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α,β-UNSATURATED OXAZOLINES AND OXAZINE, USEFUL DIENOPHILES IN THE DIELS-ALDER REACTION

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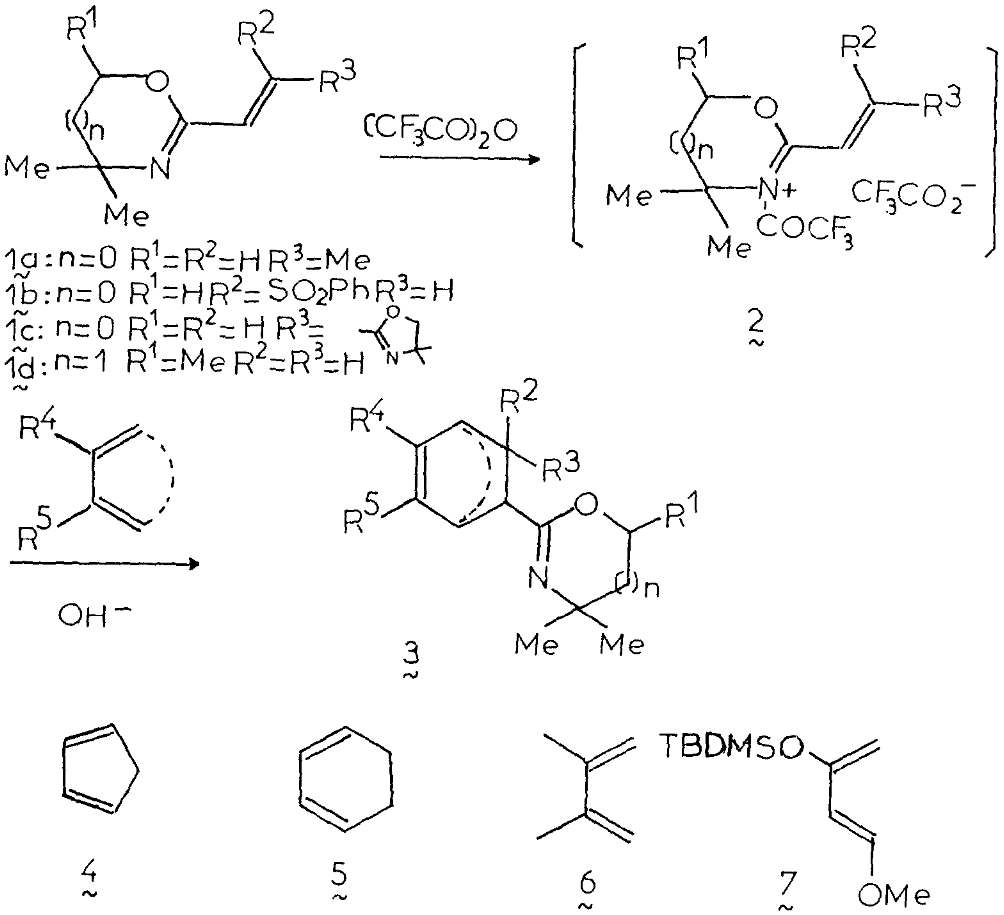
Abstract : α,β-Unsaturated oxazolines and oxazine "activated" with trifluoroacetic anhydride are reactive dienophiles in non thermic Diels-Alder reactions.

The Diels-Alder reaction (1), discovered nearly sixty years ago, is still the subject of considerable amount of work oriented towards both theory (2) and practice (3). Until a few years ago, efficient asymmetric Diels-Alder reactions have been achieved applying chiral dienes, chiral dienophiles (4) or chiral Lewis acids as catalyst (5). The high degree of asymmetric control is generally due to the use of Lewis acid catalysis which increases both the dienophilic reactivity and the chelation controlled stereoselectivity. During the course of natural products syntheses, we have been interested to develop new dienophiles which could be "activated" by reagents others than Lewis acids and which could be used in diastereo and enantioselective Diels-Alder reactions with various types of dienes. We anticipated that α,β-unsaturated oxazolines and oxazines which can be easily prepared as achiral and chiral dienophiles (6) could be activated with acyl halides or anhydrides following a concept that we developed some years ago for SN2' substitution (7,8). We wish to present our preliminary results obtained with achiral oxazolines and oxazine.

The general scheme is outlined below. In a typical experiment a solution of α,β-unsaturated oxazolines or oxazine (15 mmol) in anhydrous dichloromethane (15 ml) was treated with trifluoroacetic anhydride (1.1 eq) at - 78°C under argon. After 15 min., the diene (3 eq) was introduced and the reaction was monitored by TLC. Work-up and purification was achieved by sequential acidic and basic extractions to afford directly the Diels-Alder adduct.



Scheme

α,β-Unsaturated oxazolines **1a, 1b** and **1c** (9) and oxazine **1d** (10) have been tested in the Diels-Alder cycloaddition and the results are outlined in the Table. Several aspects of the data are noteworthy. Oxazoline **1a** reacted readily with cyclopentadiene **4** at - 78°C, the yield increased (75%) in the presence of propylene oxide or anhydrous calcium carbonate as acid scavengers. Oxazoline sulfone **1b** reacted with a variety of dienes but proved to be unreactive with the Danishefsky diene **7**. The enhanced reactivity of oxazine **1d** is probably due to the presence of the unsubstituted acrylic unit.

In the presence of trifluoroacetic acid, ethyl aluminium dichloride or without any reagent the cycloaddition of oxazoline **1a** with cyclopentadiene **4** did not take place between - 78°C and room temperature.

Dienophile	Diene	Reaction Temp [°C] (time, h)	Adduct Endo % (yield, %)
1a	**4**	- 78 (4)	$\geqslant$ 95 (65)
1b	**4**	- 78 (2)	50 (64)
1b	**5**	20 (20)	50 (54)
1b	**6**	0 (1)	(55)
1b	**7**	20 (20)	(0)
1c	**4**	- 40 (48)	(53)
1d	**4**	- 78 (1)	$\geqslant$ 90 (91)
1d	**6**	- 40 (20)	(61)

Table

Application of this original activation using an acyl oxazolinium salt intermediate is presently being investigated in our laboratory with chiral oxazolines in order to perform asymmetric Diels-Alder cycloadditions.

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