methanol in the presence of a catalytic amount of triethylamine, followed by esterification with diazomethane yielded the corresponding cis-diesters 5 in good yields.

The Diels-Alder reaction of 1 with maleic anhydride thus takes place via an ENDO transition state. In contrast, the reaction of 1 with open chain α,β-unsaturated esters was highly EXO-selective (Scheme 3, Table 1) as indicated by the values of the coupling constants of the major or single stereoisomer[7].



1

6-endo

6-exo

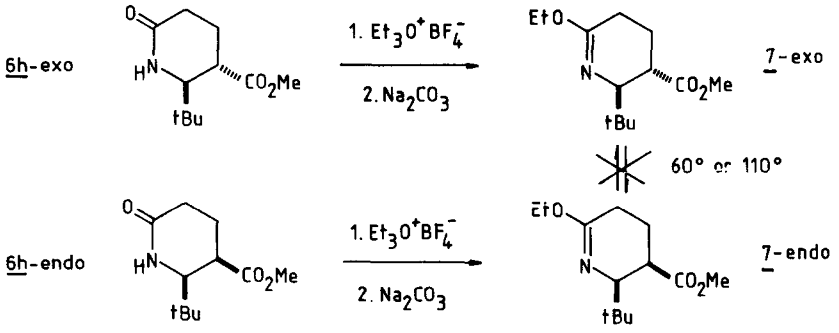
Scheme 3

A control experiment was performed in order to establish whether this unusual stereochemical outcome of an intermolecular Diels-Alder reaction was not due to equilibration of endo- and exo-stereoisomers under the reaction conditions. Iminoethers 7-endo and 7-exo were readily prepared from 6h-endo and 6h-exo respectively, using Meerwein's reagent[9] (Scheme 4).

Table 1 : Cycloaddition of 1 with α,β-unsaturated esters[8]

	R^1	R^2	R^3	R^4	Conditions	Yield of 6[a] [%]	Endo : Exo[b]
a	Ph	H	CO_2Me	H	$CHCl_3$, 61°, 4hrs	79	0 : 100
b	Ph	H	H	CO_2Me	PhH, 80°, 7hrs	82	20 : 80
c	Ph	H	H	H	PhH, 80°, 3hrs	76	0 : 100
d	Ph	H	Me	H	PhH, 80°, 24hrs	61	0 : 100
e	Ph	Me	Me	H	PhMe, 110°, 24hrs	54	0 : 100
f	Ph	Me	CO_2Me	H	$CHCl_3$, 61°, 14hrs	60	15 : 85
g	t-Bu	H	Me	H	PhMe, 110°, 24hrs	52	0 : 100
h	t-Bu	H	H	H	$CHCl_3$, 61°, 7hrs	54	25 : 75

(a) Pure products; (b) Determined on the crude reaction mixture after methanolysis



Scheme 4

Both 7-exo and 7-endo were recovered unchanged after prolonged heating in a sealed tube at 60°C or 110°C. This suggests that the Diels-Alder reaction of 1 with open-chain α,β-unsaturated esters is under kinetic control and preferentially proceeds via an EXO transition state.

In conclusion we have shown that the readily available 2-aza-1,3 dienes 1 bearing only one electron-releasing group at C-3 are still reactive enophiles. Their reaction with dienophiles provides a simple and practical route towards substituted piperidones. The reaction is totally regioselective and cis-stereospecific. The origin of the stereochemical dichotomy (endo versus exo preference) between open-chain and cyclic dienophiles is presently under study in our laboratory.

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4. These compounds have been characterized by ^1H NMR, ^{13}C NMR and IR.
5. For example : 4c : ${}^3J_{H_3H_4}$ = 5.5 Hz, ${}^3J_{H_4H_5}$ = 9.3 Hz, ${}^3J_{H_5H_6}$ = 4.6 Hz.
6. We thank Prof. M. Van Meerssche, Prof. J.P. Declercq and Dr. B. Tinant for this analysis.
7. For example : 6e-exo : ${}^3J_{H_3H_4}$ = 5.1 Hz, ${}^3J_{H_4H_5}$ = 10.9 Hz, ${}^3J_{H_5H_6}$ = 10.4 Hz
8. These compounds have been characterized by ^1H NMR, ^{13}C NMR, MS, IR and elemental analysis.
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