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[π4+π2] CYCLOADDITIONS OF ISOTHIAZOLE DERIVATIVES

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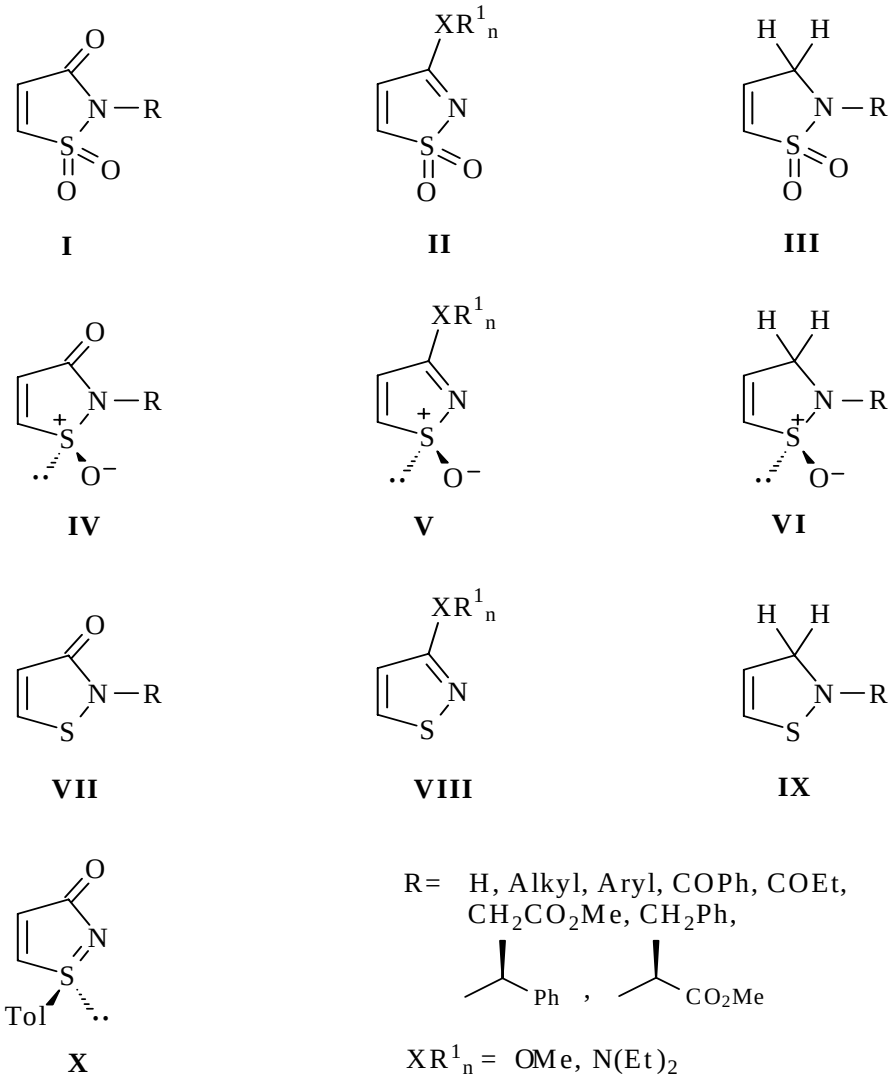
Dedicated to Professor Dr. Horst Wilde on the occasion of his 65th birthday.

Abstract - Dienophilic transformations of isothiazol-3(2*H*)-one 1,1-dioxides (**I**), 1-oxides (**IV**), α,β-unsaturated γ-sultams (**III**), and cyclic vinyl *p*-tolylsulfilimines (**X**) in Diels-Alder reactions with acyclic and cyclic dienes, 1-aza-1,3-butadienes, furan and 1,3-oxazoles are briefly considered. Isothiazol-3(2*H*)-one 1,1-dioxides (**I**), 3-alkoxy- and 3-dialkylamino-isothiazole 1,1-dioxides (**II**) also readily undergo 1,3-dipolar cycloaddition with diazoalkanes, azides, nitrile imines, nitrile oxides, oxazolones and muenchnones. This reaction is characterized by high degree of regioselectivity.

Contents

1. Introduction

There is no need to introduce cycloaddition reactions due to their generality and profound importance in organic synthesis.[1,2] Important role of sulfur functionality in the structure of olefins for cycloaddition reactions was shortly noticed earlier.[3l] In the series of isothiazoles only 1,3–and 1,4–cycloadditions (Diels-Alder reaction) have been known to this day. According to contemporary classification, based on the number of electrons involved in the process, these reactions belong to [π4+π2] cycloadditions. The subject of current review is [π4+π2] cycloaddition of isothiazoles and their oxygen-containing derivatives.



Scheme 1

Scheme 1 exhibits the main known types of isothiazole derivatives (**I-X**). Cycloaddition reactions are described only for isothiazoles of the types (**I-IV, VII, VIII,** and **X**).

Here we discuss solely 1,3- and 1,4-cycloaddition reactions of different dipoles to double C4-C5 bond of isothiazoles and their analogues. The emphasis is on the effect in these transformations of substituents at sulfur atom and influence of carbonyl and sulfonyl group in α-position to double bond of heterocycle, which acts as a dipolarophile. Reported [2+2] cycloadditions of isothiazoles of the type (**VIII**) with 2-amino-1-arylethine or diphenylketene[4-7] are not considered in the review.

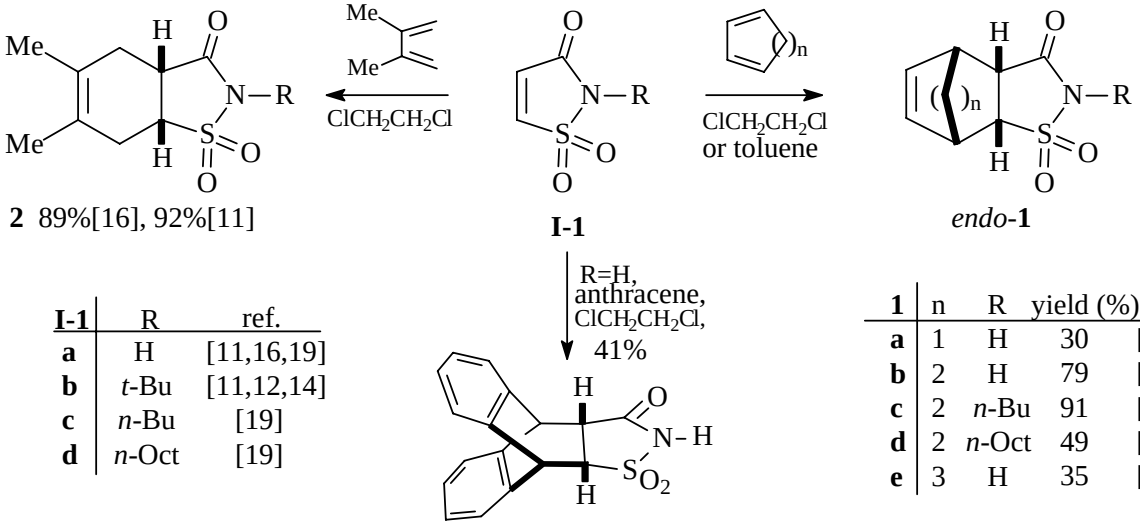
2. Diels-Alder Reactions

The Diels-Alder reaction is one of the most important methods for the preparation of cyclic systems with the potential for absolute stereochemical control at up to four contiguous centres in one step.[1]Of all isothiazole derivatives represented in Scheme 1, isothiazol-3(2*H*)-one 1,1-dioxides (**I-1**) and (**I-2**), sultams (**III-1**) and (**III-2**), chiral isothiazol-3(2*H*)-one 1-oxides (**IV-1**) and (**IV-2**), and cyclic vinyl-*p*-tolylsulfilimines (**X**) are most reactive and versatile substrates that act as dienophiles in Diels-Alder reaction. It is also noteworthy, that aforementioned compounds are much more active dienophilic components than semi-cyclic sulfoxides (**IV-2**).

In contrast, isothiazol-3(2*H*)-ones (**VII**),[8-15] the derivatives of isothiazolones (**I**) and (**IV**) with non-oxidized sulfur atom are relatively weak dienophiles and they were found not to react with several of the most reactive dienes under a range of reaction conditions including activation with Lewis acids.[16,17] Only the isothiazolone (**VII**) (R: Ph) reacts with 2,6-dichlorobenzonitrile oxide and they were considered as an exception in this transformations.[18] This reaction is depicted below in Scheme 33.

2.1. Isothiazol-3(2*H*)-one 1,1-Dioxides (I)

The first Diels-Alder reactions of isothiazol-3(2*H*)-one 1,1-dioxides (**I-1**) were successfully accomplished with 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene, and anthracene in boiling 1,2-dichloroethane to yield *endo*-cycloadducts (**1b-d**, **2** and **3**) (Scheme 2).[19] It has been reported later[11] that 1,3-cyclopentadiene and 1,3-cycloheptadiene react with **I-1a** in refluxing toluene over 2 h giving rise to 2-unsubstituted adducts (*endo*-**1a**) and (**1e**). From the spectroscopic data and on the basis of Diels-Alder mechanistic considerations, the kinetically controlled *endo*-cycloadducts (**1-3**) were predominantly formed. Saturated intermediates of **1** were prepared *via* hydrogenation of the adducts (**1a**, 53%) and (**1e**, 45%).



2 89%[16], 92%[11]

I-1

endo-**1**

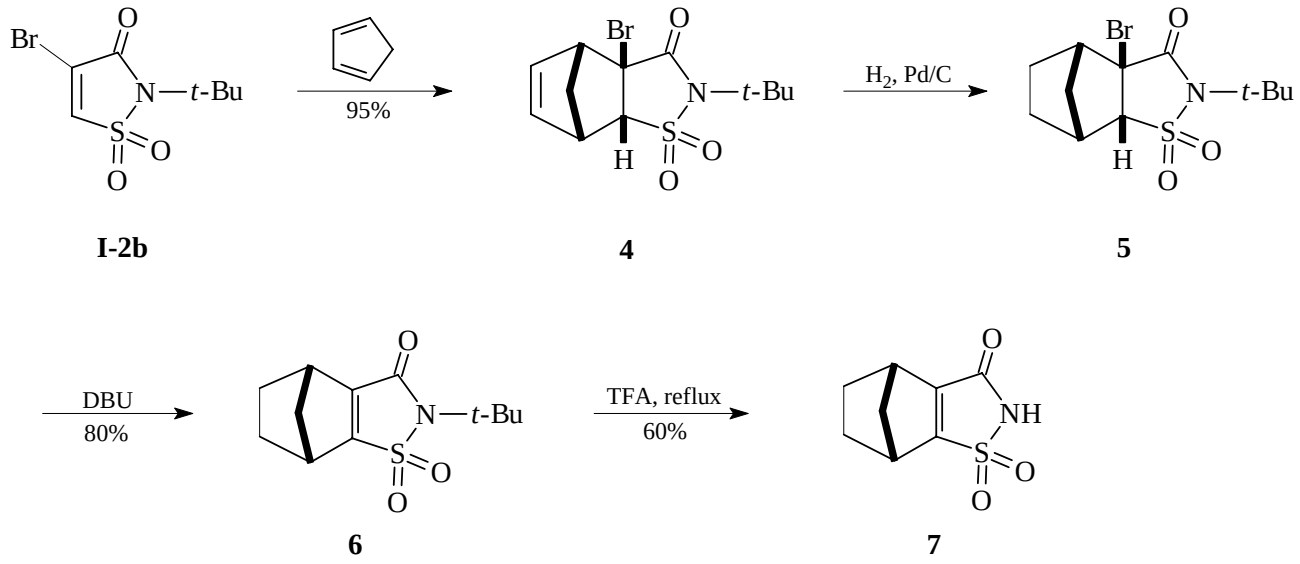
3

I-1	R	ref.
a	H	[11,16,19]
b	*t*-Bu	[11,12,14]
c	*n*-Bu	[19]
d	*n*-Oct	[19]

1	n	R	yield (%)	ref.
a	1	H	30	[11]
b	2	H	79	[19]
c	2	*n*-Bu	91	[19]
d	2	*n*-Oct	49	[19]
e	3	H	35	[11]

Scheme 2

If cycloaddition is carried out with the 4-bromo substituted isothiazole (**I-2b)**[12] using 1,3-cyclopentadiene as a diene, the *endo*-adduct (**4**) is formed in 95% yield.[20] Initial attempts to eliminate HBr from **4** led to complete decomposition of starting material. However, when the double bond in **4** was reduced by H_2 (Pd/C), elimination of HBr yielding **6** was easily achieved using DBU in benzene. Deprotection of **6** was performed with trifluoroacetic acid for 2 h to yield **7** (Scheme 3).

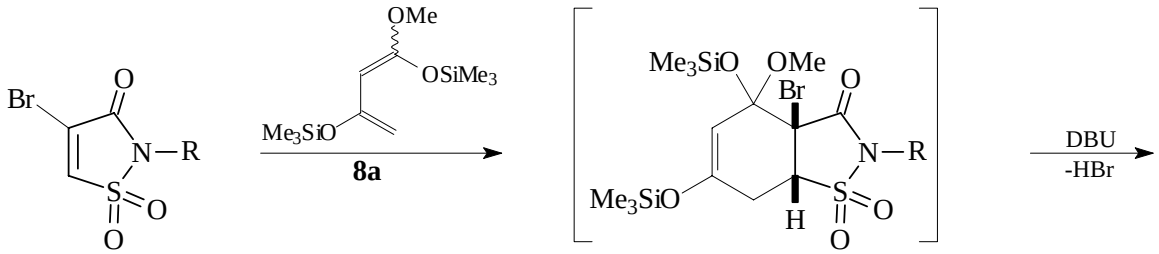


I-2b **4** **5**

6 **7**

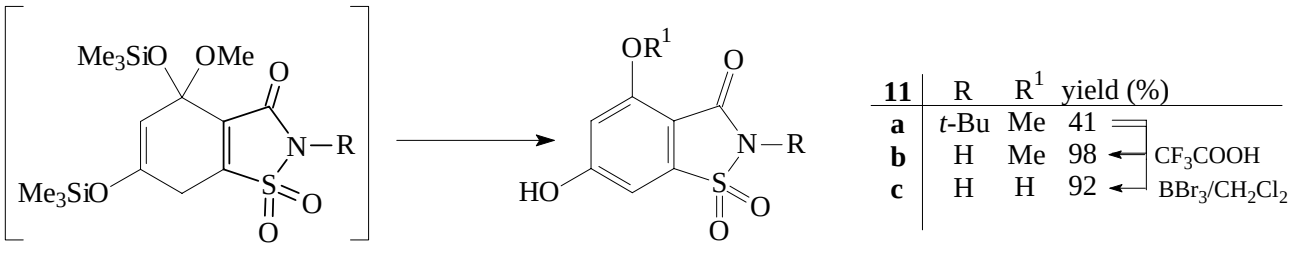
Scheme 3

A general method was developed recently for the synthesis of saccharin derivatives *via* Diels-Alder reaction. When 4-Bromoisothiazol-3(2*H*)-one 1,1-dioxides (**I-2b**,**e**) add to oxy-substituted 1,3-butadiene (**8**) in Diels-Alder fashion, [4+2] cycloadducts (**9**) are originated.[21] The subsequent cycloaromatization process is completed upon dehydrobromation of **9** with DBU, generating saccharin-like compound (**11a**) (Scheme 4). The resultant 4,6-dihydroxysaccharin (**11c**) was found to have a very sweet taste, but when the 4,6-phenolic groups were acetylated, the sweet taste was lost.



I-2b (R = *t*-Bu)
I-2e (R = CH_2CO_2Et)

9

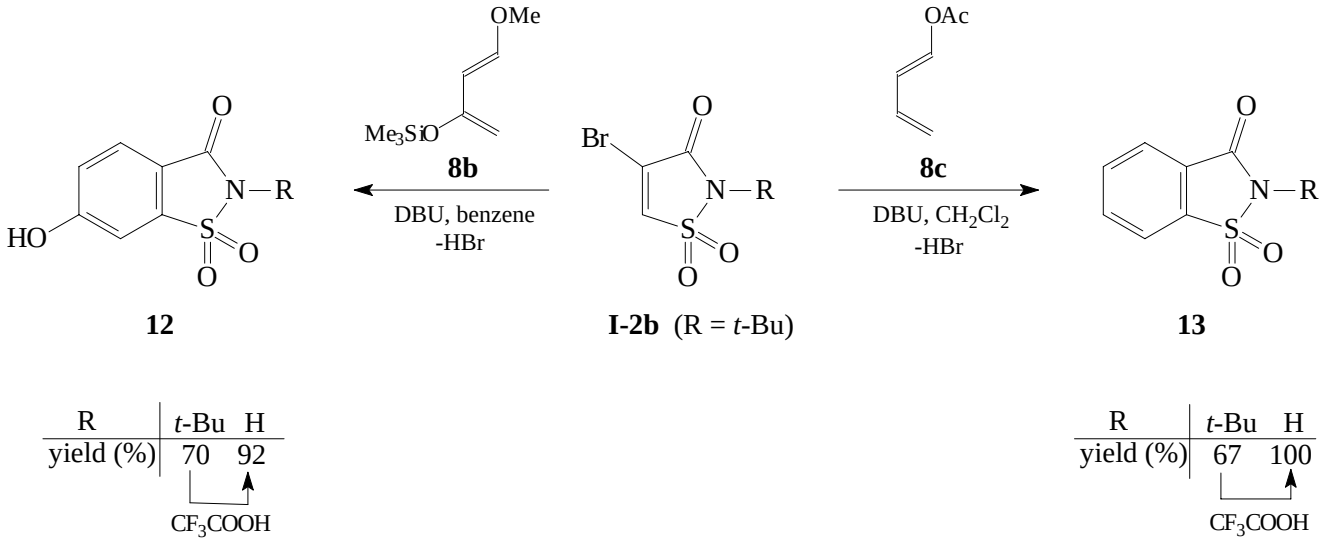


11	R	R^1	yield (%)	
a	*t*-Bu	Me	41	
b	H	Me	98	CF_3COOH
c	H	H	92	BBr_3/CH_2Cl_2

10 **11**

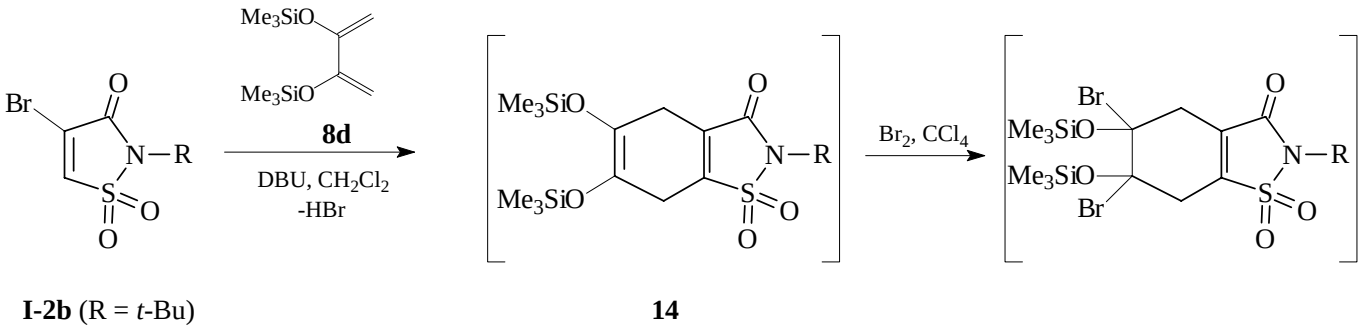
Scheme 4

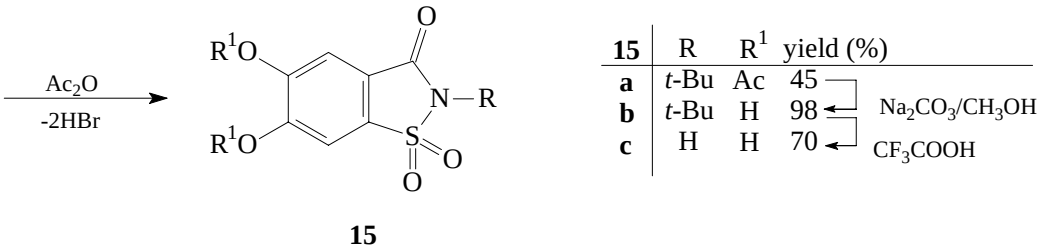
The dienophile (**I-2b**) reacts with diene (**8b)** in refluxing benzene yielding after elimination of HBr with DBU the 6-hydroxysaccharin derivative (**12a**) (R: *t*-Bu) (Scheme 5). Free 6-hydroxysaccharin (**12b**) (R: H) is formed with 92% yield when **12a** is refluxed with CF_3COOH. Pure **12b** has an extremely sweet taste.[21] The adduct with **8c** undergoes smooth dehydrobromation upon treatment with DBU furnishing 2-*tert*-butylsaccharin (**13**).



Scheme 5

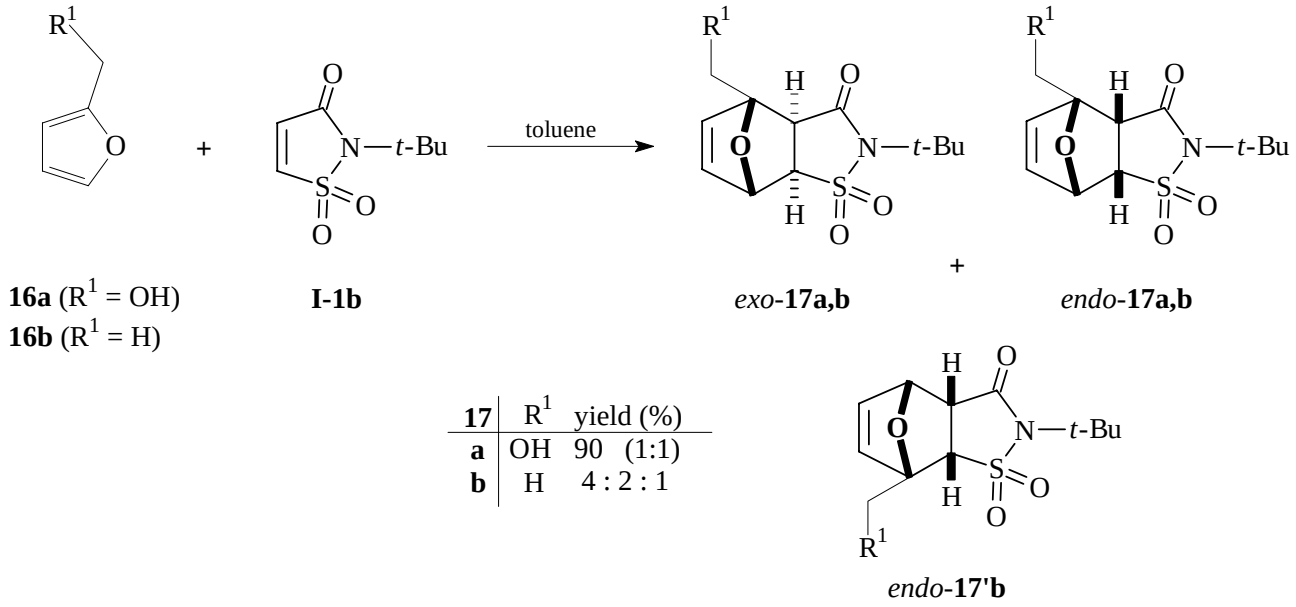
On the other hand, if both substituents at C-4 of the adduct (**14**) are H-atoms, a further dehydrogenation step is required to produce **15a** (Scheme 6). This is attained by adding of Br_2 to the electron-rich double bond of **14** followed by *in situ* elimination of two molecules of HBr.[21]





Scheme 6

Furfuryl alcohol (**16a**) smoothly reacts with **I-1b** in toluene to give 1:1 mixture of *exo*-**17a** and its *endo*-**17a** isomers in high yield. No evidence on the formation of alternative regioisomers *endo*-**17'b** was found by ^{1}H NMR spectral analysis of the crude reaction mixture. The structure of *exo*-**17a** isomer was established by X-Ray crystallography.[22] The observed regioselectivity was also confirmed by *ab initio* molecular calculations of the transition structures in this Diels-Alder reaction. It was found that the energy of the C-7 regioisomer is about 2 kcal/mol higher than that of the C-4 isomer. A secondary effect from intramolecular hydrogen bonding was also found to influence the regioselectivity of this cycloaddition (Scheme 7).

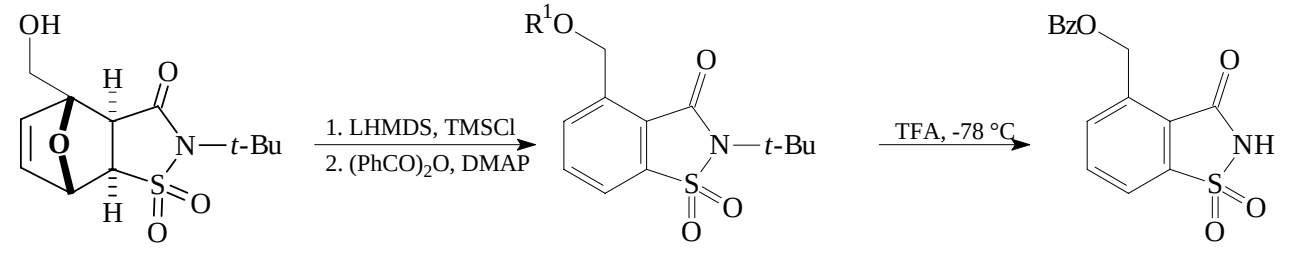


17	R^1	yield (%)
a	OH	90 (1:1)
b	H	4 : 2 : 1

endo-**17'b**

Scheme 7

If the Diels-Alder reaction is carried out with **I-1b** and 2-methylfuran (**16b**) under identical conditions**,** the products (**17**) of crude reaction mixture (^{1}H NMR) are one major *exo*-isomer **17b** and two *endo*-isomers (**17b** and **17'b**) in the ratio 4:2:1. Thus it is reasonable to assum, that regioselectivity of Diels-Alder reaction involving the asymmmetrically substituted dienophile can be influenced by intramolecular hydrogen bonding (Scheme 7).[22]
4-Hydroxymethyl-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (**18a**) could also easily be synthesized *via* highly regioselective Diels-Alder cycloaddition between furfuryl alcohol (**16a**) and isothiazole (**I-1b)**, followed by aromatization of the adduct (*exo*-**17a**) under basic conditions (Schemes 7, 8).[22] Formation of the aromatic saccharin derivative (**18a**) *via* dehydration of *exo*-**17a** and *endo*-**17a** adducts was than separately examined under various reaction conditions. It was found that dehydration of *exo*-isomer (**17a**) using LHMDS in the presence of TMSCl produced **18a** with 70% yield, and in absence of TMSCl the yield of **18a** was reduced to 33%. Interestingly, *endo*-**17a** reacts under identical conditions according to retro-Diels-Alder reaction[22] (Scheme 8). After protection of the benzylic hydroxyl group in isothiazole (**18a**) as a benzoate ester, the N-*tert*-butyl group of **18b** could be conveniently removed under acid conditions to give **19** in high yield (83%).



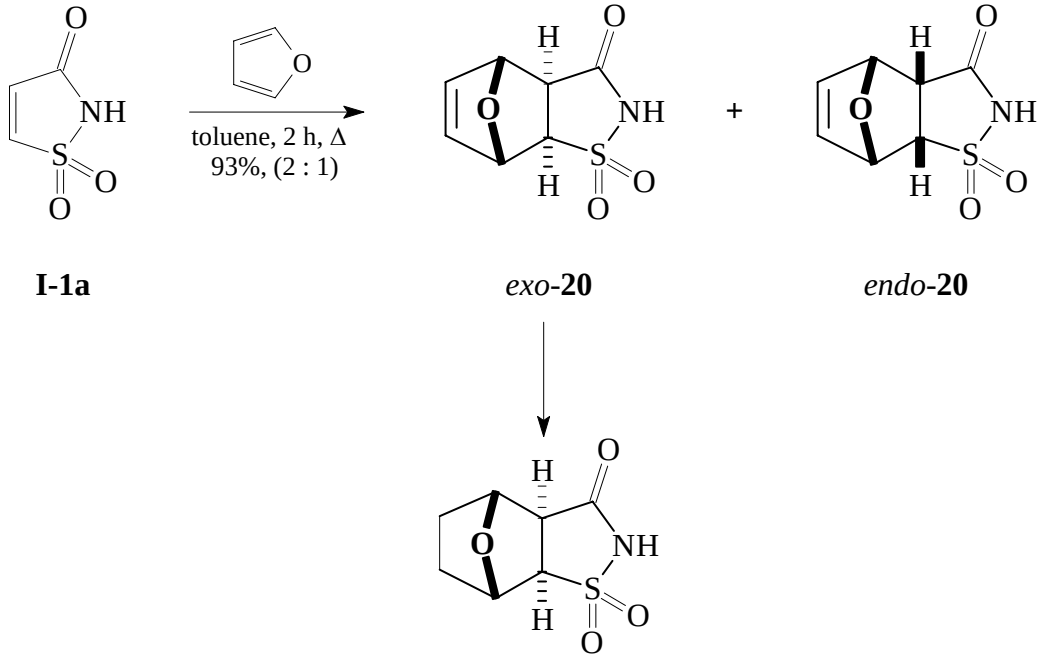
exo-**17a**

18a (R^1 = H)
18b (R^1 = PhCO)

19

Scheme 8

Futhermore, reaction of isothiazole (**I-1a)** with furan in refluxing toluene for 2 h produces a 2:1 mixture of fairly unstable *exo*- and *endo*-cycloadducts (**20**). *Exo*-isomer (**20**) was hydrogenated over Pd/C in dry THF to yield corresponding hexahydroepoxy-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (*exo*-**21**), respectively (Scheme 9).[11]

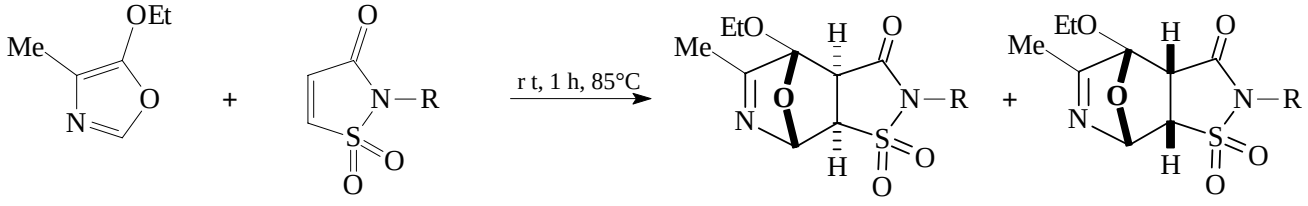


I-1a *exo*-**20** *endo*-**20**

exo-**21**

Scheme 9

Whereas the primary Diels-Alder adducts are very often too labile to be isolated, the adducts of 1,3-oxazole (**22**) with isothiazoles (**I-1b,e,f**) are apparently an exception. Surprisingly stable and isolatable Diels-Alder adducts (*exo*-**23**) and (*endo*-**23**) were formed at room temperature.[21] Usually, the *exo*-adducts prevail. Nevertheless, presence of a bulky N-substituent in **I-1b** appears to direct the kinetics of the process towards *endo*-isomer **23** (R: *t*-Bu). Thus **I-1b** reacts with **22** to produce *exo* : *endo* mixture (5:3) of **23b** (R = *t*-Bu). Transformation of the *exo*-**23b** and *endo*-**23b** isomers into pyridosaccharines (**24**) smoothly occurs with acidic catalysis. They can be isolated with up to 81% yields. The free saccharin (**24a**) could be obtained from **24b** upon treatment with CF_3COOH in the presence of anisole (Scheme 10).



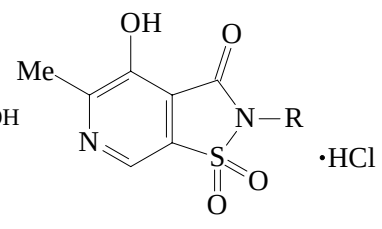
22 **I-1b** (R = *t*-Bu)
I-1e (R = CH_2CO_2Et)
I-1f (R = 4-$MeOC_6H_4CH_2$)

exo-**23** *endo*-**23**

HCl

24	R	yield (%)
a	H	34
b	*t*-Bu	63
e	CH_2CO_2Et	81
f	4-$MeOC_6H_4CH_2$	80

CF_3COOH



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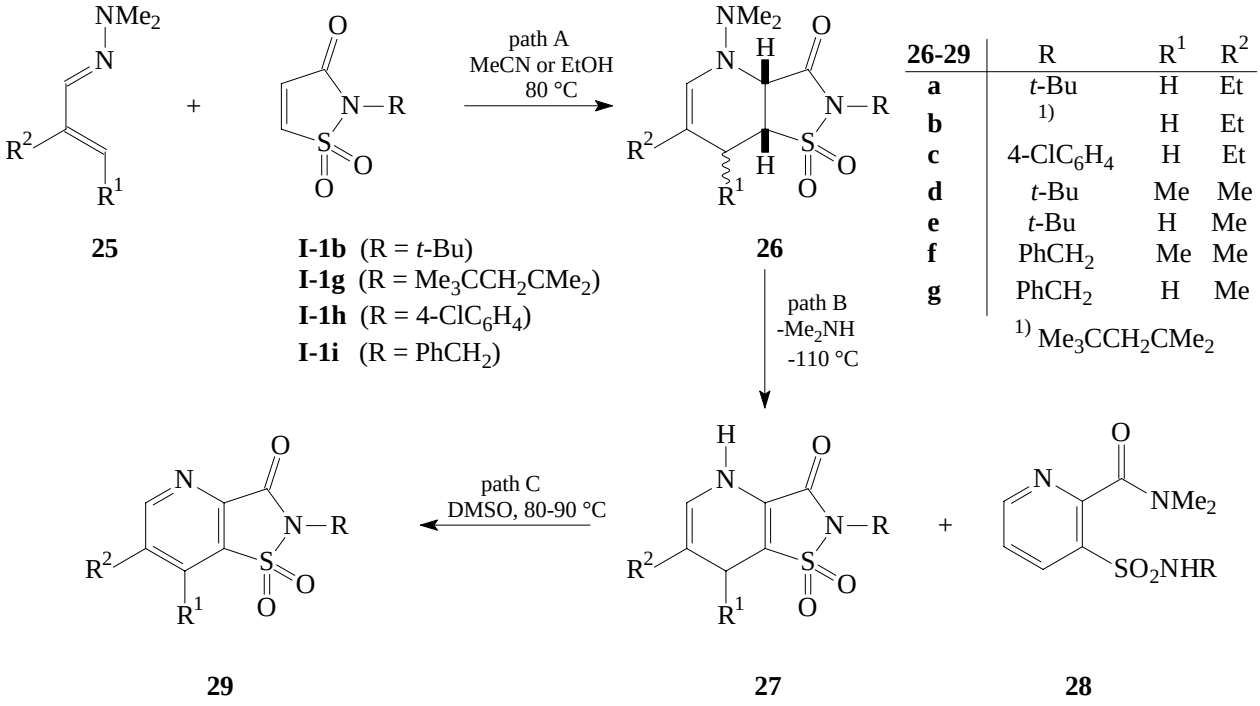
Scheme 10

Additional synthetic approach yielding stable cycloadducts of azasaccharins (**26a**, **b**, **d**) from isothiazolone 1,1-dioxides (**I-1b**, **g**-**I**) and 1-azadienes (**25**) was described recently (path A, Scheme 11).[24] Elimination of dimethylamine from **26a**, **b**, **d** (52-84%) in the mixture of toluene/silica gel at 110 °C produces dihydroazasaccharins (**27**) (48-73%, path B). In the case of **26c,** the yield of **27c** is only 6%, and 42% of **28c** is obtained . When transformation of **25** into **26** was carried out under thermo-dehydrating conditions in DMSO at 80-90 °C (path C), pyridine derivatives (**29d**, **e**, **f**) (21-58%) and sulfonamides (**28f**, **g**) (18%, 43%) were formed. The dehydration of **27a** with MnO_2 in AcOH yields **29a** (94%).



26-29	R	R^1	R^2
a	*t*-Bu	H	Et
b	[1]	H	Et
c	4-ClC_6H_4	H	Et
d	*t*-Bu	Me	Me
e	*t*-Bu	H	Me
f	$PhCH_2$	Me	Me
g	$PhCH_2$	H	Me

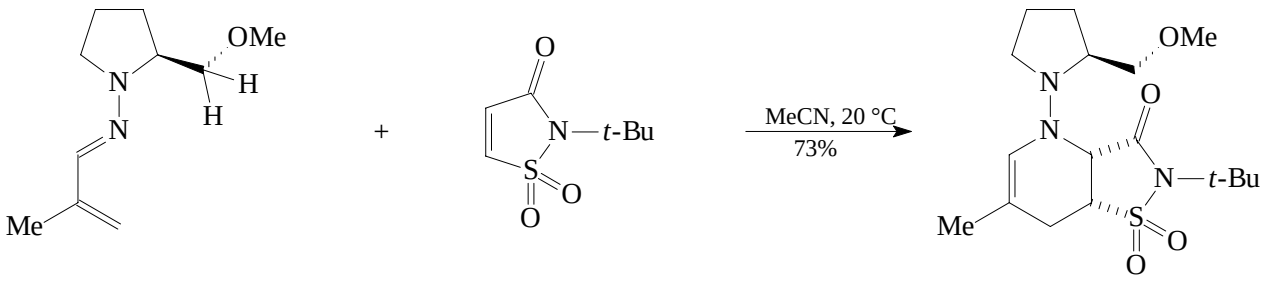
[1] $Me_3CCH_2CMe_2$

25 **I-1b** (R = *t*-Bu) **I-1g** (R = $Me_3CCH_2CMe_2$) **I-1h** (R = 4-ClC_6H_4) **I-1i** (R = $PhCH_2$) **26** **29** **27** **28**

Scheme 11

Summarizing, the direction of [4+2] cycloaddition of 1-aza-1,3-butadiens (**25**) and isothiazoles (**I-1b**, **g**, **h**, **i**) depends on the nature of substituents R, R^1, R^2 and solvents giving rise to azasaccharin derivatives (**29**) or their precursors (**26**) and (**27**). The regioselectivity of cycloaddition is apparently governed by the σ- and π-acceptor effect of carbonyl group of dienophiles (**I-1**) but not through the vinylsulfone part of isothiazole structure.[24]

The asymmetric Diels-Alder reaction is a powerful method for the synthesis of enantiomerically pure six-membered rings.[25-27] We here report the first examples of Diels-Alder cycloadditions of asymmetric hetero-1-azadienes which are readily available by condensation of α,β-unsaturated aldehydes with enantiomerically pure hydrazines.[25] The chiral 1-azadienes (**30**) smoothly react with cyclic dienophile (**I-1b**) at room temperature in acetonitrile to form cycloadduct (**31**).[28] The absolute configuration of crystalline adduct (**31**) was established on the basis of X-Ray diffraction analysis (Scheme 12).

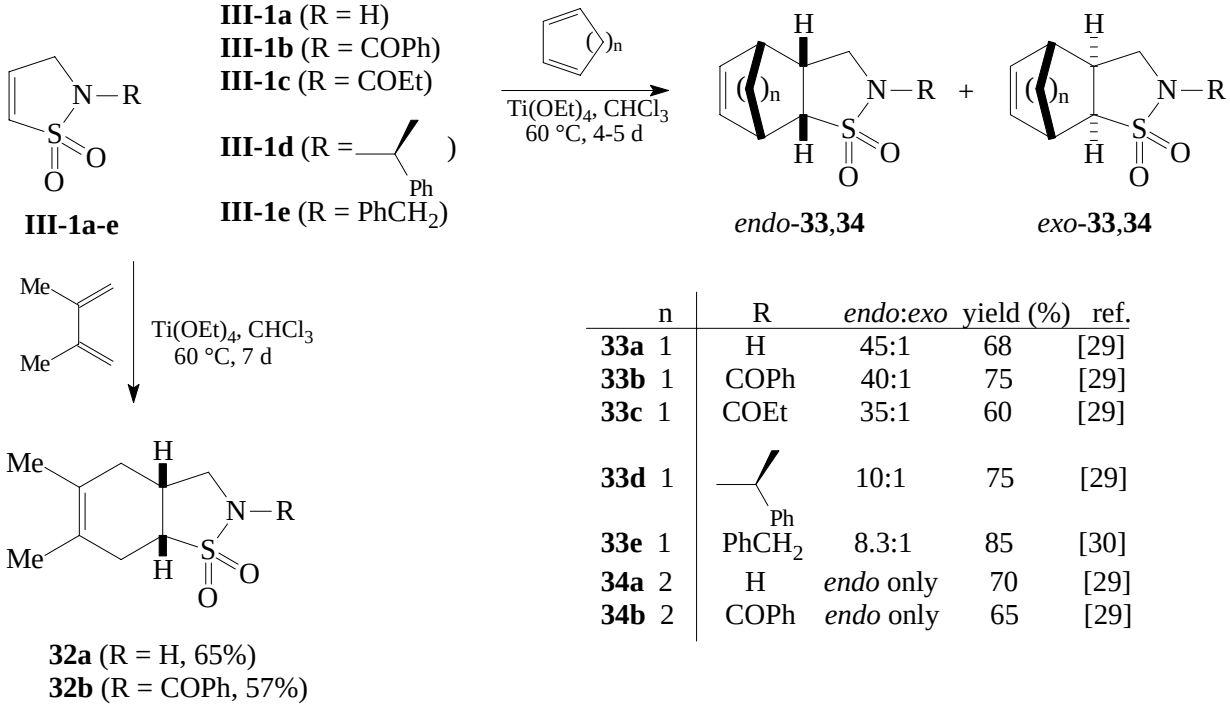


30 **I-1b** **31** (≥ 98% de)

Scheme 12

2.2. α,β-Unsaturated γ-Sultams (III)

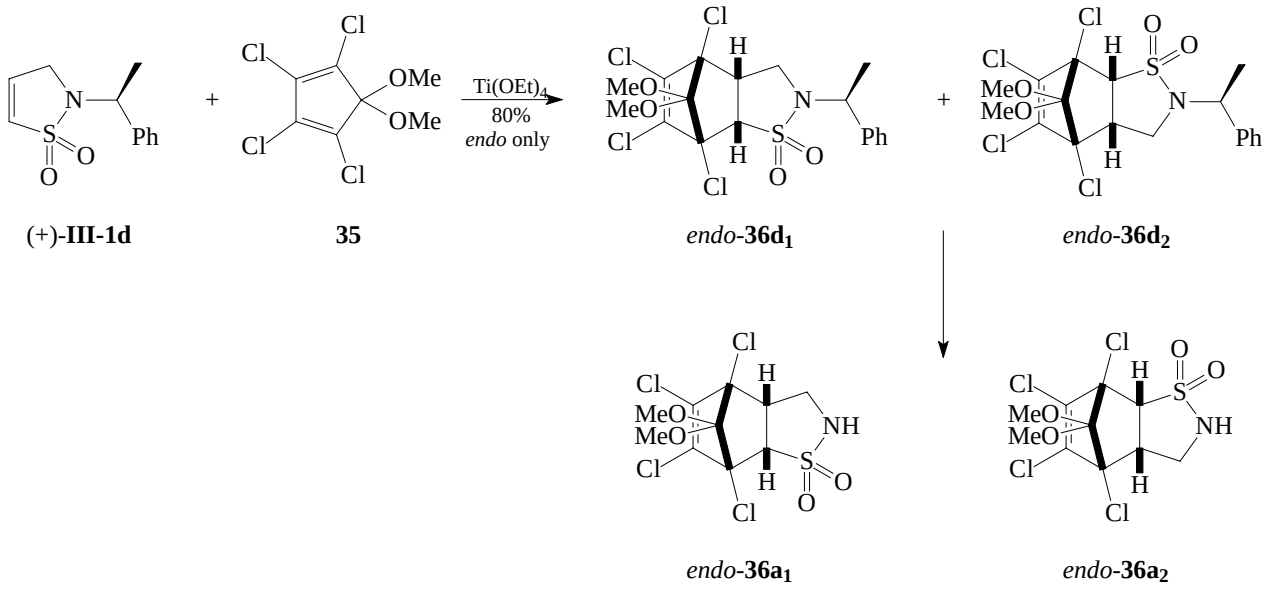
A new mode of cycloaddition was described for reaction of dienes with α,β-unsaturated γ-sultams.[29,30] In this reaction the electron withdrawing ability of sulfonamide group was shown to activate *an carbon-carbon unit as dienophile* in Diels-Alder reactions. The first example of intramolecular Diels-Alder reaction of vinylsulfonamides was reported by Metz and co-workers.[31-33] Sultams (**III-1a-d**), which are easily available from the corresponding unsaturated sulfon[34] and substituted amines, form easily stable cycloadducts (**32a**, **b**, **33a-d** and **34a**, **b**) by reaction with cyclic and acyclic 1,3-dienes in good yields (Scheme 13).[29] It requires a few days at 110 °C to complete these reactions. Several Lewis acids were screened to enhance the reactivity of **III-1** and it was found that $Ti(OEt)_4$ gave the best results. When *the* homochiral γ-sultam [(+)-**III-1d**] was subjected to uncatalyzed Diels-Alder reaction with cyclopentadiene, a mixture of diastereomeric cycloadducts (**33d**) with *endo* : *exo* ratio of 7:3 in 80% yield was obtained . They can be isolated *in* optically pure forms by column chromatography. After debenzylation, optically pure *exo* and *endo*-tricyclic sultams (**33a**) were obtained.[29] The Diels-Alder reaction of **III-1e** with cyclopentadiene at 50 °C (12 h) in the presence of Et_2AlCl as a catalyst yields a mixture of *endo*-**33e** and *exo*-**33e** adducts (8.3:1.0) (Scheme 13).[30]
The sultams (**32**) and (**33**) (R: *n*-Bu) could be also prepared from corresponding sultons after ring opening with *n*-butylamine and ring closure.[34]



	n	R	*endo*:*exo*	yield (%)	ref.
33a	1	H	45:1	68	[29]
33b	1	COPh	40:1	75	[29]
33c	1	COEt	35:1	60	[29]
33d	1		10:1	75	[29]
33e	1	$PhCH_2$	8.3:1	85	[30]
34a	2	H	*endo* only	70	[29]
34b	2	COPh	*endo* only	65	[29]

Scheme 13

In the reaction of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**35**) with isothiazole **III-1d** under uncatalyzed or Lewis acid-catalyzed conditions, only the *endo*-diastereomers (**36d$_1$**) and (**36d$_2$**) (1:1) were obtained. Both *endo*-diastereomers were isolated in optically pure forms and structure of one of them (*endo*-**36d$_1$**) was determined by X-Ray analysis. A new pair of enantiomerically pure tricyclic sultams (**36a$_1$**) and (**36a$_2$**) were obtained after debenzylation of cycloadducts **36d$_1$,d$_2$** (Scheme 14).[29]

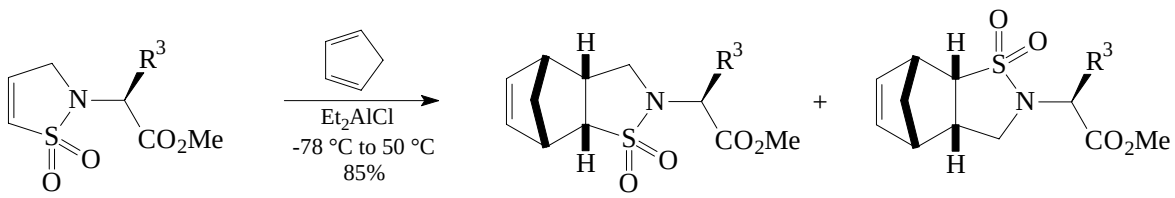


(+)-**III-1d** **35** *endo*-**36d$_1$** *endo*-**36d$_2$**

endo-**36a$_1$** *endo*-**36a$_2$**

Scheme 14

Amino acid-derived α,β-unsaturated γ-sultams (**III-1f-h**) and (**III-2a**, **b**), containing *exo*-cyclic or γ-*endo*-cyclic stereogenic centers, are generated *via* ring-closing metathesis (RCM).[35] These sultams undergo stereoselective Diels-Alder reaction to yield *endo*-norbornenylsulfonamides (**37f-h**) as the major diastereomers.[30] These cycloadducts undergo adequately ring-opening metathesis polymerisation (ROMP), yielding oligomeric sulfonamides. *endo*-Diastereomers (**37f**, **g**) were readily separated *via* large scale column chromatography and X-Ray analysis allowed to make unambiguous assignment of the *endo*-configuration of diastereomers (**37g$_1$**) and (**37g$_2$**) (Scheme 15).[30]



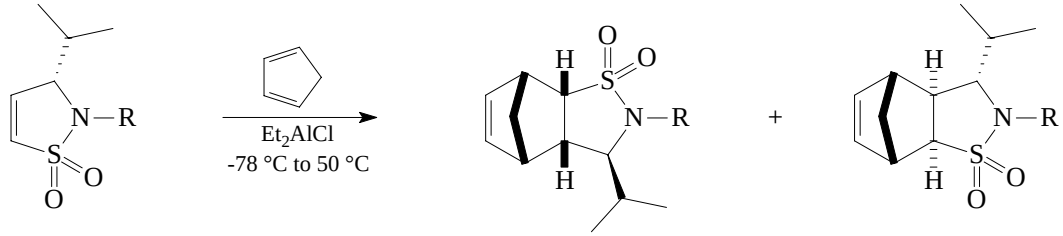
III-1f (R = $CHMe_2$)
III-1g (R = CH_2Ph)
III-1h (R = CH_2CHMe_2)

endo-**37f$_1$** (R = $CHMe_2$)
endo-**37g$_1$** (R = CH_2Ph)
endo-**37h$_1$** (R = CH_2CHMe_2)

endo-**37g$_2$** (R = CH_2Ph)
endo-**37h$_2$** (R = CH_2CHMe_2)

Scheme 15

Sultams (**III-2a**, **b**) underwent cycloaddition with cyclopentadiene under Lewis acid catalysis with complete facial selectivity arising from *anti*-approach of cyclopentadiene to isopropyl group.[30] Interestingly, the yield and *endo*/*exo* ratio of cycloadducts obtained were strongly temperature dependent.



III-2a (R = H)
III-2b (R = $PhCH_2$)

endo-**38a** (R = H)
endo-**38b** (R = $PhCH_2$)

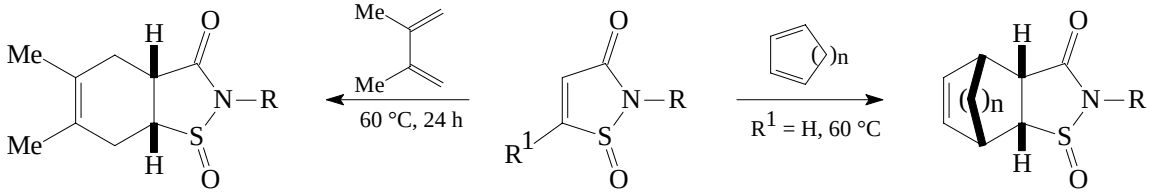
exo-**38b** (R = $PhCH_2$)
exo-**38c** (R = CH_2CHMe_2)

Scheme 16

In each case *endo*-adducts (**38a**) and (**38b**) were formed as the major diastereomers, and X-Ray crystallography provided unambiguous proof of stereochemistry for cycloadduct **38a** (Scheme 16). It was demonstrated that *endo*-**38b** and *exo*-**38b** adducts could be readily separated *via* column chromatography, whereas separation of *endo*-**38a** and *exo*-**38a** isomers at the same conditions failed.

2.3. Isothiazol-3(2*H*)-one 1-Oxides (IV)

The dienophilic behavior of racemic isothiazol-3(2*H*)one 1-oxides (**IV-1a-e**), synthesized by oxidation of isothiazolones (**VII**),[16] in Diels-Alder reactions with anthracene, cyclic and acyclic dienes was investigated by J.Brennan and coworkers.[19] It was shown that 2,3-dimethyl-1,3-butadiene, 1,3-cyclopentadiene, 1,3-cyclohexadiene underwent facile cycloaddition with **IV-1a-e** at elevated temperatures in 1,2-dichloroethane and dioxane to produce only one cycloadduct (**39a**, **d** or **40a-e**) in each case (Scheme 17).[19]

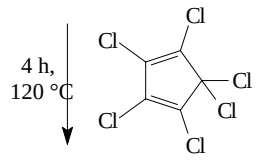


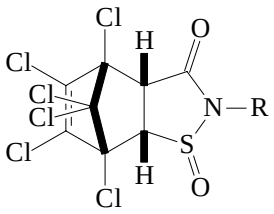
39a (90%)
39d (51%)

IV-1a-d

endo-**40**

IV-1	R	R^1	ref.
a	H	H	[16,19]
b	Me	H	[19]
c	*n*-Bu	H	[19]
d	*n*-Oct	H	[16]
e	Me	Cl	[19]



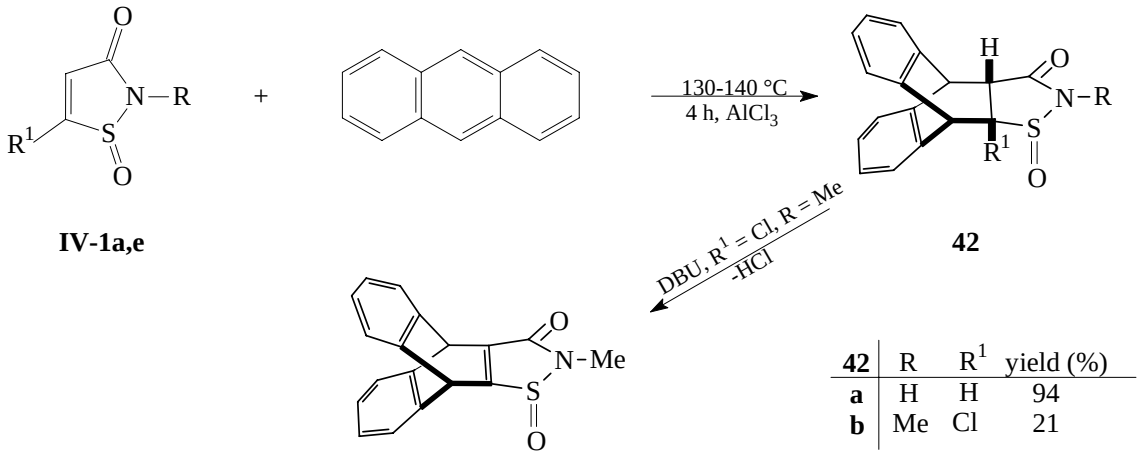


endo-**41** (33%)

40	n	R	yield (%)
a	1	H	88
b	2	H	61
c	2	Me	93
d	2	*n*-Bu	41
e	2	*n*-Oct	97

Scheme 17

Hexachlorocyclopentadiene and anthracene, the two less reactive and more sterically hindered dienes, required temperatures above 100 °C, and in these cases cycloaddition reactions were catalysed by $AlCl_3$ giving rise to **41** and **42a**, **b**. Relying on sharply outlined melting points and data of NMR spectra it was concluded that resultant adducts (**41**, **42**) were diastereoisomerically pure compounds. The authors suggested on the basis of mechanistic considerations, that the kinetically controlled *endo*-products were formed. The anthracene adduct (**42b**) was dehydrochlorinated to form (**43**) (Schemes 17 and 18).[19]

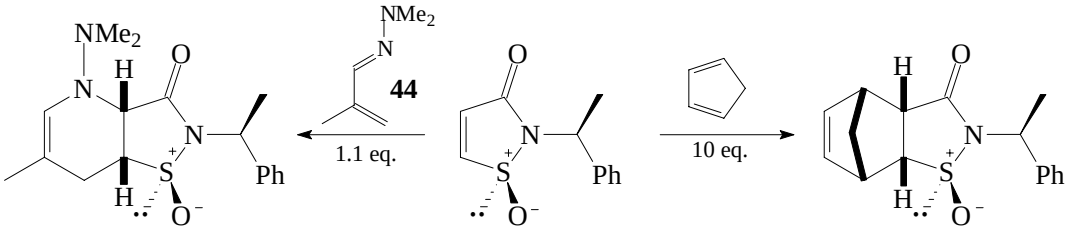


IV-1a,e **42** **43** (34%)

42	R	R^1	yield (%)
a	H	H	94
b	Me	Cl	21

Scheme 18

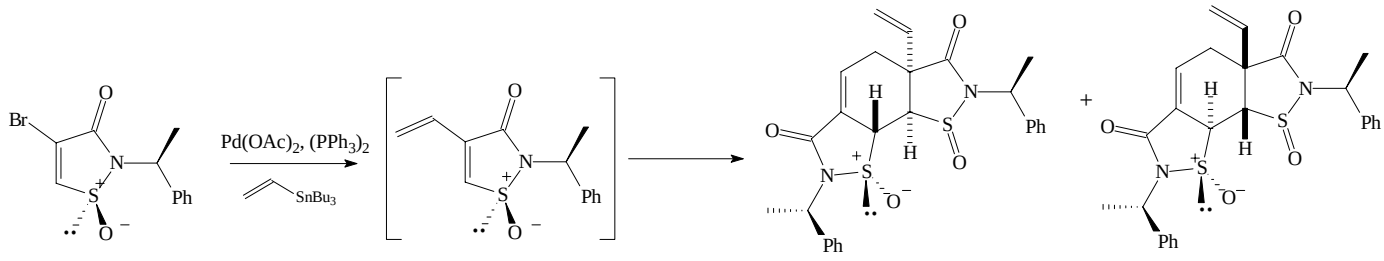
Diels-Alder cycloaddition of highly efficient dienophile, homochiral 2-((*S*)-1-phenylethyl)isothiazol-3(2*H*)-one (*S*)-1-oxide (**IV-1f**), proceeds in the *endo* fashion with cyclopentadiene and 1-azadiene (**44**) producing corresponding cycloadducts (**40f**) and (**45**) with good yields.[36] A high degree of diastereofacial selectivity was observed in the process(Scheme 19).



45 (85%, >98% de) (*S*)-**IV-1f** **40f** (94%, 96% de)

Scheme 19

Homochiral isothiazol-3(2*H*)-one (*S*)-1-oxide (**IV-2a**) was also used as dienophile in this reaction, and a high degree of diastereofacial selectivity was observed as well. At the same time the parent 2-((*S*)-1-phenylethyl)-4-vinyl-isothiazol-3(2*H*)-one (**VII**), prepared using Stille methodology from the 4-bromo derivative,[37] was unreactive as a diene in Diels-Alder reaction. Combining of the major diastereomeric sulfoxide derivative (**IV-1g**) with vinyltributyltin yielded a single product (**46**) (33%) apparently resulting from a remarkably high diastereoselective Diels-Alder dimerization (Scheme 20).[17,38]

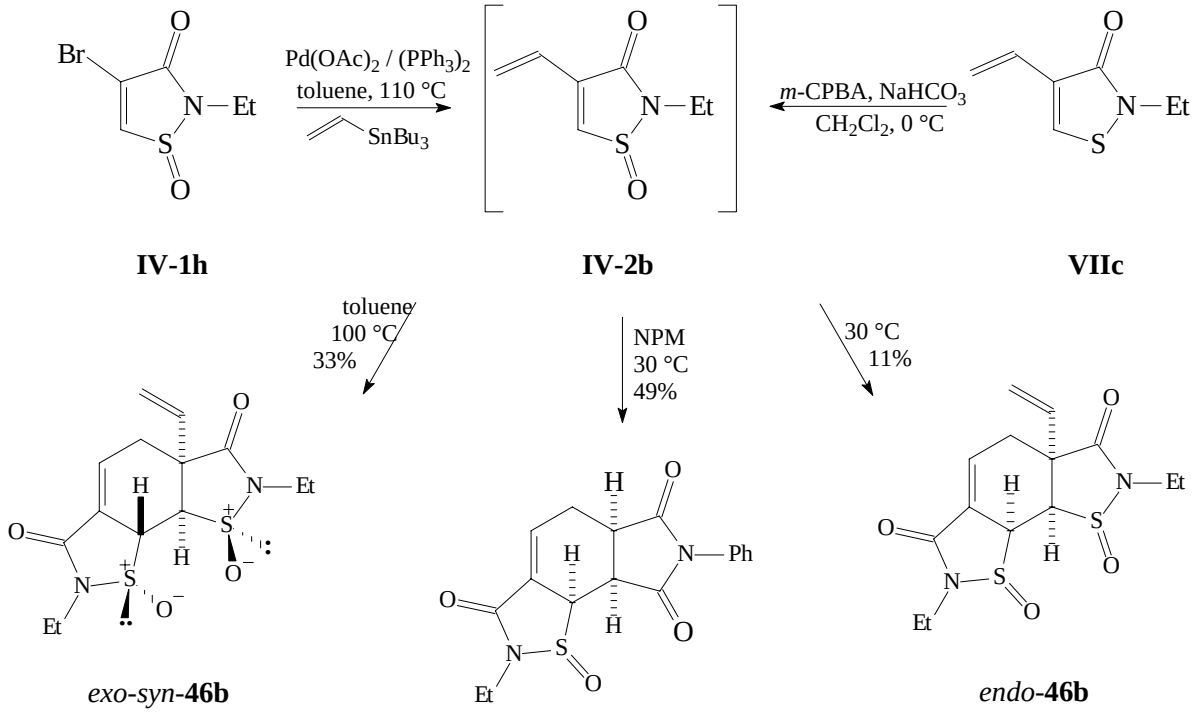


IV-1g **IV-2a** *exo-syn*-**46a** *exo-anti*-46a

Scheme 20

According to NMR and MS spectral data the obtained compound is the dimer (**46**). Unfortunately, it was not possible to prepare good crystals of this cycloadduct to determine the absolute stereochemistry by X-Ray analysis. But results of semi-empirical calculations predict a strong preference for transition state of *exo-syn*-isomer (**46a**), which is *ca.* 6 kcal*mol^{-1} lower in energy than transition state leading to the *exo-anti*-adduct (**46a**). Thus, in addition to dipole alignment, metal chelation may also greatly affect the diastereoselectivity (Scheme20).

Vinylation of **IV-1h** using CH_2=CH-$SnBu_3$ resulted in the formation of a single cycloadduct (*exo-syn*-**46b**). The dimeric product was found to be highly crystalline by single crystal X-Ray analysis. This dimer results exclusively from an *exo-syn* transition state (scheme 21).[38] To avoid the dimerization by the Stille methodology, it was necessary to generate the diene at much lower temperature. Oxidation of **VIIc** with *m*-CPBA at 0 °C gave a new product, the dimer (*endo*-**46b**). It was suggested that at these conditions the reactive intermediate of the process is **IV-2b**, but all attempts to isolate this species had failed. However, trapping *in situ* of diene (**IV-2b**) with *N*-phenylmaleimide was quite successful and *endo*-**47** was obtained with 49% yield in a completely diastereoselective cycloaddition.



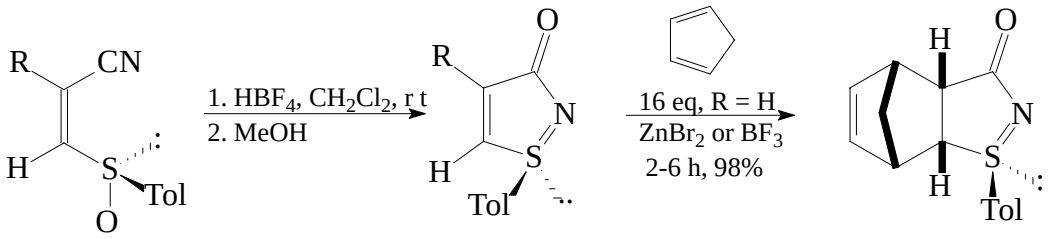
Scheme 21

In summary, it was shown that Diels-Alder dimerization of semi-cyclic sulfoxide containing dienes, 4-vinylisothiazol-3(2*H*)-ones is highly diastereoselective *via* a proposed *exo-syn* transition state stabilized by possible metal chelation. Additionally, the development of effective asymmetric oxidation of a racemic diene system could lead *via* oxidative route to a simple, homochiral dienes of the type **IV-2a**.

2.4 Cyclic Vinyl *p*-Tolylsulfilimines (VIII)

Another kind of chiral dienophiles are cyclic vinyl-*p*-tolylsulfilimines (**49a, b**) that were prepared from corresponding (*Z*)-sulfinylacrylonitriles (**48a**, **b**) by their reaction with HBF_4. The ability of the sulfilimine moiety to enhance the dienophilic reactivity of the double bond is similar to that of the sulfinyl group. This fact can be explained as a consequence of the lower bond order of the S=N bond with respect to the S-O one and a higher electronic deficiency at sulfur atom.

The asymmetric Diels-Alder reaction of optically pure **49a** with cyclopentadiene under mild thermal or catalysed conditions yielded only *endo*-**50** adduct with complete *endo* and π-facial selectivities (Scheme 22).[39] This selectivity can be easily explained by assuming a steric approach control of the diene from the less hindered face of the dienophile.



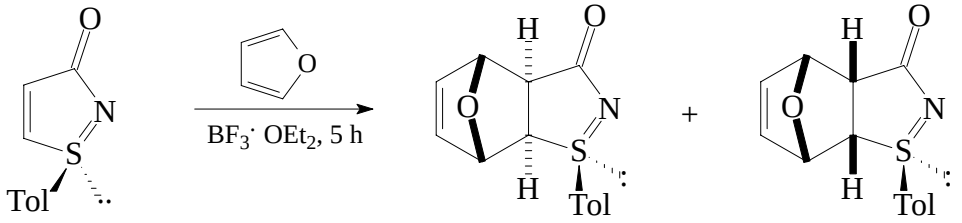
48a (R = H)
48b (R = *t*-Bu)

49a (R = H)
49b (R = *t*-Bu)

endo-**50** (>97% de)

Scheme 22

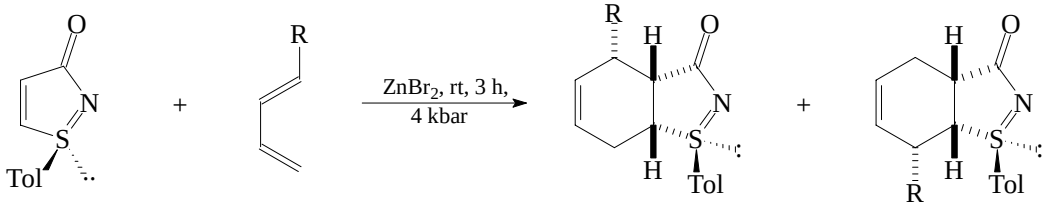
The best results in cycloaddition of **49a** with furan were obtained using low temperature (-20°C) process catalysed by $BF_3 \cdot OEt_2$. As a result, the formation of *exo*-**51** as the major product was observed, which could be easily isolated in diastereomerically pure form with 85% yield (Scheme 23).[40]



49a *exo*-**51** 94:4 *endo*-**51**

Scheme 23

The Diels-Alder reaction of sulfinilimine (**49a**) with acyclic dienes such as (*E*)-1-methoxy-1,3-butadiene (**52a**) and piperylene (**52b**) using high pressure and catalyst progressed with complete regio-, *endo*-, and π-facial selectivities, yielding solely *endo*-adduct **53a$_1$** (100%) (Scheme 24).[40] Under the same conditions, reaction with **52b** gave a mixture of the regioisomers (*endo*-**53b$_1$**) and (*endo*-**53b$_2$**) (87:13), but once again the π-facial and the *endo*-selectivity of the processes were complete.



49a

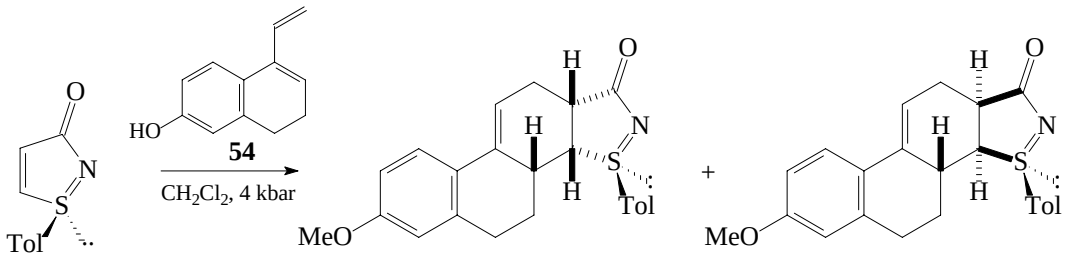
52a: R = OMe
52b: R = Me

endo-**53a$_1$** (100%)
endo-**53b$_1$** (87%)

endo-**53b$_2$** (13%)

Scheme 24

The reaction of **49a** with **54** (Dane's diene) takes place only at high pressure (4 kbar), affording mixtures of two stereoisomers (*endo*-**55**) and (*exo*-**55**) (86:14). In the presence of catalyst ($ZnBr_2$) the stereoselectivity of cycloaddition decreased (70:5).



49a *endo*-**55** (86%) *exo*-**55** (14%)

Scheme 25

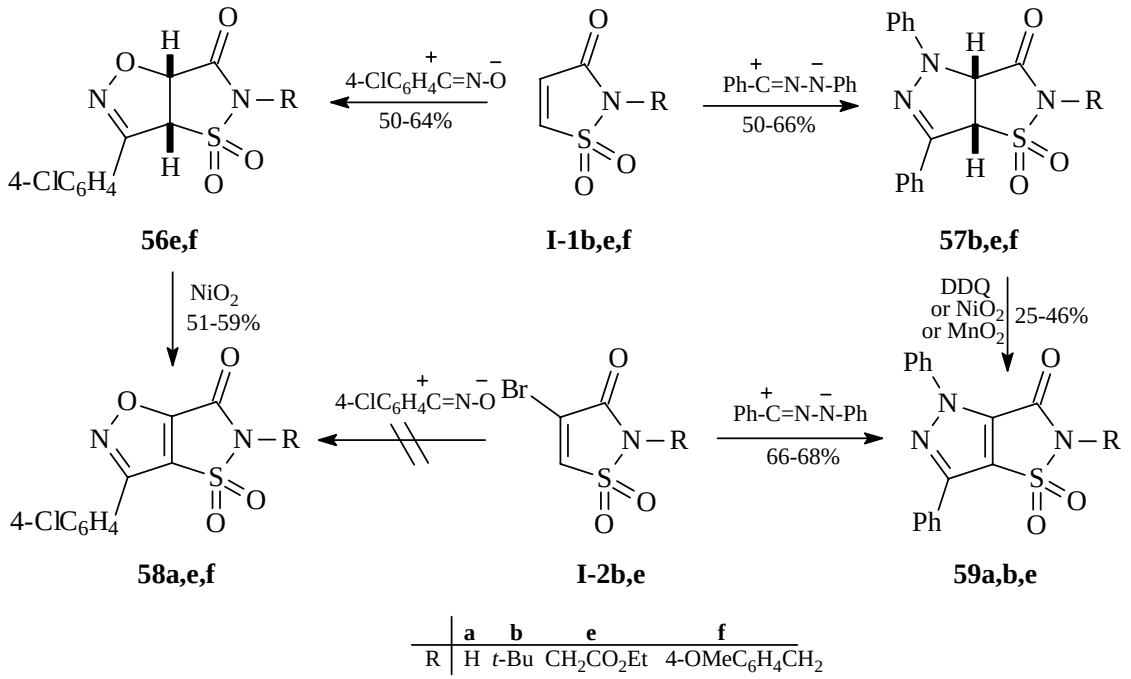
In summary, the high *exo*-selectivity observed in reactions of **51** with furan contrasts with the almost complete *endo*-selectivity with other cyclic and acyclic dienes. Theoretical studies regarding stereoselectivity, Lewis acid catalysis, and solvent effects in these Diels-Alder reactions were reported.[41]

3. 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloaddition is another method of preparation of cyclic systems,[42-45] which is of a comparable or even greater importance than Diels-Alder reaction. The 1,3-dipolar cycloaddition to isothiazoles and their derivatives makes it possible to produce unusual heterocycles, which are promising substrates for further transformations. Out of the isothiazole derivatives cited in Scheme 1, the isothiazol-3(2*H*)-one 1,1-dioxides (**I-1-3**),[12,46,47] 3-diethylaminoisothiazole 1,1-dioxides (**II-1**),[48-54] as well as 3-methoxyisothiazole 1,1-dioxides (**II-2**)[47] and isothiazol-3(2*H*)-ones (**VII**)[18] are the most reactive and versatile dipolarophiles in 1,3-dipolar cycloaddition.
Isothiazol-3(2*H*)-one 1,1-dioxides (**I**) and 3-diethylaminoisothiazole 1,1-dioxides (**II-1**) are quite reactive dipolarophiles which undergo 1,3-dipolar cycloaddition with a wide range of dipoles under mild conditions,[12,48-54] whereas the unoxidized isothiazol-3(2*H*)-ones (**VII**) are referred to as poor dieno- and dipolarophiles that are found not to react with several of the more reactive dienes.[19] The only known cycloaddition reaction to compounds (**VII**) is that of stable nitrile oxides.[18]
The 1,3-dipolar cycloaddition to 3-methoxyisothiazole 1,1-dioxides (**II-2**) is not sufficiently studied yet, and they are expected to have the same reactivity as 3-diethylaminoisothiazole 1,1-dioxides (**II-1**).[47]

3.1. Isothiazol-3(2*H*)-one 1,1-Dioxides (I)

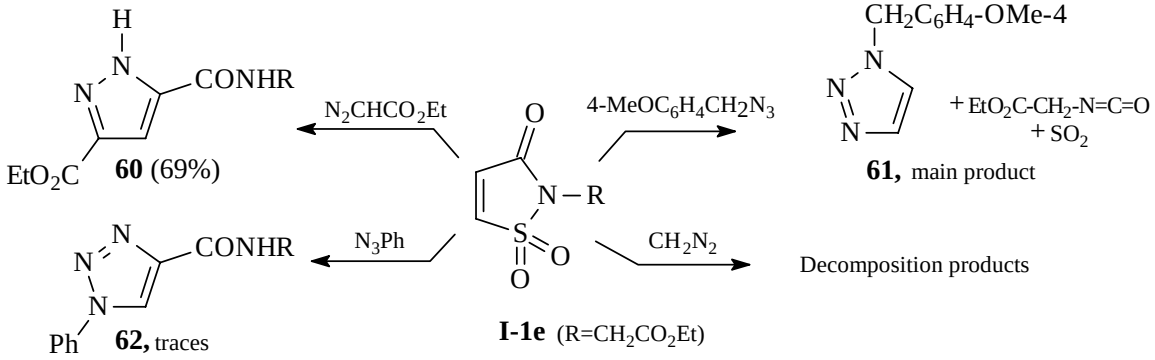
The first 1,3-dipolar cycloadditions of isothiazole derivatives were carried out with compounds of the type (**I**) as dipolarophiles. This reaction in fact represented a new approach for the synthesis of several saccharin derivatives, which there upon were converted to oxicams, a known class of anti-inflammatory agents.[12,46]
The compounds (**I-1**) can be regarded as electron-deficient dipolarophiles, thus they should resemble derivatives of maleic acid, known to form adducts with such 1,3-dipoles as diphenylnitrilimine,[55] phenyl azide,[56] benzonitrile oxide[57] and diazoalkanes.[58]
Isothiazol-3(2*H*)-one 1,1-dioxide (**I-1**) as it was shown previously, forms cycloadducts with nitrile imines and nitrile oxides (Scheme 26).[12]



Scheme 26

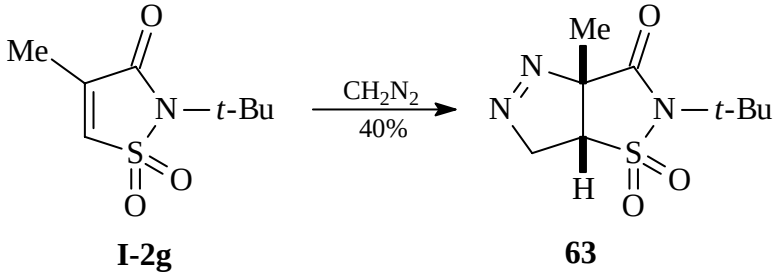
Out of many examined agents, only DDQ, MnO_2 and NiO_2 are able to dehydrogenate **57** to form aromatic system (**59**) with low yield. Identical pyrazoles (**59**) can be generated more efficiently by adding of a dipole to 4-bromoisothiazol-3(2*H*)-one 1,1-dioxide (**I-2b,e**) followed by *in situ* dehydrobromination.

Interestingly, the stability of adducts in the case of cycloaddition of azides and diazo compounds depends on a presence of a substituent at C4-C5 double bond. In the case of cycloaddition to 4,5-unsubstituted isothiazol-3(*2H*)-one 1,1-dioxide (**I-1e**), no simple cycloadducts were detected (Scheme 27).[12]



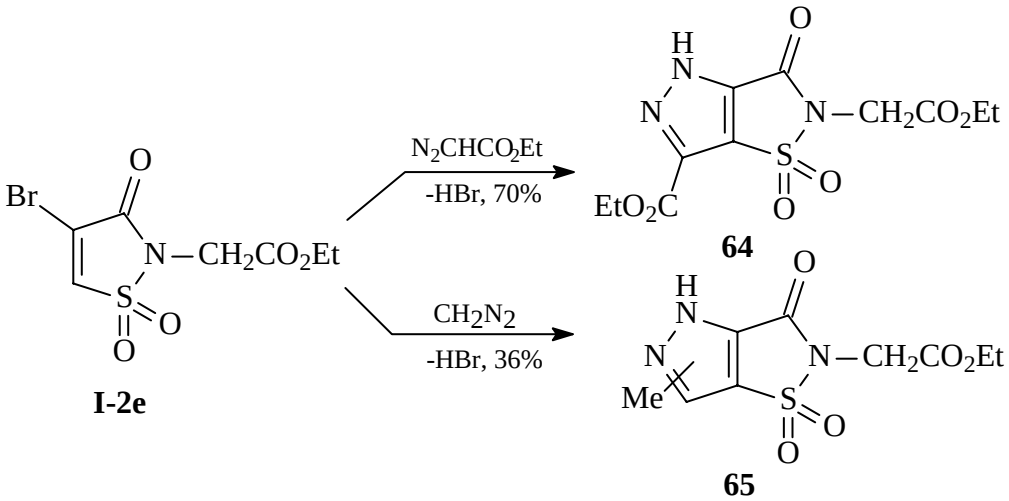
Scheme 27

The presence of a bridgehead methyl group presumably stabilizes the cycloaddition adduct (Scheme 28).[12]



Scheme 28

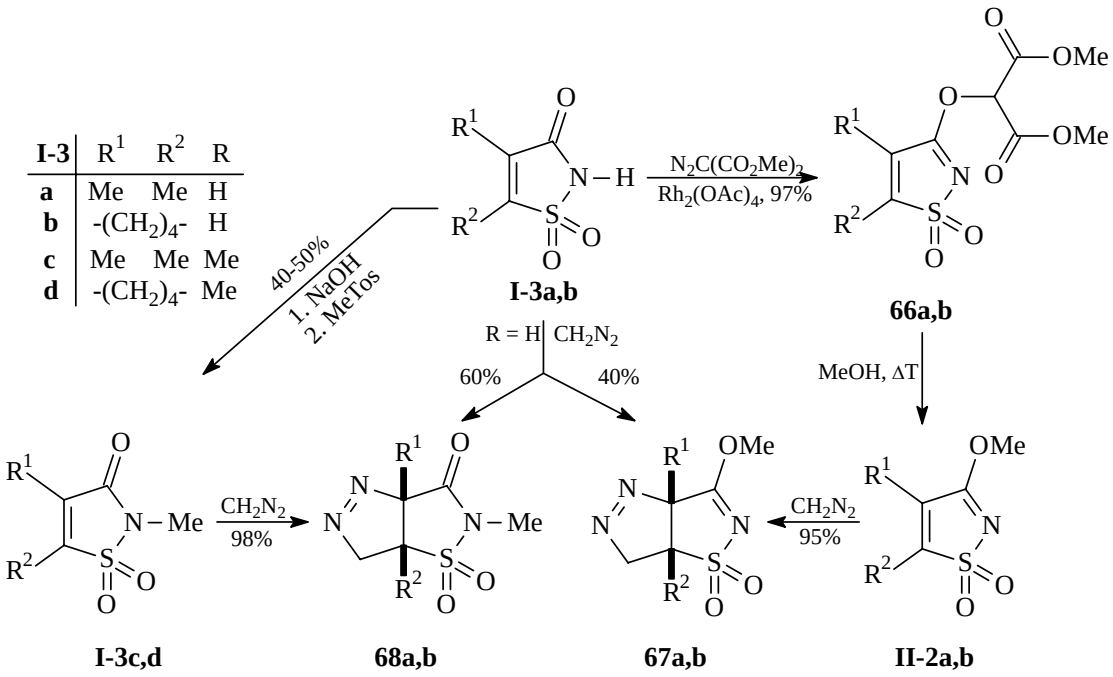
The presence of Br at C4 allows stabilisation of cycloadduct by means of losing of HBr and aromatizing to pyrazoles (**64,65**) (Scheme 29).[12]



Scheme 29

4,5-Alkyl- or aryl-disubstituted isothiazol-3(2*H*)-one 1,1-dioxides[59-63] are proposed not to undergo 1,3-dipolar cycloaddition reaction as all of the attempts of Diels-Alder cycloaddition to the C4-C5 double bond of these substrates failed. It was postulated that a cycloaddition is not possible because of a steric hindrance by a double bond.[60]

Nevertheless, the cycloaddition of diazomethane to 4,5-dimethylisothiazol-3(2*H*)-one (**I-3a**) and tetrahydrosaccharin (**I-3b**) was observed (Scheme 30).[47] These compounds (**I-3a,b**) form stable adducts with diazomethane with a high yield. Remarkably, 2-unsubstitutued isothiazol-3(2*H*)-one 1,1-dioxides (**I-3a,b**) form a mixture of *N*- and *O*-methylated adducts (**67**) and (**68**) in the ratio of 2:3. The cycloadducts (**67a,b**) can also be obtained from **II-2a,b** and diazomethane in high yield.



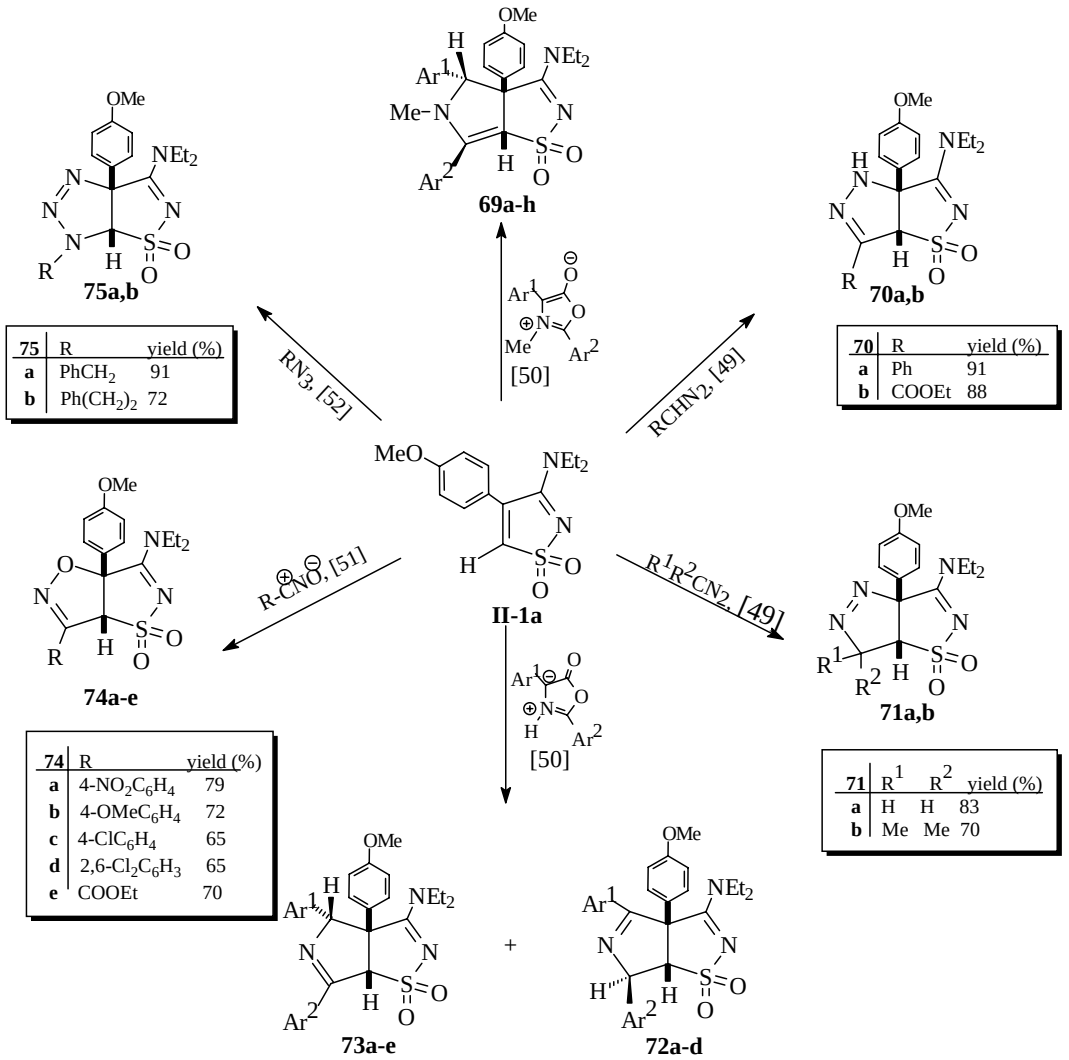
Scheme 30

The cycloaddition of more voluminous 1,3-dipoles such as diphenyldiazomethane and diazoacetic ester to 4,5-bisubstituted substrates (**I-3a,b**) was not observed.[47]

3.2. 3-Aminoisothiazole 1,1-Dioxides (II)

This group of isothiazoles (**II**) is known to be very reactive in 1,3-dipolar cycloadditions. The 3-aminoisothiazole 1,1-dioxide (**II-1a**) readily undergoes cycloaddition with a wide range of 1,3-dipoles, such as oxazolones, azomethine ylides, and muenchnones,[50] diazo compounds,[49] azides,[48,52] and nitrile oxides with a high degree of regioselectivity at the C4-C5 bond (Scheme 31).[51] The primary bicyclic cycloaddition products (**69-75**) could easily undergo transformations affording functionalised single-ring heterocycles by cleavage of one ring. They are also versatile intermediates for many other interesting heterocyclic synthesis.[48-52]

69	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
Ar^1	Ph	Ph	4-MeC_6H_4	Ph	4-$OMeC_6H_4$	Ph	Ph	Ph
Ar^2	Ph	4-MeC_6H_4	Ph	4-$OMeC_6H_4$	Ph	4-FC_6H_4	4-BrC_6H_4	4-$NO_2C_6H_4$
yield (%)	90	91	90	75	90	90	63	70



75	R	yield (%)
a	$PhCH_2$	91
b	$Ph(CH_2)_2$	72

70	R	yield (%)
a	Ph	91
b	COOEt	88

74	R	yield (%)
a	4-$NO_2C_6H_4$	79
b	4-$OMeC_6H_4$	72
c	4-ClC_6H_4	65
d	2,6-$Cl_2C_6H_3$	65
e	COOEt	70

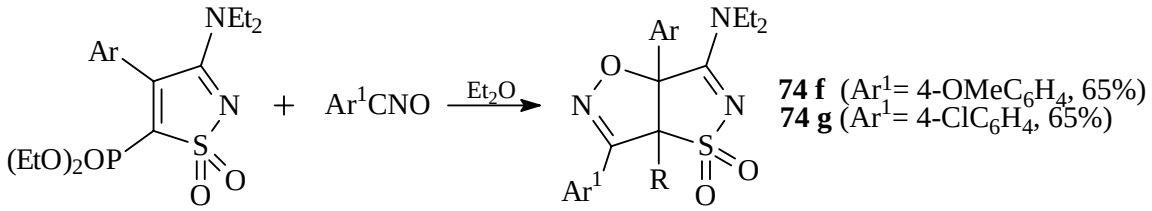
71	R^1	R^2	yield (%)
a	H	H	83
b	Me	Me	70

73	**a**	**b**	**c**	**d**	**e**
Ar^1	Ph	4-ClC_6H_4	Ph	4-MeC_6H_4	Ph
Ar^2	Ph	Ph	4-ClC_6H_4	Ph	4-MeC_6H_4
yield (%)	60	65	74	70	70

72	**a**	**b**	**c**	**d**
Ar^1	Ph	4-ClC_6H_4	Ph	4-MeC_6H_4
Ar^2	Ph	Ph	4-ClC_6H_4	Ph
yield (%)	10	not purified	13	5

Scheme 31

In recent years, a new class of 4-dimethylaminoisothiazole dioxides – isothiazolylphosphonates (**II-1b**) was studied. Compounds of this class form cycloadducts with diazomethane with unusual regiochemistry (Scheme 36) and undergo cycloaddition with nitrile oxides with usual regiochemistry to **74f,g** (Scheme 32).[54]



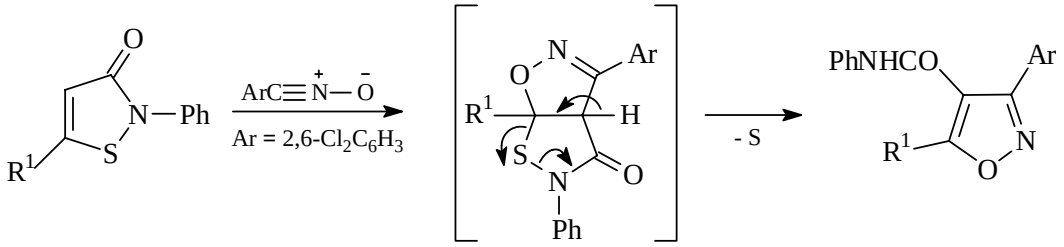
II-1b (Ar = 4-$OMeC_6H_4$) **74f,g** (R = $PO(EtO)_2$)

Scheme 32

The 3-diethylamino-4-(4-methoxyphenyl)-5-vinylisothiazole (**II-1c**) was reacted with nitrile oxides and muenchnones at the 5-vinyl group, exclusively.[53]

3.3. Isothiazol-3(2*H*)-ones (VII)

As it was already mentioned, isothiazol-3(2*H*)-ones are referred to as poor dipolarophiles, as they have an unoxidized sulfur atom. They were found not to react with several of the most reactive dienes.[19] The isothiazolones (**VIIa,b**) react only with 2,6-dichlorobenzonitrile oxide and they were reported as an exception (Scheme 33).[18]

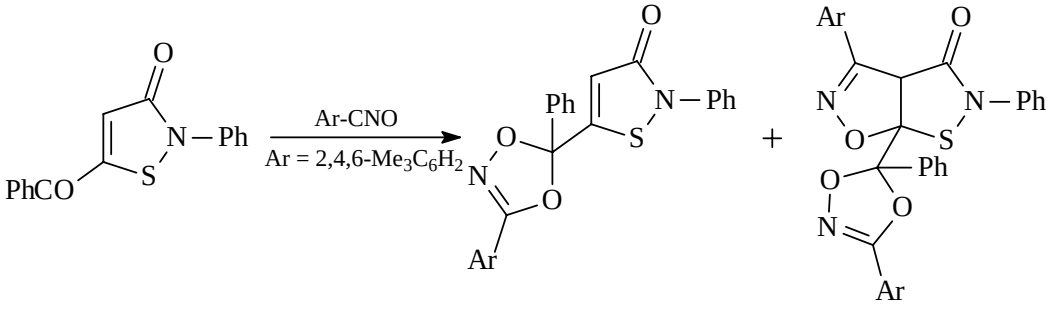


VIIa,b (R^1: H, PhCO) **75a,b** **76a,b**

Scheme 33

The reaction was carried out in refluxing methylene chloride for 10-30 hours. Both isothiazol-3(2*H*)-one (**VIIa**) and 5-benzoylisothiazol-3(*2H*)-one (**VIIb**) react with 2,6-dichlorobenzonitrile oxide yielding the first cycloaddition products (**75**), which transform to the isoxazoles (**76a,b**) during column chromatography.

Mesitonitrile oxide (Ar=2,4,6-$Me_3C_6H_2$) reacts quite differently with isothiazolones (**VIIa,b**). Isothiazolone (**VIIa**) (R^1=H) failed to form any cycloaddition product, whereas isothiazolone (**VIIb**) is more reactive and produces mono- and bis-cycloadducts (**77**) and (**78**) with mesitonitrile oxide with 50 and 15% yields, respectively (Scheme 34).



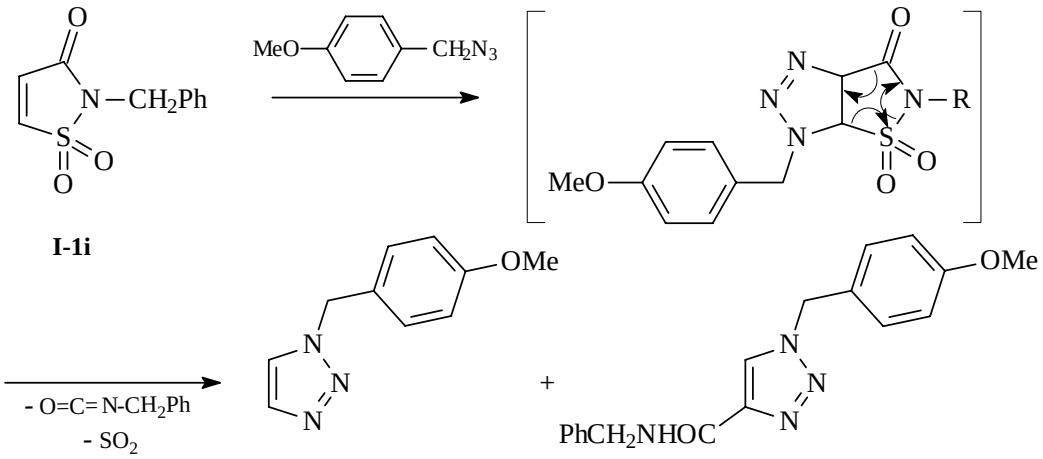
VII b **77** (50%) **78** (15%)

Scheme 34

The bis-cycloadduct (**78**) was isolated as a mixture of two diastereomers with ratio 3:2.

3.4. Regioselectivity of 1,3-Dipolar Cycloaddition

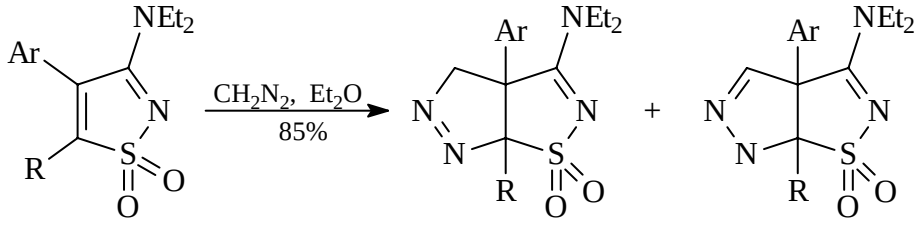
The 1,3-dipolar cycloaddition to C4-C5 double bond of isothiazole derivatives is highly regioselective. Isothiazol-3(2*H*)-one 1,1-dioxides (**I-1-3**), 3-diethylaminoisothiazole 1,1-dioxides (**II-1**), and also 3-methoxyisothiazole 1,1-dioxides (**II-2**) are viewed as electron-deficient dipolarophiles.
For such dipolarophiles the perturbation theory[64] predicts that cycloaddition should be dipole HO-controlled, except for the nitrile oxide case, where dipole LU-control should be expected. In practice, the C=O group (or C=N for compounds of type **II**) seems to be the main regiocontrolling factor. The sulfonyl group can be ignored for the purpose of predicting regioselectivity (Scheme 35).[46]



I-1i **79** (53%) **80**

Scheme 35

The sulfonyl group lies not in the same plane as the whole isothiazole ring, so we consider only the inductive effect of this substituent, whereas the C=O (or C=N group in compounds of type (**II**) respectively) reveals both inductive and mesomeric effects. Therefore, the C=O (C=N) group is considered to determine the regiochemistry of 1,3–dipolar cycloaddition to C4-C5 double bond of isothiazole 1,1-dioxide derivatives.
Other substituents at C4 and C5 atoms besides sulfonyl and C=O (or C=N, respectively) groups can also exert an influence upon the regiochemistry of 1,3-dipolar cycloaddition. In the case of cycloaddition of diazomethane to isothiazolephosphonate (**II-1b**), the presence of phosphono group by C5 atom dramatically affects the regiochemistry of the process (Scheme 36).[54] Isothiazolylphosphonate reacts with an ethereal solution of diazomethane generating a mixture of two tautomeric 1- and 2-pyrazoline (**81**) and (**82**).[54] The 1-pyrazoline (**81**), which is the primary cycloadduct, tautomerizes at a slower rate into the more stable 2-pyrazoline (**82**).



II-1b (Ar = 4-OMeC$_6$H$_4$, R = PO(OEt)$_2$) **81** **82**

Scheme 36

In contrast, the opposite regioselectivity is observed for cycloaddition to isothiazol-3(2*H*)-ones (**VII**) (Scheme 33). Here we have an unoxidized sulfur atom that works as electron donor substituent with a positive mesomeric effect. In all cases the electron donor substituent controls the regiochemistry of the reactions, and consequently the sulfur

atom of the isothiazole ring should be the main regiocontrolling factor of the cycloaddition to isothiazol-3(2*H*)-ones (**VII**).

So we can conclude that in all examined cases we deal with highly regioselective charge-controlled 1,3-dipolar cycloaddition processes.

4. Conclusions

In conclusion, the Diels-Alder reactions of trimethylsilyl-substituted 1,3-butadienes, furfuryl alcohol or 1,3-oxazoles with isothiazol-3(*2H*)-one 1,1-dioxides (**I**) followed by aromatisation of the cycloadducts under basic conditions, provide a general and efficient method for the synthesis of azasaccharin and 6-azasaccharin derivatives.
Chiral 1-aza-1,3-butadienes, that are derived from α,β-unsaturated aldehydes and Ender's hydrazines, transform with high facial selectivity to 4-azasaccharin, which in there turn can be readily converted into enantiomerically pure piperidines with high facial selectivity. The σ- and π-acceptor effects of the carbonyl group of the dienophil (**I-1**) determine the regioselectivity in the process.
Amino acid derived α,β-unsaturated γ-sultams (**III**) with *exo*- or γ-*endo*-cyclic stereogenic centers undergo stereoselective Diels-Alder reactions to yield *endo*-norbornenylsulfonamides as the major diastereomers. These adducts undergo ring opening metathesis polymerisation (ROMP).
Racemic isothiazol-3(*2H*)-on 1-oxides (**IV**) react with acyclic and cyclic dienes to produce only one *endo*-cycloadduct. Homochiral isothiazol-3(*2H*)-one (*S*)-1-oxide (**IV-1f**) reacts with cyclopentadiene and 1-azadiene producing *endo*-cycloadducts with a high degree of diastereofacial selectivity.
The Diels-Alder dimerization of semicyclic 4-vinylsulfoxide is highly diastereoselective reaction that takes place *via* a *exo-syn* transition state, that is stabilized by metal chelatation.
The asymmetric Diels-Alder reaction of cyclic vinyl *p*-tolylsulfilimines with dienes occurs with good regio-, *endo*- and π-facial selectivities, producing solely one *endo*-adduct.
The 1,3-dipolar cycloaddition of the isothiazol-3(*2H*)-one 1,1-dioxides (**I**) and 3-methoxy- and 3-dialkylamino-isothiazol 1,1-dioxides (**II**) has been investigated with diazoalkanes, azides, nitrile imines, nitrile oxides, oxazolones and muenchnones. In most instances primary cycloadducts to C4-C5 double bond of isothiazole 1,1-dioxides (**I, II**) are formed with high degree of regioselectivity, and this selectivity is presumably controlled by participation of C=O or C=N-bonds in isothiazole ring system. The resulting bicyclic adducts can undergo further transformations providing new heterocyclic compounds or new routes to known heterocyclic systems.

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