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FACE SELECTIVITY DURING THE CYCLOADDITION REACTION OF NITRILE OXIDES WITH IRON COMPLEXED TRIENES.

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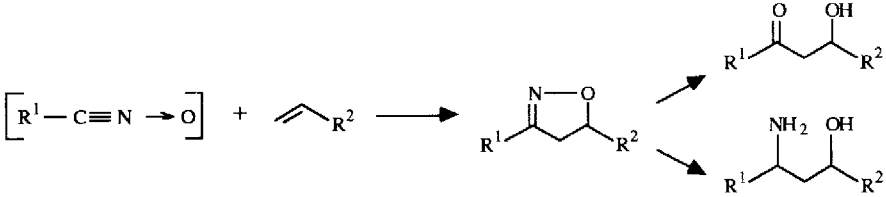
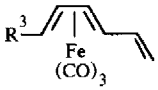
Summary : Various nitrile oxides were reacted with iron complexed trienes of type **1**. The reaction proceeded with good yield and diastereoselectivity (c.a. 90/10) to give Δ^2-isoxazolines which structures were determined by X-Ray and ^{1}H-NMR spectroscopy.

Δ^2-isoxazolines, obtained by [3+2] dipolar cycloaddition of nitrile oxides with olefins, are useful intermediates in the synthesis of β-hydroxyketones and γ-amino alcohols (1) (scheme 1).



Scheme 1

A chiral R^2 residue on the alkene can be used to discriminate the two Π-faces of the double bond during the cycloaddition reaction (2). We thought that the butadiene iron tricarbonyl residue would be suitable, and consequently compounds of type **1** would lead to



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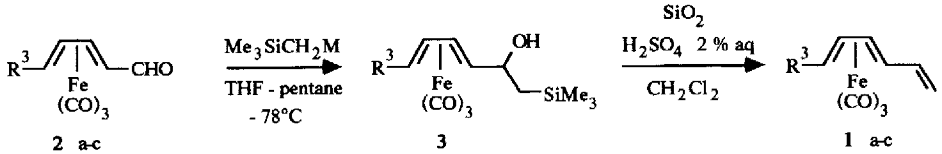
diastereoselective reactions. Since several butadiene iron tricarbonyl complexes have been prepared in optically active form (3), chiral isoxazolines could be synthesized in this way.

This communication presents the preparation of the complexed trienes **1** and their cycloaddition with nitrile oxides ; the study was carried out in the racemic series.

1 - Preparation of the complexed trienes 1

Aldehydes **2** a-c available in optically active form (R^3 = Me (4), $CH_2OSitBuPh_2$ (5), CO_2Me (6)) were chosen as precursors of the corresponding trienes **1** a-c. The Wittig reaction of **2a** with methylene triphenylphosphorane proceeded only in poor yield (≅ 25 %) in our hands (7). However, the Peterson olefination (8) gave satisfactory results (scheme 2). Thus, trimethylsilylmethyl lithium or magnesium chloride (1.5 equivalent, 1.0 M solution in pentane) was reacted with a THF solution of **2** at - 78°C for one hour. After usual workup, a mixture of diastereomeric alcohols **3** was obtained and converted without separation to the olefins **1** (9) by treatment with acidic silica gel in dichloromethane (2 % aqueous H_2SO_4, 70-230 mesh Merck Silica gel, 3-4 hours).



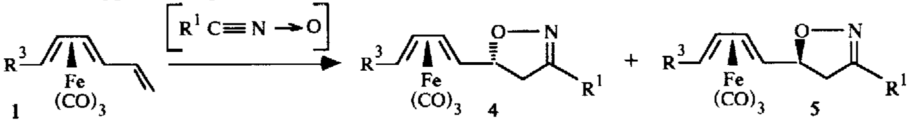
Entry	R^3	Me$_3$SiCH$_2$M	Overall yield of 1 from 2
a	Me	Me$_3$SiCH$_2$Li	90 %
b	CH$_2$OSitBuPh$_2$	Me$_3$SiCH$_2$Li	80 %
c	CO$_2$Me	Me$_3$SiCH$_2$MgCl	50 %

Scheme 2

2 - Nitrile oxide cycloaddition with complexed trienes 1 a-c

The results are summarized in table 1. The complexes 1 a-c (1 equivalent) were reacted with 1.25-2 equivalents of nitrile oxides generated in situ either by dehydration of nitro compounds (PhNCO, cat. Et$_3$N, benzene, room temp., 22 hours ; entries a-d, table 1) (10) or by dehydrohalogenation of hydroxymoyl chlorides (Et$_3$N, ether, room temp., 2 hours ; entries e-f, table 1) (11). A mixture of the two diastereomeric isoxazolines 4 and 5 was obtained. By-products were filtered off when necessary through a short silica gel pad (hexane-ethyl acetate) and the 4/5 ratio was determined by NMR integration of the methylene protons signals of the isoxazoline ring (C$_6$D$_6$, 300 MHz). In most cases, the major less polar product 4 was isolated by silica gel flash chromatography (9) in 65-83 % yield.

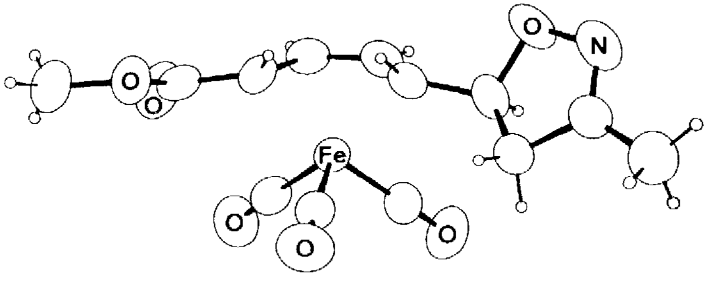
The stereochemistry of the cycloadducts is based on a single-crystal X-ray analysis of compound 4c (12) (R^3 = CO$_2$Me, R^1 = Me ; figure 1). By analogy, the major product in each case was assigned the same stereochemistry ; we have also noted that the chemical shifts for the methylene protons of the isoxazoline ring in compounds 4 are consistently deshielded ($\Delta\delta$ = 0.13-0.34 ppm), compared with the corresponding protons in compounds 5.



Entry	R^3	R^1	4 / 5 Ratio	Yield of 4 ^{a}
a	Me	Me	88/12	72 %
b	tBuPh$_2$ SiOCH$_2$	Me	90/10	70 %
c	CO$_2$Me	Me	88/12	75 %
d	Me	Et	86/14	65 %
e	Me	tBu	90/10	83 % ^{b}
f	Me	Ph	91/9	71 %

a) Unless noted, yield of product isolated by flash chromatography.
b) The two diastereomers could not be separated by flash chromatography ; the yield was evaluated by ^{1}H-NMR of the purified mixture.

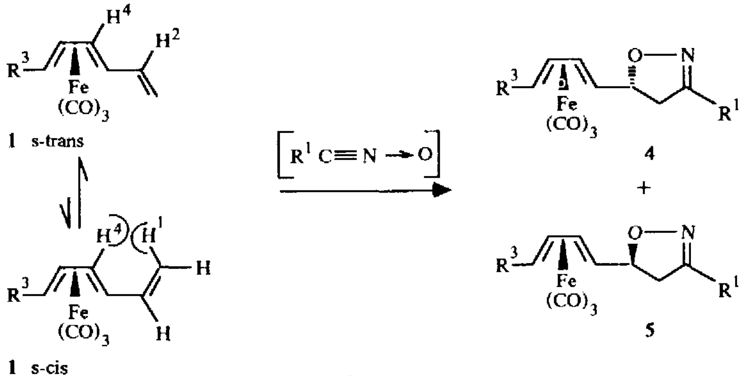
Table 1



X-Ray structure of the complexed isoxazoline 4c
Fig. 1

The diastereomer ratio 4/5 (about 90/10) does not seem to depend on the structure of the complex 1 or of the nitrile oxide. For compound 1f only, the cycloaddition reaction was carried out at a lower temperature (- 40°C), which did not improve the 4/5 ratio or the cycloaddition yield.

According to scheme 3, the observed diastereoselectivity can be explained assuming that :



Scheme 3

a) The nitrile oxide attacks anti to the bulky iron tricarbonyl group ;

b) The rotamers of 1 involved in the cycloaddition transition state are those having one face of the vinyl group sterically less hindered i.e. 1s-trans and 1s-cis rotamers. The attack of the nitrile oxide on the 1 s-trans form would lead to isoxazoline 4, whereas the attack on the 1 s-cis form would lead to its diastereomer 5.

Examination of a Dreiding model of the complexed triene 1 shows that the s-cis form is less probable, due to the steric interaction between the two protons H^1 and H^4, which would explain that the corresponding cycloadduct 5 is the minor isomer. The diastereoselectivity does not depend on :

a) The nature of the R^3 substituent of the complex, which does not significantly affect the rotameric preference.

b) The nature of the nitrile oxide, probably because in the transition state, R^1 is relatively far from the new asymmetric center.

The use of chiral complexed trienes 1 in cycloaddition reactions with nitrile oxides appears to be an interesting method to prepare optically active isoxazolines, which are precursors of β-hydroxy ketones (13) and γ-amino alcohols.

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