HETEROCYCLES, Vol 12, No 8, 1979

SYNTHESIS OF HETEROCYCLES USING HETEROCUMULENES CONJUGATED WITH THE CARBONYL GROUP

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Abstract - This review covers the contributions to the synthesis of heterocycles using heterocumulenes such as acyl and thioacyl isocyanates, and α-ketosulfenes which have been reported in recent years.

INTRODUCTION

Heterocumulenes are known as compounds having the allenic cumulative system, in which one or more carbon atoms are replaced by hetero atoms such as oxygen, nitrogen, or sulfur. Thus, one can imagine a variety of heterocumulenes by kinds and arrangements of atoms in the cumulative system. Many kinds of heterocumulenes have been known up to date.

The chemical reactivity of heterocumulenes ranges from highly reactive species to almost inert compounds, and the order of which is approximately as follows: sulfenes $\geq$ carbon suboxide > ketenes > isocyanates > carbodiimides > isothiocyanates > sulfinylamines > SO_2 > COS > CS_2 > CO_2. Some heterocumulenes such as sulfenes can only be generated in situ, whereas carbon dioxide is almost inert gas. The effect of substituents on the reactivity of some heterocumulenes has been investigated. Generally, electron-withdrawing substituents attached to the cumulative system enhance the reactivity of heterocumulenes.

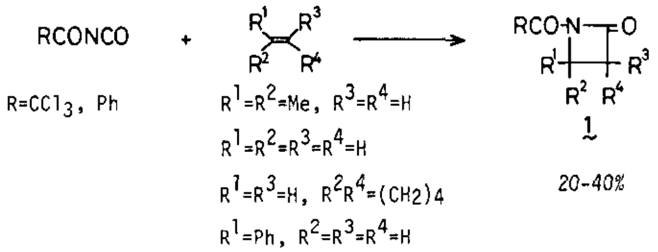
A comprehensive monograph on heterocumulenes has been published by Ulrich[1], and the chemistry on selected heterocumulenes has been also reviewed. Heterocumulenes conjugated with the electron-withdrawing carbonyl group are more reactive than the corresponding simple heterocumulenes, and offer the possibility of entry into complex heterocyclic system through [$\pi 2 + \pi 2$] or [$\pi 4 + \pi 2$] cycloadditions. In this review the reactions of acyl and thioacyl isocyanates as well as of α-ketosulfenes are presented from the viewpoint of syntheses of heterocycles.

I. HETEROCYCLES FROM ACYL AND THIOACYL ISOCYANATES

Acyl and thioacyl isocyanates are one of the most reactive systems among analogous compounds. The facile methods for the preparation of acyl[2] and thioacyl isocyanates[3] by the reaction of primary amides or thioamides with oxalyl chloride have been reported in early 1960's. Since then, a great deals of interesting information on the isocyanates have been obtained, and the chemistry of acyl[4-6] and thioacyl isocyanates[5,6] has been partially reviewed.

I-1) Azetidinones and Other Four-membered Heterocycles

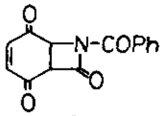
Although the reactions of aryl isocyanates with activated olefins such as enamines, ketenacetals and ketenaminals afford the corresponding azetidinones, no additions of aryl isocyanates to non-activated olefins take place. However, acyl isocyanates as well as *chlorosulfonyl isocyanate react* with nonactivated olefins by a [π2 + π2] cycloaddition process to give the corresponding azetidinones 1 (Scheme 1)[7-9].



Scheme 1

Benzoyl isocyanate adds to p-benzoquinone and 1,4-naphthoquinone, giving the [π2 + π2] cycloadducts 2 and 3 in 45.6 and 40.5% yields respectively[10].

Similarly, acyl isocyanates react with acyclic and cyclic 1,3-dienes to afford the corresponding 1:1 adducts 4 and 5 of azetidinone type *in moderate yields (Scheme 2)*[9, 11, 12].



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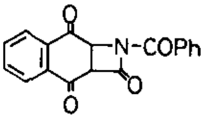

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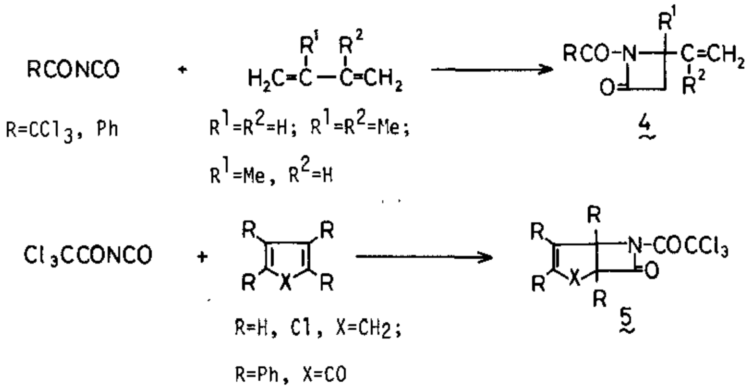


Scheme 2

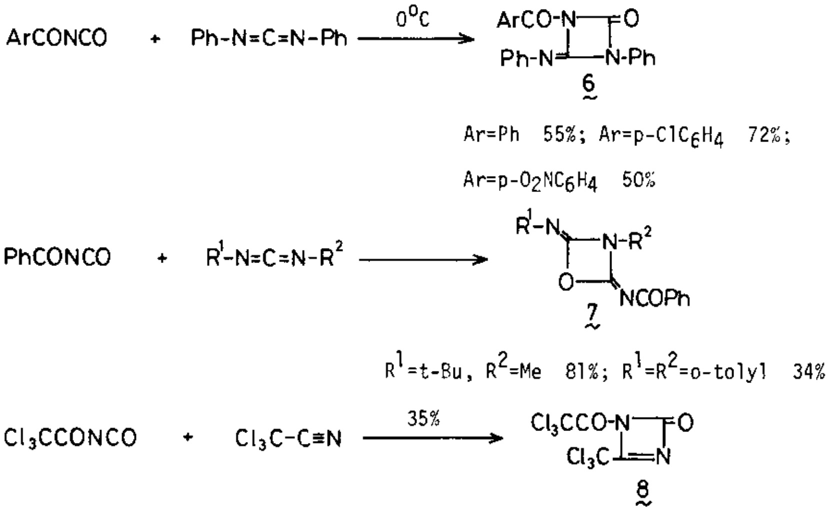
It has been demonstrated that the interaction between trichloroacetyl isocyanate and enamines dereived from cyclohexanone and cyclopentanone afforded the [π2 + π2] cycloadducts in good yields (77-

83%)[13]. However, this reaction mode seems to be exceptional for the reaction of acyl isocyanates (see I-5)).

The reaction of benzoyl isocyanate with acetylenes gives the corresponding azetinones[8, 14, 15], but this reaction seems not to be valuable as the preparative method because of very low yields.

Although the reaction of acyl isocyanates with carbodiimides will be described below (see I-6)), in some cases benzoyl isocyanates react with carbodiimides to form the four-membered heterocycles.

The reaction of benzoyl isocyanates with diphenylcarbodiimides at 0°C affords the 1,3-diazetidinone compound 6[16]. On the other hand, Ulrich et al.[17] have reported that in the reaction of benzoyl isocyanate with methyl-t-butylcarbodiimide and di(o-tolyl)carbodiimide, the corresponding 1,3-oxazetidine compounds 7 are formed through a [π2 + π2] cycloaddition of the carbodiimide to the C=O bond of the isocyanato group. Trichloroacetyl isocyanate reacts with trichloroacetonitrile to afford the diazetinone compound 8[18].



Scheme 3

I-2) Five-membered Heterocycles Containing Two Hetero Atoms

In the reactions with isonitriles, acyl and thioacyl isocyanates act as 1,4-dipoles, while isonitriles act as 1,1-dipoles. Additions to isonitriles occur readily, and 5-iminooxazolinone or -thiazolinone compounds 9 are formed[19-21] (Table 1).

Both functional groups of p-phenylene- and 1,4-cyclohexylene-diisonitriles take part in the reaction with benzoyl and thiobenzoyl isocyanates, the corresponding bis-5-iminooxazolinone and -thiazolinones 10 being formed, respectively[22].

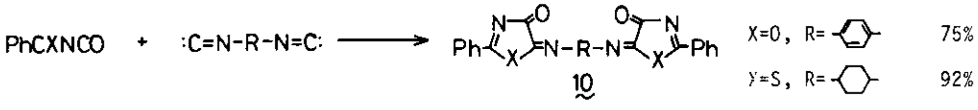
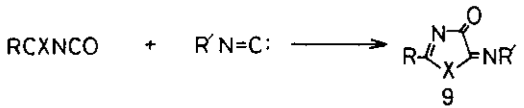


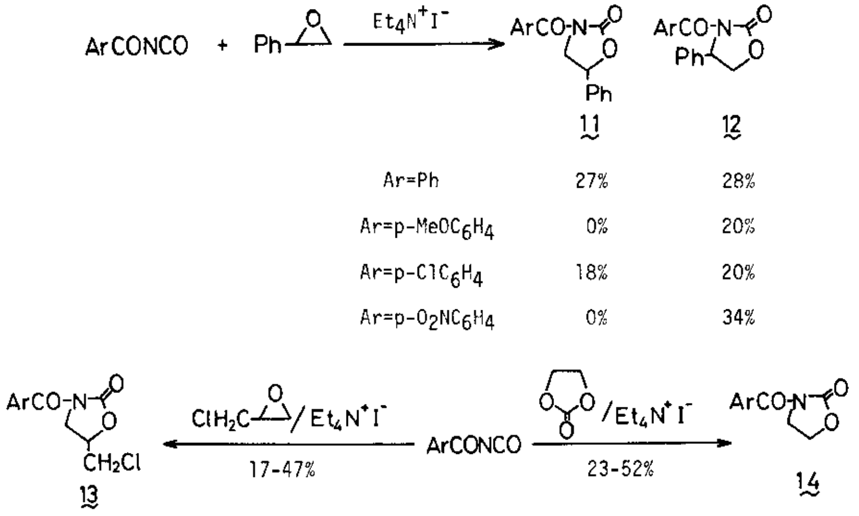
Table 1.



9

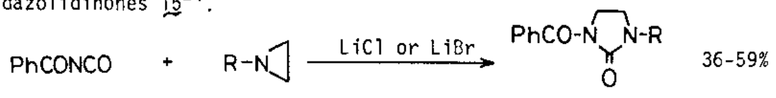
R	X	R'	Yield, %	Lit.
Ph	O	Ph	93	19
Ph	O	c-C_6H_{11}	83	19
Ph	O	p-$O_2NC_6H_4$	57	19
$CHCl_2$	O	Ph	96	19
Ph	S	Ph	70	21
Ph	S	p-$MeOC_6H_4$	88	21
1-$C_{10}H_7$	S	p-$MeOC_6H_4$	29	21

Benzoyl isocyanates react with styrene oxide, epichlorohydrin and ethylene carbonate in the presence of tetraethylammonium iodide, giving the corresponding oxazolidinones 11-14 (Scheme 4)[23]. In the reaction with styrene oxide, benzoyl and p-chlorobenzoyl isocyanates afford two isomeric oxazolidinones in almost equal yields. In a similar reaction with N-substituted aziridines, benzoyl isocyanate gives the imidazolidinones 15[24].



	11	12
Ar=Ph	27%	28%
Ar=p-$MeOC_6H_4$	0%	20%
Ar=p-ClC_6H_4	18%	20%
Ar=p-$O_2NC_6H_4$	0%	34%

Scheme 4

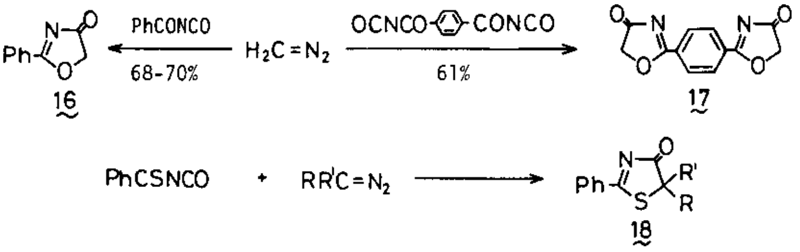


R=PhCO, p-O NC H , PhO

15

However, the above reactions are not characteristic of acyl isocyanates, because aryl isocyanates react with oxirans and aziridines under similar conditions to form the corresponding five-membered heterocycles.

Benzoyl isocyanate[25] and terephthaloyl diisocyanate[26] react readily with diazomethane to give the corresponding oxazolones 16 and 17 respectively. The formation of oxazolones is the reaction characteristic of acyl isocyanate, because phenyl isocyanate forms the β-lactam in the same reaction[27]. Similarly, the reaction of thiobenzoyl isocyanate with diazoalkanes affords the thiazolone derivatives 18[28] (Scheme 5).

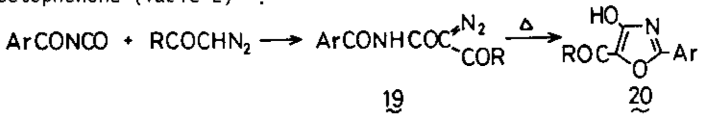


R=Ph, R'=H	30%
R=R'=Ph	78%
$RR'=(C_6H_4)_2C$	62%

Scheme 5

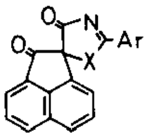
It has been reported that the reaction of benzoyl isocyanate with ethyl diazoacetate formed a 1,2,3-triazolone compound[19]. However, it has been later revealed that the products from benzoyl isocyanates and the diazoacetate are not the triazolone, but the benzoylcarbamoyldiazoacetates 19, which are thermally decomposed to the oxazole compounds 20. Similar results are also observed in the reaction with diazoacetophenone (Table 2)[29].

Table 2.



Ar	R	19 Yield, %	20 Yield, %
Ph	OEt	59	44
p-ClC_6H_4	OEt	45	33
Ph	Ph	25	55
p-ClC_6H_4	Ph	72	61

Although 2-diazoacenaphthenone does not react with phenyl isocyanate, the diazoketone reacts with benzoyl and thiobenzoyl isocyanates to give the spiro-oxazolinones and -thiazolinones 21[30].



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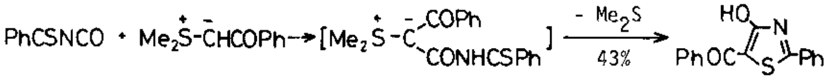
The reaction with a resonance-stabilized sulfonium ylide is applicable to the preparation of oxazole and thiazole compounds[29]. Benzoyl isocyanates react with dimethylsulfonium phenacylide to form the corresponding stable benzoylcarbamoylsulfonium ylids (yields 75-90%) which on

Ar=Ph, X=O	38.5%
Ar=p-ClC_6H_4, X=O	59%
Ar=Ph, X=S	28%

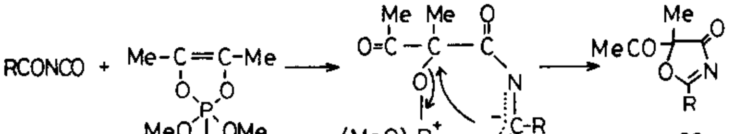
pyrolysis, are converted into the oxazoles 20 in 47-51% yields. However, thiobenzoyl isocyanate directly affords the thiazole compound 22.



22

In the reaction with dimethyloxosulfonium methylide, benzoyl isocyanate gives the benzoylcarbamoyl- and bis(benzoylcarbamoyl)oxosulfonium ylides. Pyrolysis of both the adducts gives the same oxazolone compound[29].

An unique method for the preparation of oxazoles has been reported[31]. The reaction of acyl isocyanates with the dioxaphospholene proceeds through a dipolar adduct to give the 2-oxazolin-4-ones 23 (Scheme 6).



23

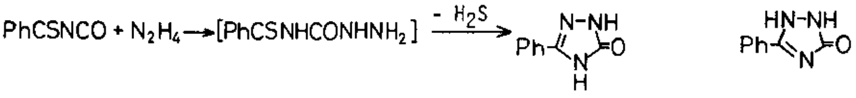
R=Ph 92%; R=p-FC_6H_4 78%; R=p-$MeOC_6H_4$ 87%; R=CCl_3 60%

Scheme 6

Formation of the imidazolidinone compound by the reaction of benzoyl isocyanate with bis-cyclohexylethylenediimine has been reported[32] (see I-6)).

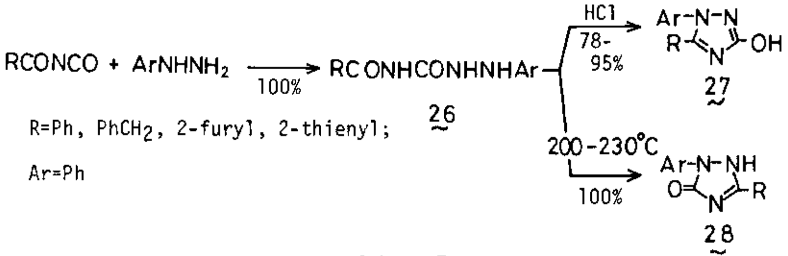
I-3) Compounds Related to 1,2,4-Triazolinones

The reactions of acyl and thioacyl isocyanates with hydrazines provide useful methods for the preparation of thiazolinone derivatives. Benzoyl isocyanate reacts with hydrazine to yield 1,2-bis-benzoylcarbamoylhydrazine[33], while thiobenzoyl isocyanate gives the triazolinone 24, which has arisen from the semicarbazide by the evolution of hydrogen sulfide[34]. The triazolinone 24 is a tautomer of the triazolinone 25 which is obtained from the semicarbazone of phenylglyoxylic acid[35].



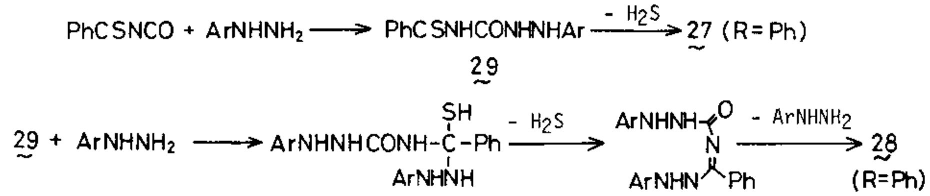
24 25

Acyl isocyanates easily react with phenylhydrazine to give the corresponding semicarbazides 26 quantitatively. On treatment with hydrochloric acid, semicarbazides 26 are converted to the 3-hydroxytriazoles 27, whereas thermal ring closure produces the triazolinones 28 (Scheme 7)[36]. Similarly, bis-triazoles or bis-triazolinones are obtained by using isophthaloyl and terephthaloyl diisocyanates[36].



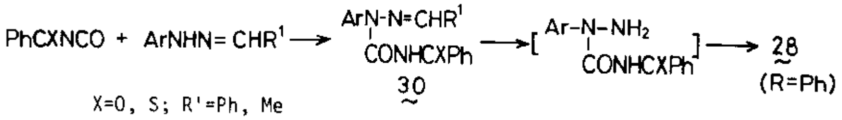
Scheme 7

The reaction of thiobenzoyl isocyanate with arylhydrazines yields unstable semicarbazides 29, which are easily converted to triazoles 27. However, the isocyanate reacts with a slight excess of arylhydrazines to give directly triazolinones 28[34, 37]. As illustrated in Scheme 8, the formation of 28 can be understood in terms of the further addition of the hydrazine to the semicarbazide 29. This is followed by the elimination of hydrogen sulfide from the adduct, and subsequent loss of the hydrazine gives the triazolone 28[37].



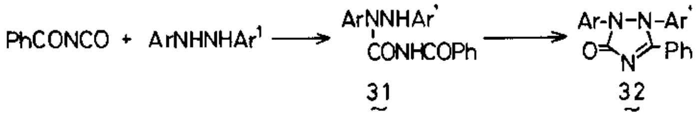
Scheme 8

The triazolinones 28 are also prepared by the reaction with aldehyde arylhydrazones[38]. As shown in Scheme 9, benzoyl and thiobenzoyl isocyanates react with the arylhydrazones to give the corresponding semicarbazones 30 quantitatively. Hydrolysis of the semicarbazones 30 with hydrochloric acid affords readily the triazolinones 28.

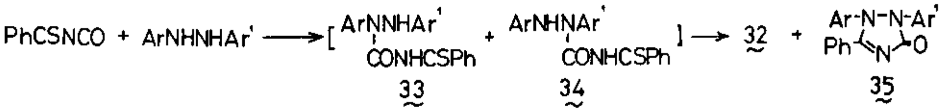


Scheme 9

The reactions of benzoyl and thiobenzoyl isocyanates with hydrazobenzenes provide a useful method for the preparation of triaryl-substituted triazolinone compounds[37]. Benzoyl isocyanate reacts exclusively with the more basic nitrogen atom of hydrazobenzenes to give the corresponding stable semicarbazides 31, which on treatment with hydrochloric acid undergo ring closure to the triazolinones 32 by loss of water. On the other hand, thiobenzoyl isocyanate attacks both nitrogen atoms of hydrazobenzenes to yield a mixture of unstable semicarbazides 33 and 34, which on heating are easily converted to two isomeric triazolinones 32 and 35 with the elimination of hydrogen sulfide (Scheme 10).



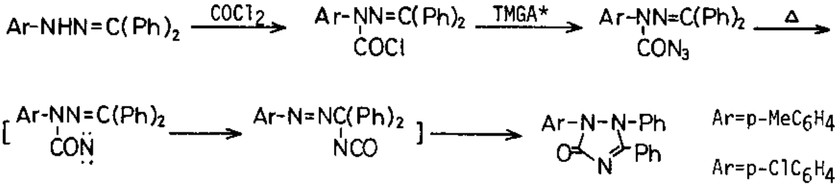
	31	32
Ar=Ar'=Ph	95%	93%
Ar=Ph, Ar'=p-ClC_6H_4	99	84
Ar=p-MeC_6H_4, Ar'=Ph	94	97
Ar=p-$MeOC_6H_4$, Ar'=Ph	94	74



	32	35
Ar=Ar'=Ph	92%	-
Ar=Ph, Ar'=p-ClC_6H_4	52.5	22.5%
Ar=p-MeC_6H_4, Ar'=Ph	59	25
Ar=p-$MeOC_6H_4$, Ar'=Ph	90	0

Scheme 10

Although the triazolinones 32 (Ar=p-MeC_6H_4, Ar'=Ph) and 35 (Ar=Ph, Ar'=p-ClC_6H_4) are prepared from the corresponding benzophenone arylhydrazones according to the route illustrated in Scheme 11, the yields from the hydrazones are below 30%[37].



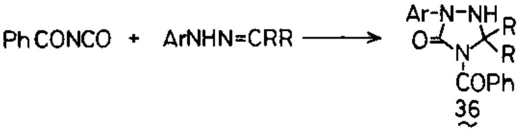
Ar=p-MeC_6H_4

Ar=p-ClC_6H_4

*tetramethylguanidinium azide

Scheme 11

As mentioned above, the reaction with aldehyde arylhydrazones provides the simple method for the preparation of triazolinones 28 (Scheme 9). In the reaction with acetone or cyclohexanone arylhydrazones, however, the triazolidinones 36, whose structures correspond to the ring tautomers of semicarbazones, are obtained from the reaction of benzoyl isocyanate[38].

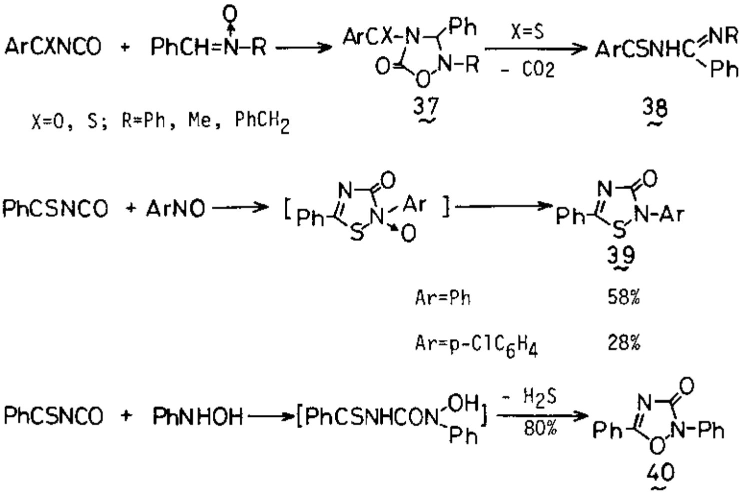


R=Me, RR=$(CH_2)_5$

I-4) Other Five-membered Heterocycles

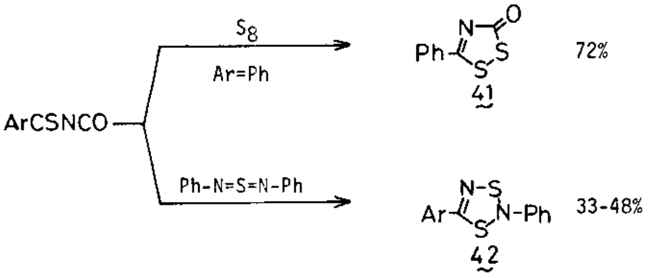
In analogy with aryl isocyanates, benzoyl[39, 40] and thiobenzoyl isocyanates[28] react with nitrones via a 1,3-dipolar cycloaddition, giving 1,2,4-oxadiazolines 37 respectively. However, the adducts

37 (X=S) are labile and easily change into the amidines **38** with the elimination of carbon dioxide. Thiobenzoyl isocyanate affords the thiadiazoles **39** or oxadiazole **40** by the reaction with nitrosobenzenes or phenylhydroxylamine respectively[28]. The thiadiazole **39** is probably formed via the initial 1,4-cycloadduct, followed by the exclusion of oxygen atom.



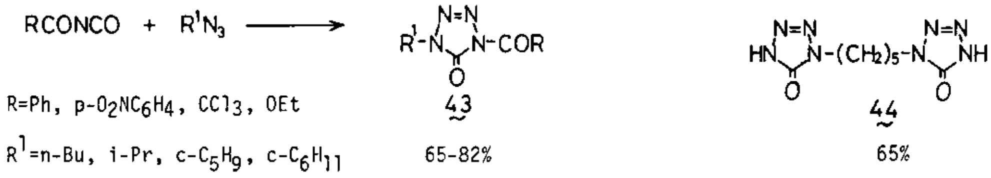
Scheme 12

When 2-phenylthiazoline-4,5-dione which is a precursor of thiobenzoyl isocyanate, is heated with excess of sulfur, 5-phenyl-3H-1,2,4-dithiazol-3-one **41** is obtained[41]. In the reaction with diphenylsulfurdiimide, the 1,3,2,4-dithiadiazoline **42** is formed as major product together with by-products such as **41** from the reaction of thiobenzoyl isocyanate [42] (Scheme 13).



Scheme 13

Acyl isocyanates as well as aryl and sulfonyl isocyanates react with alkyl azides to give the tetrazolinones **43**[43]. The cycloaddition of trichloroacetyl isocyanate to diazidopentane, and subsequent methanolysis of the adduct afford the bis-tetrazolinone **44**[43].

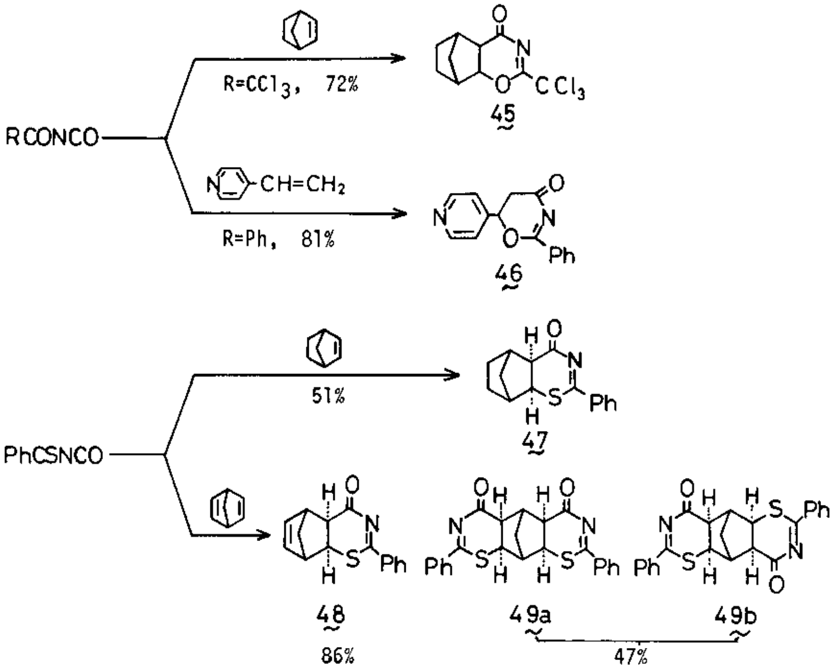


Scheme 14

I-5) Oxazine and Thiazine Derivatives

As described in Section I-1), in some cases acyl isocyanates react with olefins and acetylenes to give the corresponding [π2 + π2] cycloadducts in low yields. However, the reaction preferentially proceeds via a [π4 + π2] cycloaddition. Particularly, thioacyl isocyanates exhibit high reactivity of 1,4-cycloaddition, and do not form the [π2 + π2] cycloadducts.

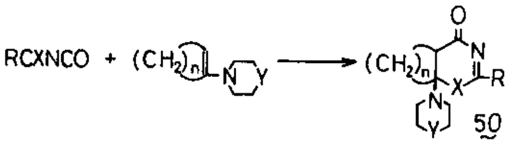
The reactions of acyl isocyanates with norbornene[7] or 4-vinylpyridine[14], and of thiobenzoyl isocyanate with norbornene[44] afford the corresponding [π4 + π2] cycloadducts 45-47. As shown in Scheme 15, thiobenzoyl isocyanate adds to norbornadiene to give a mixture of 1:1 adduct 48 and two isomeric 1:2 cycloadducts 49a and 49b[44].



Scheme 15

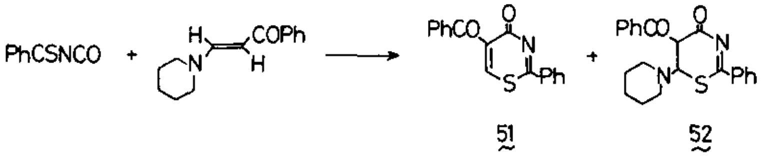
In contrast to benzoyl isocyanate (see Section I-1)), the reaction of trichloroacetyl isocyanate with p-benzoquinone yields the oxazinone compound[10]. The [π4 + π2] cycloadducts 50 obtained from the reaction with cyclic enamines are shown in Table 3.

Table 3



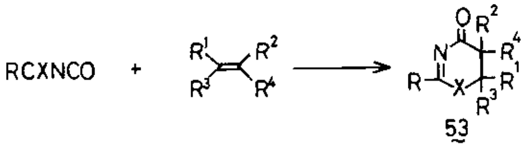
R	X	Y	n	Yield, %	Lit.
Ph	O	O	4	64	13
Ph	O	CH_2	4	66	13
CCl_3	O	O	3	76	13
Ph	S	O	3	62	21

Benzoyl isocyanate reacts with enaminoketones to give the corresponding acyclic carbamoyl compounds, while the reaction of thiobenzoyl isocyanate affords the products 51 and 52 through a [π4 + π2] cycloaddition process[45].



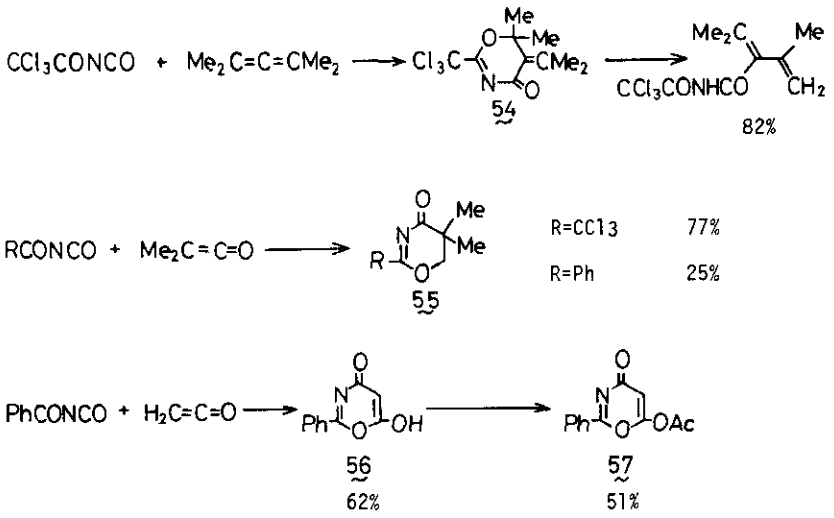
The [π4 + π2] cycloadducts 53 from the reaction with other nucleophilic olefins are shown in Table 4.

Table 4



R	X	R^1	R^2	R^3	R^4	Yield, %	Lit.
CCl_3	O	OMe	OMe	H	H	69	7
CF_3	O	$-OCH_2O-$		H	H	51	7
CCl_3	O	Me	OMe	Me	OMe	100	46
Ph	S	$-(CH_2)_3O-$		H	H	44	21
CCl_3	O	H	SEt	H	H	76	47
CCl_3	O	H	SBu-n	H	H	88	48

Acyl isocyanates add to the C=C bond of allenes or ketenes to form the [π4 + π2] cycloadducts respectively. For example, trichloroacetyl isocyanate reacts with tetramethylallene to form unstable cycloadduct 54, which easily rearranges to the acyclic compound[49]. Acyl isocyanates add to ketenes,

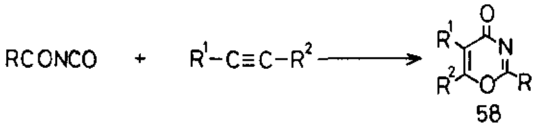


Scheme 16

giving the corresponding cycloadducts 55 and 56[50]. The adduct 56, which presumably formed via a 1,4-cycloaddition followed by enolization, is formed in cold diethyl ether, but in benzene at 30-40°C the acetylated product 57 is obtained[50] (Scheme 16).

The oxazinone compounds 58 from acyl isocyanates and acetylenic compounds are listed in Table 5.

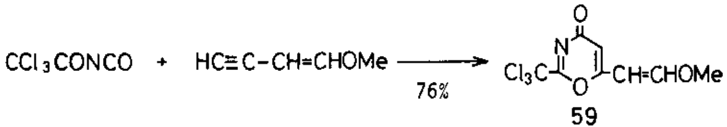
Table 5



58

R	R^1	R^2	Yield, %	Lit.
CCl_3	H	OEt	100	46
Ph	H	OEt	85	46
CCl_3	H	CH=CHOMe	72	46
CCl_3	Ph	Ph	5	51
CCl_3	p-$MeOC_6H_4$	p-$MeOC_6H_4$	22	51
Ph	CHO	NMe_2	74	52
Ph	COMe	NMe_2	82	52
Ph	COOMe	NMe_2	92	52
OEt	CHO	NMe_2	59	52
OEt	COMe	NMe_2	81	52
OEt	COOMe	NMe_2	89	52

As shown in Table 5, the reactions with ethynyl ethers and ynamines afford the cycloadducts in good yields. In the reaction with 1-butene-3-ynyl methyl ether, the cycloaddition involving only the C≡C bond takes place and the [π4 + π2] cycloadduct 59 is formed[46].

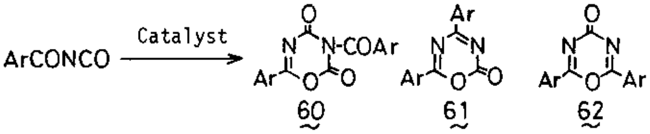


59

I-6) Compounds Related to Oxadiazines and Thiadiazines

There has been a number of [π4 + π2] cycloadditions of acyl and thioacyl isocyanates to C=N bonds. p-Substituted benzoyl isocyanates give oxadiazine derivatives when treated with appropriate catalysts such as NEt_3 and pyridinium salt. The yields of the products strongly depend on the nature of catalysts and substituents as well as on the reaction conditions[53]. The isolated results are listed in Table 6.

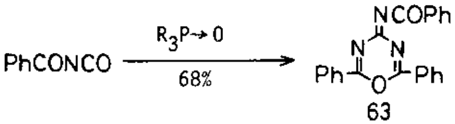
Table 6



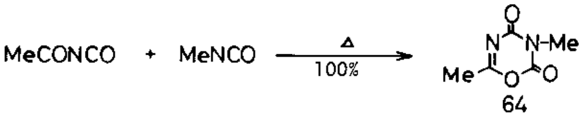
Ar	Catalyst	Yield, % 60	61	62
Ph	NEt_3	90	-	-
p-$MeOC_6H_4$[a)]	NEt_3	-	-	-
p-ClC_6H_4	NEt_3	-	90-93	-
p-$NO_2C_6H_4$	NEt_3	-	90-100	-
Ph	$C_5H_5\overset{+}{N}COPhCl^-$	-	-	70
p-$MeOC_6H_4$	$C_5H_5\overset{+}{N}COPhCl^-$	-	-	23
p-ClC_6H_4	$C_5H_5\overset{+}{N}COPhCl^-$	-	-	86
p-$NO_2C_6H_4$	$C_5H_5\overset{+}{N}COPhCl^-$	-	-	50

a) The trimer is formed in ca. 40% yield.

Benzoyl isocyanate reacts with a phospholene oxide catalyst to give the 4-benzoylimino-1,3,5-oxadiazine 63, whose structure corresponds to the compound from trimer with the elimination of two molecules of carbon dioxide[54]. Acetyl isocyanate reacts with methyl isocyanate to yield a mixed dimer 64 quantitatively[55].



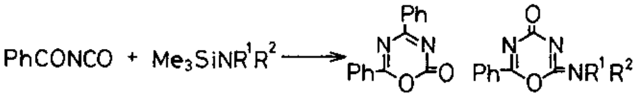
63



64

An unique method for the preparation of oxadiazine compounds such as 61 and 62 has been reported[56]. When benzoyl isocyanate is treated with N-trimethylsilyldialkylamine in a 2:1 molar ratio, two oxa-

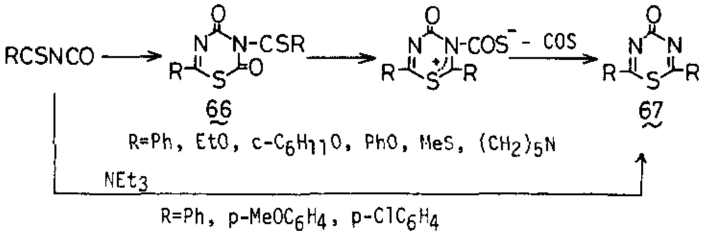
Table 7



R^1	R^2	61	65
Me	Me	0%	83%
Et	Et	66	0
n-Pr	n-Pr	27	48
n-Bu	n-Bu	47	0
Me	c-C_6H_{11}	58	35

diazinones 61 and 65 are formed. The relative yields of 61 and 65 are greatly affected by the nature of the alkyl substituents on the nitrogen atom (Table 7). On the other hand, N-trimethylstannyldimethylamine (Me$_3$SnNMe$_2$) reacts with an excess of the isocyanate to give the oxadiazine 62 (Ar=Ph) in 52% yield.

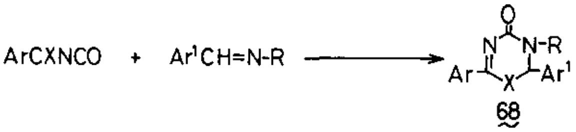
Thiobenzoyl isocyanate dimerizes readily without a catalyst to the dimer 66, which on further heating converted to the thiadiazinone 67[3, 57, 58]. However, the reaction of thiobenzoyl isocyanates with NEt3 at room temperature affords 67 directly in 86-88% yields[40].



Scheme 17

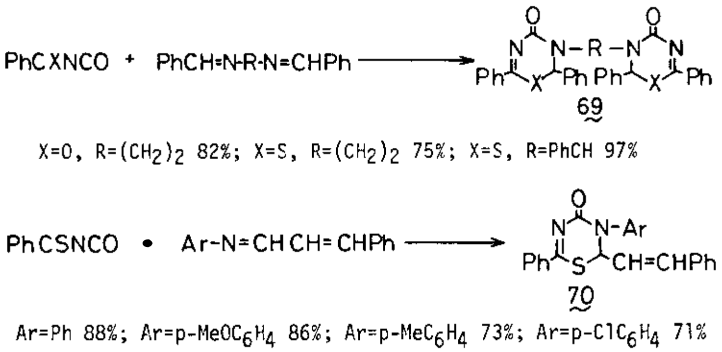
Acyl and thioacyl isocyanates add to a variety of C=N bonds other than the C=N bond of isocyanates mentioned above, giving [π4 + π2] cycloadducts. For instance, the reactions of benzoyl and thiobenzoyl isocyanates with Schiff bases afford the corresponding oxadiazinones and thiadiazinones 68 in good yields respectively (Table 8)[40, 59]. Furthermore, benzoyl and thiobenzoyl isocyanates add

Table 8



Ar	X	Ar'	R	Yield, %
Ph	0	Ph	PhCH$_2$	100
p-MeOC$_6$H$_4$	0	Ph	PhCH$_2$	92
p-ClC$_6$H$_4$	0	Ph	PhCH$_2$	100
p-NO$_2$C$_6$H$_4$	0	Ph	PhCH$_2$	100
Ph	S	Ph	PhCH$_2$	88
p-MeOC$_6$H$_4$	S	Ph	PhCH$_2$	80
p-ClC$_6$H$_4$	S	Ph	PhCH$_2$	100
Ph	S	Ph	n-Pr	73
Ph	S	Ph	c-C$_6$H$_{11}$	74
Ph	S	Ph	Ph	100
p-MeOC$_6$H$_4$	S	Ph	Ph	100
p-ClC$_6$H$_4$	S	Ph	Ph	100
Ph	S	p-MeOC$_6$H$_4$	Ph	88
Ph	S	Ph	p-MeOC$_6$H$_4$	94
Ph	S	p-NO$_2$C$_6$H$_4$	Ph	89
Ph	S	Ph	p-NO$_2$C$_6$H$_4$	70

to dianils, giving the bis[π4 + π2] cycloadducts 69 in good yields[59]. Thiobenzoyl isocyanate does not add to the C=C bond of cinnamylideneanilines, but it reacts with the C=N bond by a 1,4-cycloaddition process to afford the thiadiazinones 70[59] (Scheme 18).

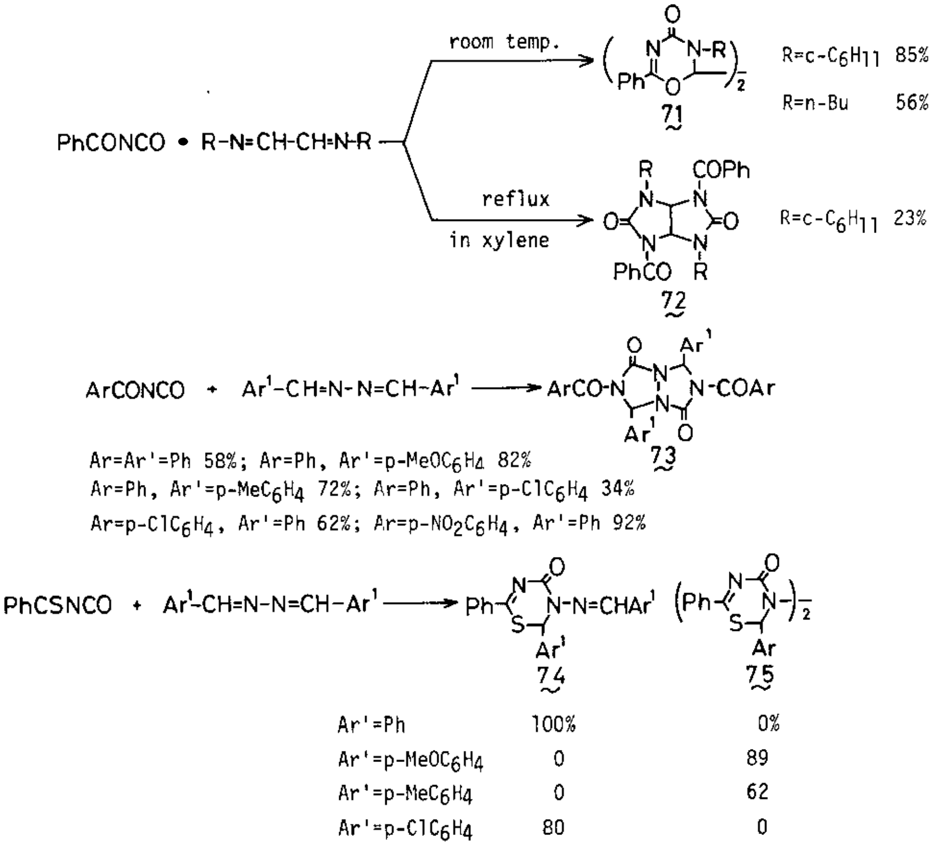


X=O, R=$(CH_2)_2$ 82%; X=S, R=$(CH_2)_2$ 75%; X=S, R=PhCH 97%

Ar=Ph 88%; Ar=p-$MeOC_6H_4$ 86%; Ar=p-MeC_6H_4 73%; Ar=p-ClC_6H_4 71%

Scheme 18

The reactions of N,N'-bis(alkyl)ethylenediimines[32] and benzaldazines[60] having the conjugated two C=N bonds are illustrated in Scheme 19. Benzoyl isocyanate reacts with the ethylenediimine to give



Ar=Ar'=Ph 58%; Ar=Ph, Ar'=p-$MeOC_6H_4$ 82%
Ar=Ph, Ar'=p-MeC_6H_4 72%; Ar=Ph, Ar'=p-ClC_6H_4 34%
Ar=p-ClC_6H_4, Ar'=Ph 62%; Ar=p-$NO_2C_6H_4$, Ar'=Ph 92%

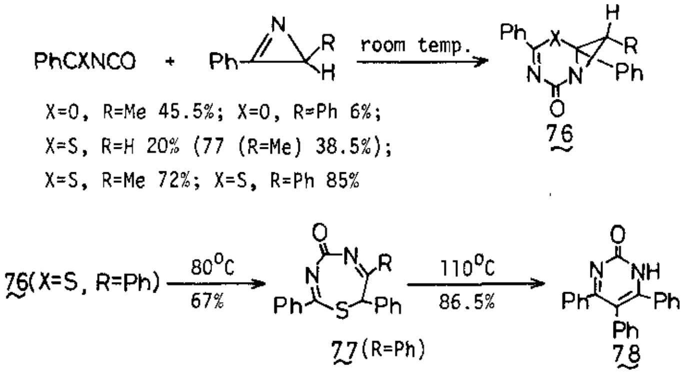
	74	75
Ar'=Ph	100%	0%
Ar'=p-$MeOC_6H_4$	0	89
Ar'=p-MeC_6H_4	0	62
Ar'=p-ClC_6H_4	80	0

Scheme 19

the bis-oxadiazinone 71 or criss-cross adduct 72 depending on the reaction conditions. While benzoyl isocyanates do not react with benzaldazines at room temperature, criss-cross adducts 73 are formed if the reaction is conducted in xylene under reflux. On the other hand, thiobenzoyl isocyanate reacts easily with the azines under mild conditions to afford mono- 74 or bis-oxadiazinones 75 depending on the nature of the substituent of the azine.

Although benzoyl isocyanate does not react with p-tosyl- and benzoylhydrazones, thiobenzoyl isocyanate reacts with the hydrazones to give exclusively [π4 + π2] cycloadducts, thiadiazinones[38].

A few addition reactions with cyclic C=N bonds have been studied. The reaction of benzoyl isocyanate with 2-phenyl-1-azirines affords the corresponding [π4 + π2] cycloadducts 76 (X=O) in low yields. Thiobenzoyl isocyanate easily adds to the azirines at room temperature, giving the [π4 + π2] cycloadducts 76 (X=S), which at higher temperature are transformed into thiadiazepinones 77 and then pyrimidine compound 78 (Scheme 20)[61].



X=O, R=Me 45.5%; X=O, R=Ph 6%;
X=S, R=H 20% (77 (R=Me) 38.5%);
X=S, R=Me 72%; X=S, R=Ph 85%

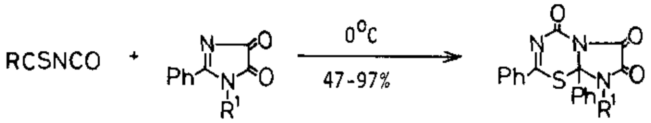
76

77 (R=Ph)

78

Scheme 20

Similarly, thioacyl isocyanates react with the C=N bond of imidazoline-4,5-dione to form the [π4 + π2] cycloadducts 79[62].



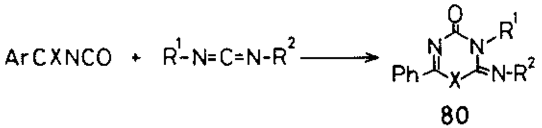
$R=NEt_2$, NPh_2, PhO, Ph, $c\text{-}C_6H_{11}O$
$R'=c\text{-}C_6H_{11}$, Ph

79

The cycloaddition reaction to 2-thiazolines will be mentioned below (see Section I-8)).

Although benzoyl isocyanates react with diphenylcarbodiimide at 0°C to form the [π2 + π2] cycloadducts (Scheme 3), in general the reactions of benzoyl isocyanates as well as thiobenzoyl isocyanates with carbodiimides afford the corresponding [π4 + π2] cycloadducts 80 (Table 9). As shown in Table 9, benzoyl isocyanates add across the cyclohexyl-N=C bond of N-cyclohexyl-N'-phenylcarbodiimide to form the corresponding [π4 + π2] cycloadducts 80, whereas thiobenzoyl isocyanate reacts with both the N=C bonds of the carbodiimide to afford two isomeric [π4 + π2] cycloadducts 81 and

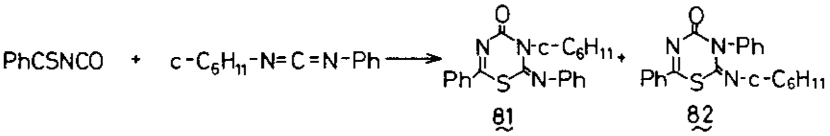
Table 9



80

Ar	X	R^1	R^2	Temp.	Yield, %	Lit.
Ph	O	c-C_6H_{11}	c-C_6H_{11}	r.t.	54	16
p-ClC_6H_4	O	c-C_6H_{11}	c-C_6H_{11}	r.t.	76	16
p-$NO_2C_6H_4$	O	c-C_6H_{11}	c-C_6H_{11}	r.t.	87	16
p-$MeOC_6H_4$	O	c-C_6H_{11}	c-C_6H_{11}	r.t.	64	16
Ph	S	c-C_6H_{11}	c-C_6H_{11}	r.t.	75	21
p-$MeOC_6H_4$	S	c-C_6H_{11}	c-C_6H_{11}	r.t.	98	21
p-$Me_2NC_6H_4$	S	c-C_6H_{11}	c-C_6H_{11}	r.t.	98	21
Ph	O	c-C_6H_{11}	Ph	70°C	75	16
p-ClC_6H_4	O	c-C_6H_{11}	Ph	70°C	71	16
p-$NO_2C_6H_4$	O	c-C_6H_{11}	Ph	70°C	75	16
p-$MeOC_6H_4$	O	c-C_6H_{11}	Ph	70°C	66.5	16

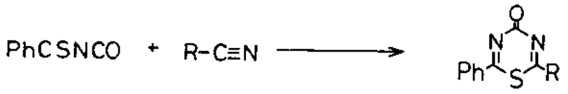
82[16]. Furthermore, thiobenzoyl isocyanate adds to the C=N bond of aromatic ketenimines, giving the thiadiazinones[63].



81 23%

82 20%

Trichloroacetyl isocyanate reacts with a nitrile to afford a [π2 + π2] cycloadduct[18] (Scheme 3), whereas thiobenzoyl isocyanate adds to aryl cyanates and disubstituted cyanamides by a 1,4-cycloaddition to give thiadiazinones 83[64].



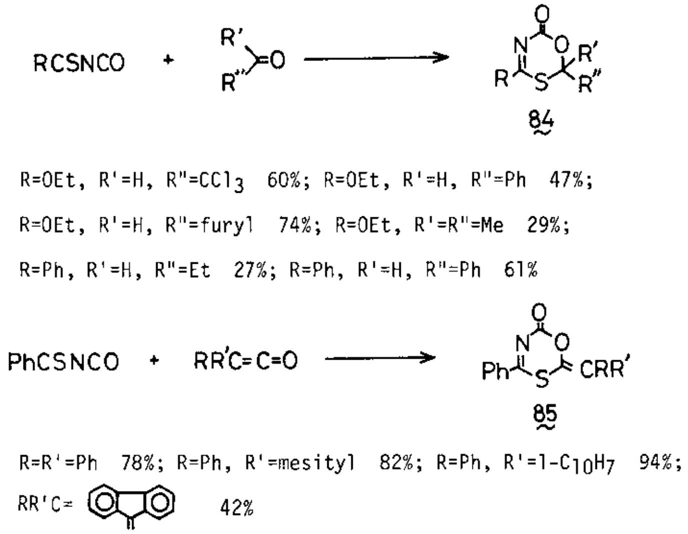
83

R=PhO 71%, R=p-$MeOC_6H_4O$ 67%,

R=p-$NO_2C_6H_4O$ 61%, R=NMe_2 83%, R=N(Me)Ph 27%, R=NPh_2 4%

I-7) Compounds Related to Oxathiazines

Trichloroacetyl isocyanate reacts easily with diphenylcyclopropenone[65] and tropone[66] to give the corresponding imino derivatives through a 1,2-cycloaddition, followed by the elimination of carbon dioxide. On the other hand, thioacyl isocyanates add to the C=O bonds of aldehydes, acetone[67], and ketenes[63] to form the corresponding oxathiazine derivatives 84, 85 by a 1,4-cycloaddition process (Scheme 21). The reaction of thioacyl isocyanates with ketenes is a contrast to that of acyl isocyanates (cf. Scheme 16).



84

$R=OEt, R'=H, R''=CCl_3$ 60%; $R=OEt, R'=H, R''=Ph$ 47%;
$R=OEt, R'=H, R''=$furyl 74%; $R=OEt, R'=R''=Me$ 29%;
$R=Ph, R'=H, R''=Et$ 27%; $R=Ph, R'=H, R''=Ph$ 61%

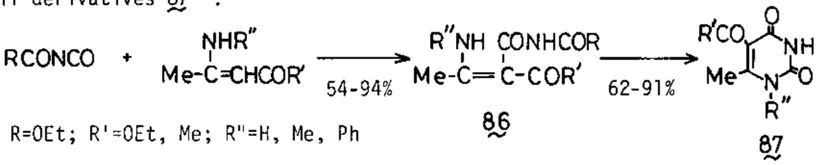
85

$R=R'=Ph$ 78%; $R=Ph, R'=$mesityl 82%; $R=Ph, R'=1-C_{10}H_7$ 94%;
RR'C= 42%

Scheme 21

I-8) Pyrimidine Derivatives

The introduction of an electron-withdrawing substituent to the β-carbon atom of enamines decreases the nucleophilicity of the C=C bond, and makes its hydrogen atom more labile. Therefore, conjugated addition takes place in the reactions of benzoyl isocyanate with 1-dimethylamino-2-ethylene[68], and of ethoxycarbonyl isocyanate with enaminoketones[69] and 6-aminouracils[70]. Upon treating with amine or heating, the conjugated adducts afford pyrimidine derivatives. For instance, treatment of the adducts 86 which are obtained from the reaction with enaminoketones, with aqueous trimethylamine gives the uracil derivatives 87[69].



R=OEt; R'=OEt, Me; R''=H, Me, Ph

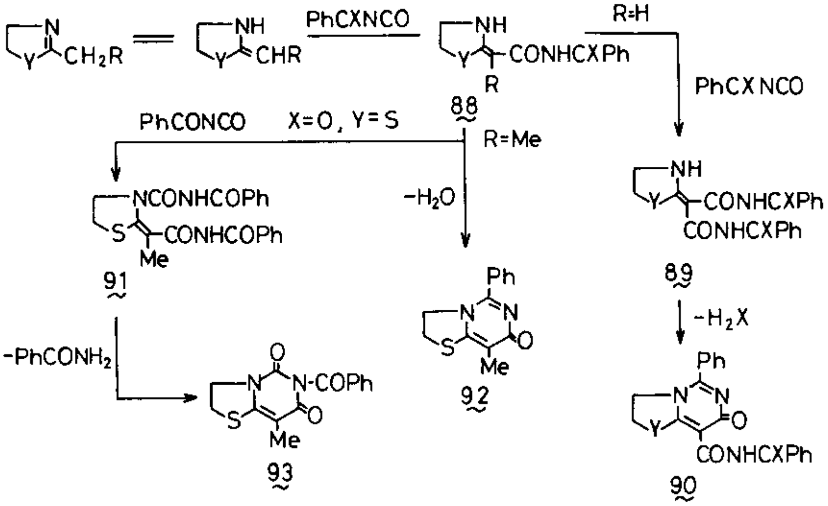
86

87

In addition, benzoyl isocyanate reacts with piperidinoisobutene to form the 2:1 adduct, hexahydropyrimidine derivative[71,72].

The reactions of benzoyl and thiobenzoyl isocyanates with 2-alkyl-2-thiazoline or 2-oxazoline are unusual[73]. Thiobenzoyl isocyanate adds to 2-thiazoline and 2-methyl-2-thiazoline at low temperature, affording the [π4 + π2] cycloadducts in 65 and 67% yields respectively.

In the reactions of 2-methyl-2-thiazoline with benzoyl isocyanate at room temperature and with thiobenzoyl isocyanate at 90°C, however, the corresponding thiazolo[3,2-c]pyrimidin-7-ones 90 (Y=S), whose structures correspond to those derived from a 2:1 adduct with loss of water or hydrogen sulfide, are obtained in 66 and 17% yields respectively. Thiobenzoyl isocyanate reacts with 2-methyl-2-oxazoline to form directly the oxazolo[3,2-c]pyrimidin-7-one 90 (X=S, Y=O), whereas benzoyl isocyanate affords the 2:1 adduct 89 (X=Y=O), which on treatment with acetic acid is transformed into 90 (X=Y=O). On the other hand, benzoyl isocyanate react with 2-ethyl-2-thiazoline to afford the methylthiazolopyrimidinone 92 and methylthiazolopyridinedione derivative 93.



Scheme 22

These reactions can be understood as illustrated in Scheme 22. The isocyanate initially attacks on the β-carbon atom of the tautomeric enamine of 2-alkyl-2-thia(oxa)zoline to yield the 1:1 adduct 88. When R is hydrogen atom, the 2:1 adduct 89 is formed by a second addition of the isocyanate to the β-carbon atom of 88. Subsequent cyclization of 89 with elimination of water or hydrogen sulfide leads to 90.

On the other hand, since the 1:1 adduct 88 (R=Me) does not possess a hydrogen atom on the β-carbon atom, the isocyanate reacts preferentially with the ring NH to give the 2:1 adduct 91, followed by ring closure and the elimination of benzamide to give 93. The formation of 92 can be also understood by the ring closure from 88 with loss of water.

II. HETEROCYCLES FROM α-KETOSULFENES

In 1911, Wedkind and Schenk[74] postulated the intermediacy of $PhCH=SO_2$ for the formation of trans-stilbene from phenylmethanesulfonyl chloride and triethylamine (NEt_3) (Scheme 23), and first used the name sulfene to molecules of the formula $RR'C=SO_2$. The name sulfene was selected to express the

$$PhCH_2SO_2Cl \quad + \quad NEt_3 \longrightarrow PhCH=SO_2 \quad + \quad Et_3\overset{+}{N}H\overset{-}{Cl}$$

$$PhCH=SO_2 \longrightarrow PhCH: \quad + \quad SO_2$$

$$2\ PhCH: \longrightarrow PhCH=CHPh$$

Scheme 23

relationship to ketene.

Although no notable studies on sulfenes have reported until 1950's, the chemistry of sulfenes has been rapidly developed since the almost simultaneous publication of papers by Opitz and Adolph[75] and by Stork and Borowitz[76] on the formation of sulfene-enamine cycloaddition products.

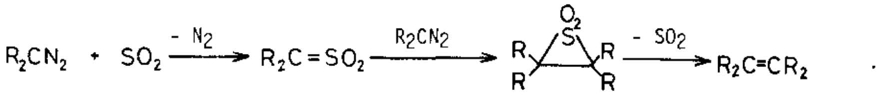
As pointed out in the beginning of this review, sulfenes are one of the most reactive species among heterocumulenes, and can only be generated in situ. However, the existence of sulfenes as reactive intermediates has been conclusively demonstrated[77].

The principal methods for the generation of sulfenes are as follows.

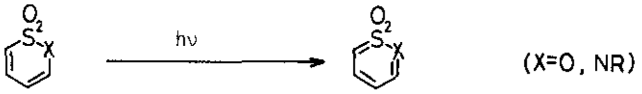
i) Dehydrochlorination of alkanesulfonyl chlorides $RR'CHSO_2Cl$ (R, R'=H, alkyl, aryl) with base. This is most commonly for the generation of sulfenes, and tertiary amines such as NEt_3 are employed as base[74, 78].

$$RR'CHSO_2Cl \xrightarrow[-\ HCl]{base} RR'C{=}SO_2$$

ii) Reaction of diazoalkanes with sulfur dioxide. This is an apparently general route. This method has little used except for the formation of episulfones (and olefins) since sulfenes react with excess diazoalkane[79].



iii) A less general method for the generation of sulfenes is the photolysis of cyclic unsaturated sultones[80] and sultams[81].



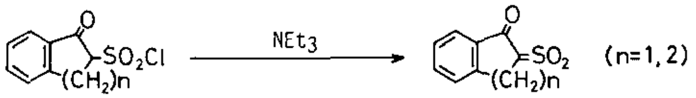
Other methods such as Sulfo-Cope rearrangement[82] and thermolysis of benzothiazete 1,1-dioxide[83] have little synthetic application.

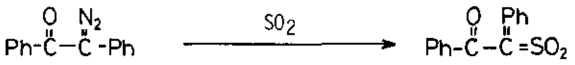
II-1) Generation of α-Ketosulfenes

The methods for the generation of α-ketosulfenes are similar to those for simple sulfenes, and two methods, i) and ii) mentioned above, have been reported. In 1963, the study by Fusco et al.[84] on

$$PhCOCH_2SO_2Cl \xrightarrow{NEt_3} PhCOCH{=}SO_2$$

$$EtOOCCH_2SO_2Cl \xrightarrow{NEt_3} EtOOCCH{=}SO_2$$



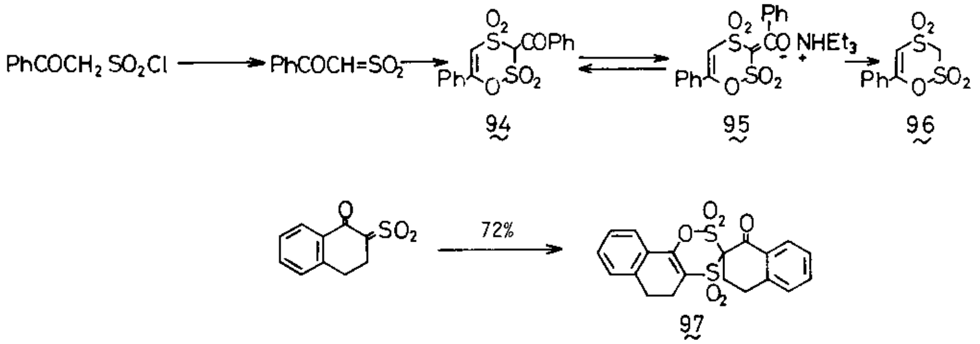


$$Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{N_2}{\overset{\|}{C}}\text{-}Ph \xrightarrow{SO_2} Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{Ph}{\overset{|}{C}}{=}SO_2$$

the formation of a dimer of benzoylsulfene by the reaction of benzoylmethanesulfonyl chloride with NEt_3 provided the first information regarding α-ketosulfene. Later, the generation of the corresponding α-ketosulfenes by dehydrochlorination of ethyl (chlorosulfonyl)acetate[85], 2-chlorosulfonylindanone, and 2-chlorosulfonyl-1-tetralone[86], and by the reaction of azibenzil with sulfur dioxide[87] has been reported.

II-2) Oxadithiines Derivatives

In principle, simple sulfenes might undergo dimerization via a [π2 + π2] cycloaddition. However, no examples of the dimerization of simple sulfenes are known. As described above, the long sought dimerization of a sulfene was finally achieved by Fusco et al[84]. Fusco et al.[84] obtained the dimer 94 in 40-60% yield from the reaction of benzoylmethanesulfonyl chloride with NEt_3, and formulated the cyclization as a Diels-Alder reaction of benzoylsulfene. However, the chloride reacts with 2 equivalents of NEt_3 to give the triethylammonium salt of dimer 95. An interconversion between 94 and 95 is also observed (Scheme 24). This reaction gives the dimer 94 in 88-95% yield. Hydrolysis of 94 or 95 with hydrochloric acid affords the oxaditiine tetraoxide 96 in almost quantitative yield[88].



Scheme 24

On the other hand, dehydrochlorination of 2-chlorosulfonyl-1-tetralone with 1 equivalent of NEt_3 gives the dimer 97 like 94. However, 2-chlorosulfonylindanone does not give the dimer, but instead 2,2'-diindanylidene 1,1'-dione is formed[89].

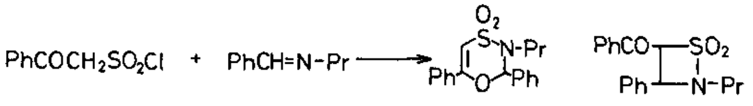
II-3) Cycloadditions and Their Related Reactions to C=N Bonds

The two examples have been reported on the reactions of simple sulfenes with C=N bonds. One is the reaction of diphenyldiazomethane with sulfur dioxide in the presence of benzylideneaniline[79a], and the other is the concerted [π2 + π2] cycloaddition of phenylsulfene, generated in situ from phenylmethanesulfonyl chloride and NEt_3, to benzylidenemethylamine leading to the formation of the 1,2-thiazetidine 1,1-dioxide[90].

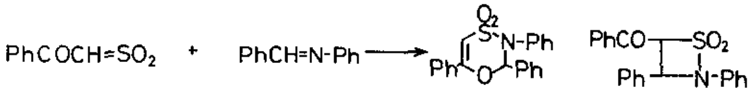
New heterocyclic compounds may be formed by the cycloadditions of α-ketosulfenes to the C=N bond, because the electron-withdrawing acyl group will make α-ketosulfenes more reactive than simple sulfenes. Thus the reactions of α-ketosulfenes with various compounds having the C=N bond have been investigated.

II-3-1) Reaction with Schiff Bases. The reactions of benzoylsulfene, generated *in situ* from benzoylmethanesulfonyl chloride and base, with Schiff bases give the corresponding [π4 + π2] and/or [π2 + π2] cycloadducts, whose yields depend on the nature of amine components of Schiff bases and on the reaction conditions[91].

For instance, benzoylsulfene, generated from the chloride and NEt_3, reacts with benzylidene-n-propylamine to give the [π4 + π2] cycloadduct 98 as the sole product, whereas the reaction of the chloride with 2 equivalents of the Schiff base affords the [π4 + π2] cycloadduct 98 and [π2 + π2] cycloadduct 99. In the reaction of the chloride with benzylideneaniline in the presence of NEt_3, the yield of the [π4 + π2] cycloadduct 100 decreases, and that of the [π2 + π2] cycloadduct 101 increases with the reaction time (Scheme 25).



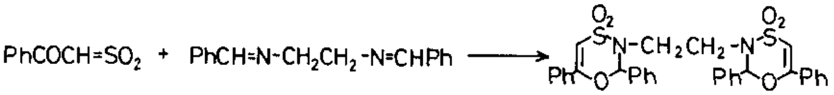
base	98	99
NEt_3	82%	-
anil	82%	13%



Reaction time, h	100	101
1	38%	-
12	14%	20%
24	-	30%

Scheme 25

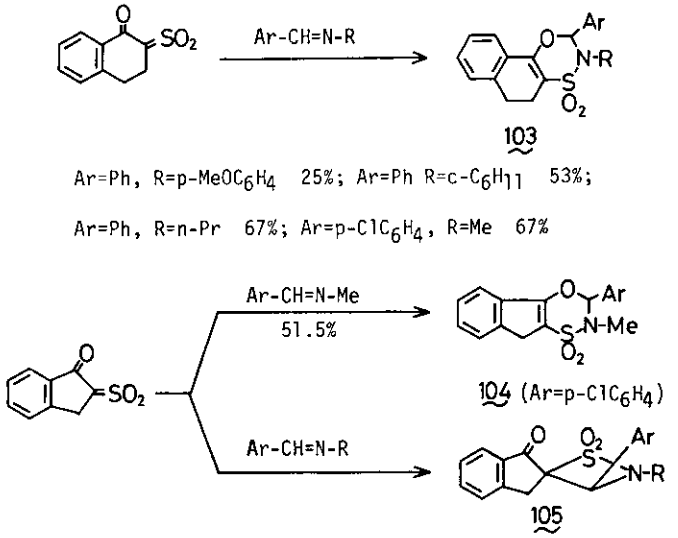
The chloride reacts with dibenzylidenethylenediamine in the presence of NEt_3 to give the corresponding bis[π4 + π2] cycloadduct 102[91].



102

Cyclic α-ketosulfenes, tetralonesulfene and indanonesulfene, show different characteristics in the cycloadditions to Schiff bases[86]. Tetralonesulfene, generated *in situ* from 2-chlorosulfonyl-1-tetralone and NEt_3, does not react with benzylideneanilines (Ar=R=Ph; Ar=p-ClC_6H_4, R=Ph; Ar=p-MeO-

C_6H_4, R=Ph), and adds to benzylidenealkylamines and benzylidene-p-methoxyaniline to form the corresponding [π4 + π2] cycloadducts 103. Indanonesulfene, generated in situ from 2-chlorosulfonylindanone and NEt_3, reacts with p-chlorobenzylidenemethylamine to give the [π4 + π2] cycloadduct 104, but the reaction of indanonesulfene with Schiff bases generally proceeds via a 1,2-cycloaddition process to yield the [π2 + π2] cycloadducts 105 (Scheme 26).



103

Ar=Ph, R=p-$MeOC_6H_4$ 25%; Ar=Ph R=c-C_6H_{11} 53%;

Ar=Ph, R=n-Pr 67%; Ar=p-ClC_6H_4, R=Me 67%

104 (Ar=p-ClC_6H_4)

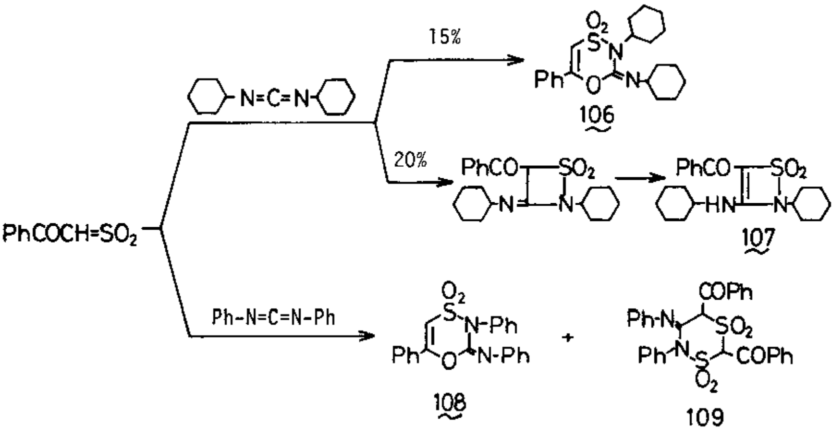
105

Ar=R=Ph 32%; Ar=p-ClC_6H_4, R=Ph 24%; Ar=p-$MeOC_6H_4$, R=Ph 31%;

Ar=Ph, R=p-$MeOC_6H_4$ 39%; Ar=Ph, R=c-C_6H_{11} 43%; Ar=Ph, R=n-Pr 40%

Scheme 26

II-3-2) Reaction with Carbodiimides or Ketenimines. Simple sulfenes do not react with carbodiimides[1]. However, benzoylsulfene reacts with carbodiimides to give the cycloadducts[92]. For instance, the reaction of benzoylsulfene with dicyclohexylcarbodiimide proceeds through both



106

107

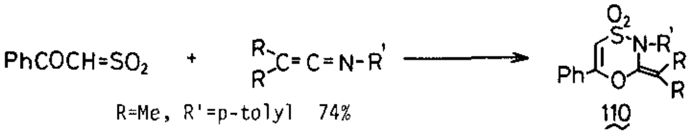
108
45%

109
40%

Scheme 27

1,4- and 1,2-cycloaddition processes to give the [π4 + π2] cycloadduct **106** and 1,2-thiazete compound **107** which is arisen from the initial [π2 + π2] cycloadduct. On the other hand, benzoylsulfene reacts with diphenylcarbodiimide to afford the [π4 + π2] cycloadduct **108** and 2:1 adduct **109** (Scheme 27).

In general, the cycloaddition to ketenimines takes place across the C=C bond of the ketenimines. However, benzoylsulfene adds across the C=N bond of the ketenimines to give 2-methyleneoxathiazine derivatives **110**[93].

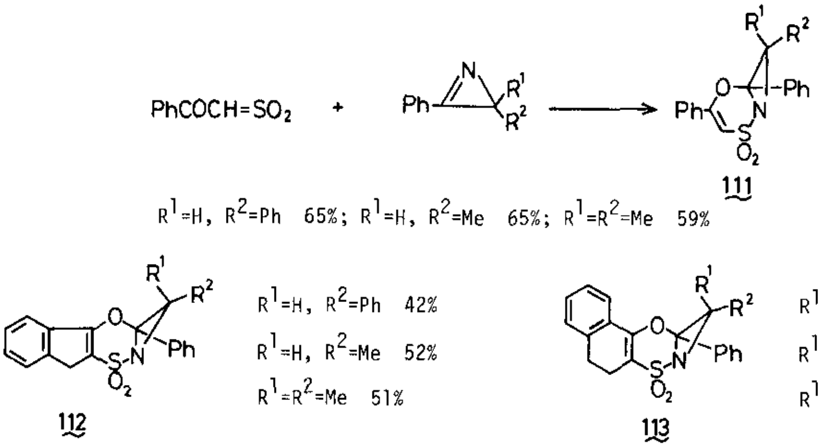


110

R=Me, R'=p-tolyl 74%

R=Ph, R'=n-Bu 48%

II-3-3) Reaction with 1-Azirines[94]. Phenylsulfene does not react with 1-azirines, but instead trans-stilbene is formed. However, α-ketosulfenes react with 1-azirines. That is, the reactions of benzoylsulfene, indanonesulfene, and tetralonesulfene with 3-substituted 2-phenyl-1-azirines proceed through a concerted [π4s + π2s] process to give the corresponding endo-R^1-cycloadducts **111**-**113** (Scheme 28).



111

R^1=H, R^2=Ph 65%; R^1=H, R^2=Me 65%; R^1=R^2=Me 59%

112

R^1=H, R^2=Ph 42%
R^1=H, R^2=Me 52%
R^1=R^2=Me 51%

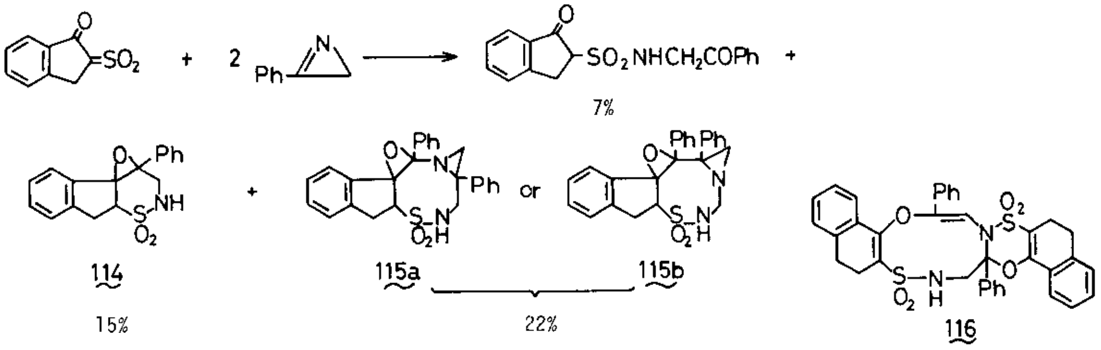
113

R^1=H, R^2=Ph 72%
R^1=H, R^2=Me 70%
R^1=R^2=Me 51%

Scheme 28

2-Phenyl-1-azirine (R^1=R^2=H) shows an unusual behaviour toward α-ketosulfenes. In the reaction of benzoylsulfene the sulfonamide, which is arisen from hydrolysis of the initial [π4 + π2] cycloadduct, is formed in 41% yield. Indanonesulfene reacts with the azirine to give new 1:1 adduct **114** and 2:1 adduct **115** along with the sulfonamide, whose yields depend on the amounts of the azirine employed. The result employed 2 mol. of theazirine is shown in Scheme 29.

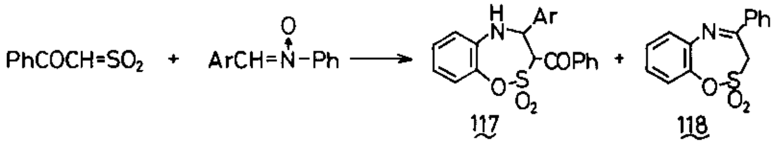
On the other hand, the reaction of tetralonesulfene with the azirine gives the sulfonamide and 2:2 adduct **116** (34.5%) instead of the expected cycloadduct.



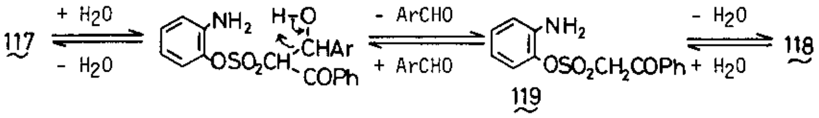
Scheme 29

II-4) Reaction with Nitrones

Although α-ketosulfenes, in analogy with simple sulfenes[95], react with C,N-diarylnitrones through 1,3-cycloaddition, followed by rearrangement via a four-membered cyclic transition state to o-position of the N-phenyl group of the nitrone to yield the corresponding rearranged adducts, seven-membered cyclic azasultones, the by-products which arise from the rearranged adducts with the elimination of the benzaldehyde are invariably accompanied in the reaction of α-ketosulfenes[96]. Thus, the reaction of benzoylsulfene with the nitrones gives a mixture of two seven-membered cyclic azasultones 117 and 118. Interconversion between 117 and 118 can be interpreted as illustrated in Scheme 30.



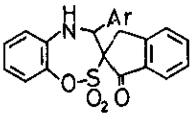
	117	118
Ar=Ph	28%	8%
Ar=p-$MeOC_6H_4$	10	5
Ar=p-ClC_6H_4	36	6
Ar=p-$NO_2C_6H_4$	35	6



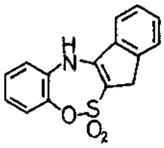
Scheme 30

Hydrolysis of 117 under mild conditions gives the sulfonate 119, which is easily transformed to 118 by dehydration. The sulfonate 119 reacts with the benzaldehyde to form 117. Further, thermolysis of 117 under reduced pressure affords 118 with the elimination of the benzaldehyde (ArCHO). Similarly, indanonesulfene and tetralonesulfene afford a mixture of the corresponding two azasultones

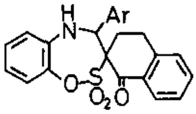
120 and 121, and 122 and 123, respectively.



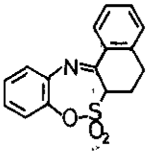
120



121



122

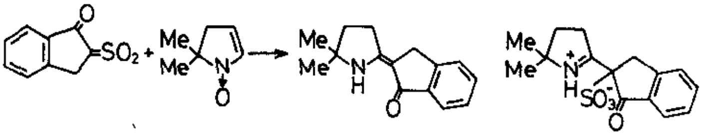


123

	120	121	122	123
Ar=Ph	28%	4%	23%	6%
Ar=p-MeOC$_6$H$_4$	0	30	13.5	5
Ar=p-ClC$_6$H$_4$	31	5	30	5
Ar=p-NO$_2$C$_6$H$_4$	52	3	26	5

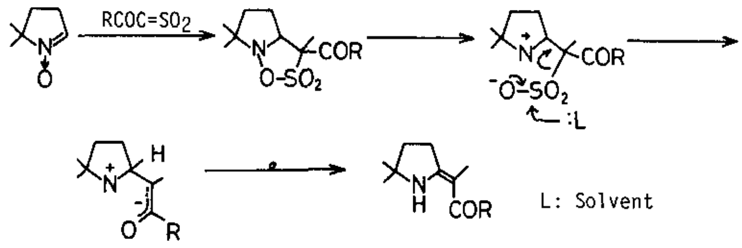
The reaction of α-ketosulfenes with cyclic nitrones such as 1-pyrroline 1-oxides gives cis-s-cis β-aminoenones and/or β-imino sulfonic acids, whose yields greately depend on the nature of solvents employed[97]. The results of the reaction of indanonesulfene with 5,5-dimethyl-1-pyrroline 1-oxide are shown in Table 10.

Table 10



Solvent	124	125
dioxane	69%	0%
THF	63	0
MeCN	8	70
CH$_2$Cl$_2$	11	66

As shown in Table 10, it seems reasonable to conclude that β-aminoenone 124 is predominantly formed in solvents such as dioxane and THF which have a strong affinity for sulfur trioxide, but β-imino sulfonic acid 125 is obtained as a major product in acetonitrile which does not exhibit affinity for sulfur trioxide. The pathway for the formation of β-aminoenones is outlined in Scheme 31. The formation of β-aminoenones is characteristic of α-ketosulfenes, and might be classified into a



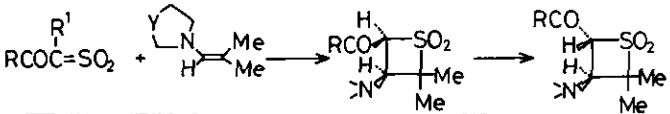
Scheme 31

special reaction.

II-5) Miscellaneous Reactions

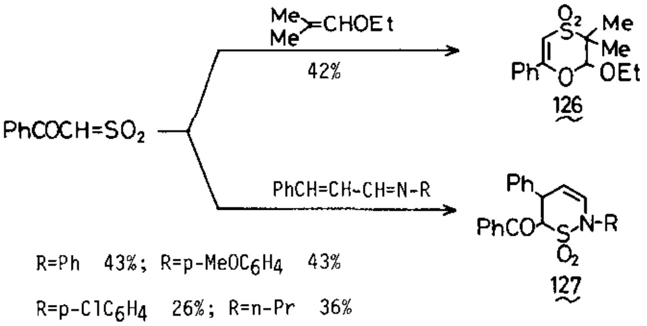
It is well known that simple sulfenes react with enamines to give the corresponding thietane 1,1-dioxides. Benzoylsulfene[78a, 98] and ethoxycarbonylsulfene[85,98] as well as simple sulfenes add to acyclic enamines to form the corresponding $[\pi2 + \pi2]$ cycloadducts. Truce and Rach[98] studied the stereochemistry of adducts of sulfenes to acyclic enamines, and found that simple sulfenes give cis-cycloadducts, whereas benzoylsulfene and ethoxycarbonylsulfene form trans-cycloadducts which are arisen from the postepimerization of initial cis-cycloadducts (Table 11). On the other hand, the reaction of benzoylsulfene with enamines derived from cyclohexanone does not give the thietane 1,1-dioxides, but instead acyclic sulfonyl compounds are formed[99].

Table 11



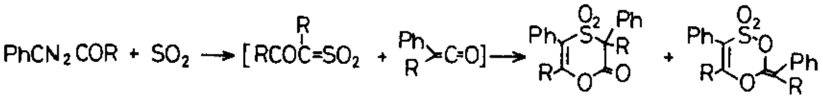
R	R'	Y	cis	trans
Ph	H	CH_2	-	64%
Ph	H	OCH_2	-	88
OEt	Me	CH_2	-	93
OEt	Me	OCH_2	27%	62

Opitz briefly described in a review[78a] the formation of $[\pi4 + \pi2]$ cycloadduct 126 in the reaction of benzoylsulfene with enol ether. In the reaction with cinnamylideneamines, benzoylsulfene acts as dienophile to give the Diels-Alder adducts 127[100] (Scheme 32).



Scheme 32

The reaction of α-diazoketone with sulfur dioxide affords occasionally the cycloadducts of α-ketosulfene to ketene which are generated in situ. The four-membered cyclic structures were postulated for the cycloadducts[87], but it has been later clarified that the cycloadducts are $[\pi4 + \pi2]$ cycloadducts 128 and 129 by 1,4-cycloadditions of the α-ketosulfene across the C=C and C=O bonds of the

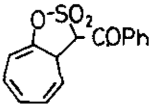


R		**128**	**129**
Ph	70^{0}C (in benzene)	44%	7%
Me	60^{0}C (in benzene)	49	5
Ph	hν	35	17
Me	hν	54	11

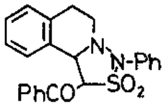
Scheme 33

ketene respectively. The results of thermal and photochemical reactions of α-diazoketones with sulfur dioxide are shown in Scheme 33.

Benzoylsulfene as well as simple sulfenes reacts with tropone[103] and azomethine ylide[104] to give the $[\pi 8 + \pi 2]$ cycloadduct **130** and $[\pi 4 + \pi 2]$ cycloadduct **131** respectively.



130(85%)



131 (31%)

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Received, 19th May, 1979