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A Review on the Photochemistry of 2H-Azirines

Dedicated to Professor T. R. Govindachari

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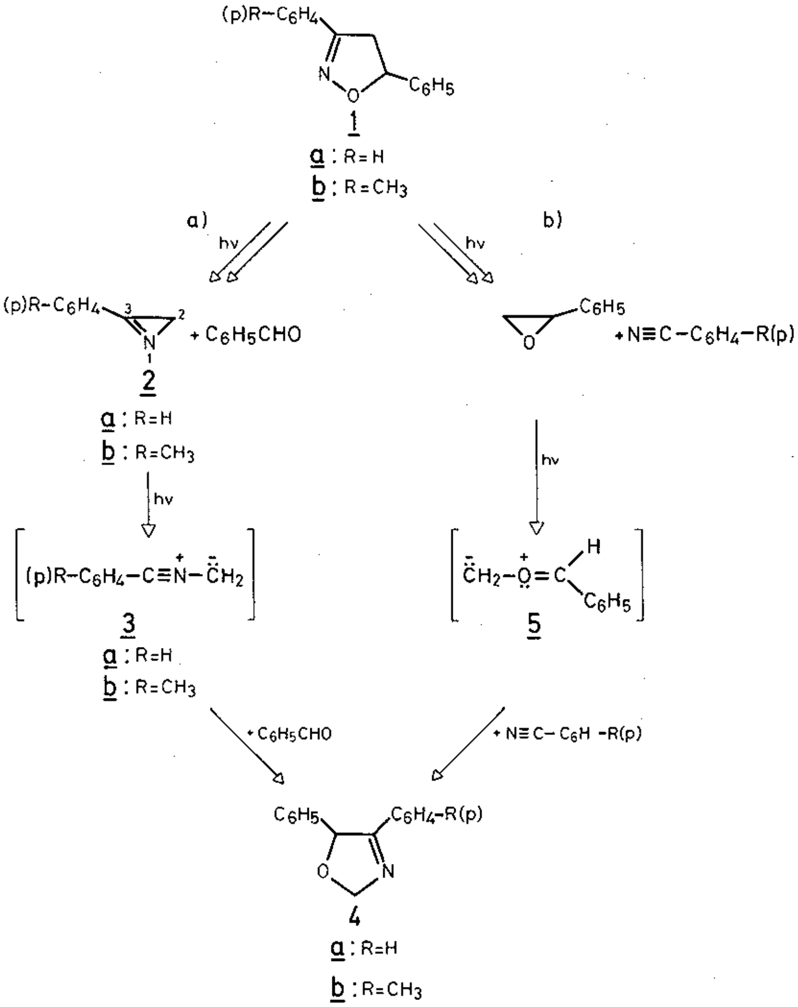
1. Introduction

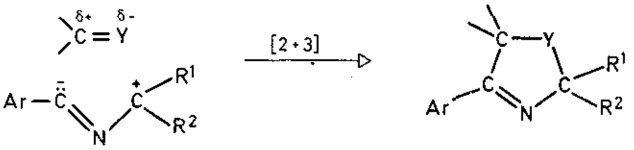
In connection with the study of the photochemistry of 2-isoxazolines, it was observed in our laboratory that the irradiation of 3,5-diphenyl- and 3-p-tolyl-5-phenyl-2-isoxazoline (1a and 1b) with a mercury high pressure lamp in benzene solution in quartz vessels yielded benzaldehyde (from 1a or 1b), benzonitrile (from 1a) or p-tolunitrile (from 1b) as well as β-aminochalcone (from 1a) or 4-methyl-β-aminochalcone (from 1b) and the 3-oxazolines 4a and 4b, respectively (scheme 1).[1-3] The formation of the 3-oxazolines provoked special interest since, with respect to the distribution of the substituents, their generation could not be explained by an intramolecular photo-isomerization (via aziridines). Hence, two routes a) and b) (scheme 1) for the intermolecular formation of the oxazolines 4 were envisaged. An unequivocal distinction between route a) and b) was accomplished by the irradiation of 1a in the presence of benzaldehyde-(carbonyl-^{14}C). The fact that the isolated oxazoline 4a was highly radio-active demanded the occurrence of the 3-aryl-2H-azirine 2a as intermediate via route a). Indeed, azirine 2a could be detected gas-chromatographically when the irradiation of 1a was interrupted shortly after commencement.[3] Accordingly, irradiation of 2a in the presence of benzaldehyde gave 4a in high yield. On the other hand, irradiation of styrene-oxide in the presence of benzonitrile (according to route b)) failed to produce 4a.

Scheme 1



The detection of the new photoreaction 2 → 4 inspired in our laboratory the development of the photochemistry of 2H-azirines, essential parts of which were contributed independently by Prof. Padwa and co-workers.[4,5] As explained subsequently, the reaction of the 2H-azirines is characterized by a photochemical cleavage of the C(2), C(3)-bond and formation of highly reactive dipolar intermediates of the benzonitrilio-methanides 3 type. The latter reacts with dipolarophiles C=Y such as aldehydes[6], activated esters[7], polarized olefins[8], activated nitriles[9, 10] among others in a mostly regiospecific way to form five-membered heterocycles (see scheme 2). The dipolar intermediates combine in an analogous manner with electron-deficient alkenes and alkynes like dimethyl fumarate[8] and dimethyl acetylenedicarboxylate.[2, 8] Thus, 3-aryl-2H-azirines represent valuable synthons for the preparation of nitrogen-containing five-membered heterocycles.

Scheme 2



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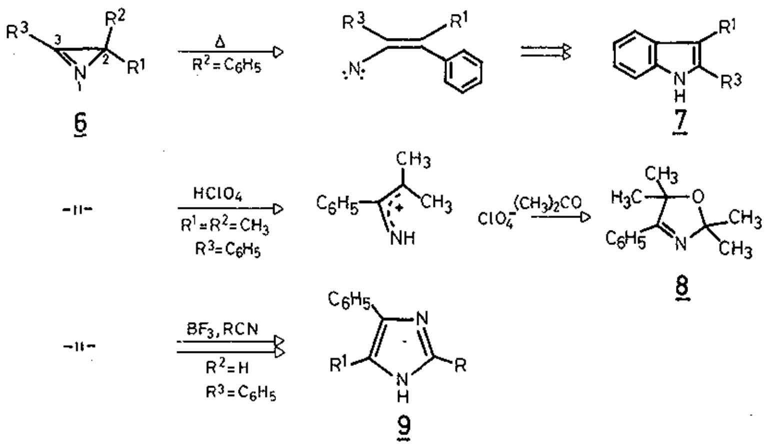
$\underline{a}$: Ar = C_6H_5, $R^1 = R^2 = H$ $\underline{c}$: Ar = C_6H_5, $R^1 = CH_3$, $R^2 = H$ $\underline{d}$: Ar = $R^1 = C_6H_5$, $R^2 = H$

$\underline{e}$: Ar = C_6H_5, $R^1 = R^2 = CH_3$ $\underline{f}$: Ar = $R^1 = R^2 = C_6H_5$

It should be mentioned that 2H-azirines may also react via cleavage of the N(1), C(2)-bond (see scheme 3) or of the N(1), C(3)-bond (see scheme 4, cf. [11]). Thermolysis of 2-phenyl-2H-azirines $\underline{6}$ ($R^2 = C_6H_5$), for example, yields (via vinyl nitrenes) 2-substituted indoles $\underline{7}$ [12-14] (cf. [15]). Treatment of 2H-azirines $\underline{6}$ ($R^1 = R^2 = CH_3$, $R^3 = C_6H_5$) with perchloric acid in the presence of acetone leads - also by splitting of the N(1), C(2)-linkage - to the formation of oxazolines $\underline{8}$ [16], and with nitriles in the presence of boron trifluoride $\underline{6}$ ($R^2 = H$, $R^3 = C_6H_5$) can be converted into imidazoles $\underline{9}$ [17] (see also [16]). Vinyl nitrenium ions (= 1-aza-allyl cations) are intermediates in these reactions.

Scheme 3

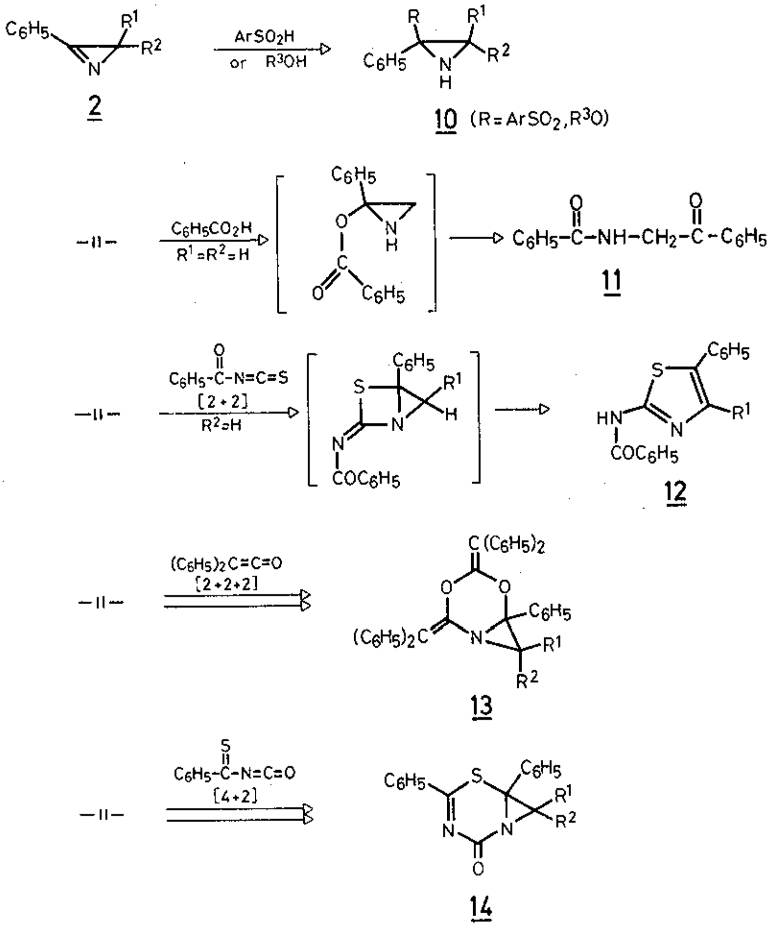
N(1)-C(2)-Cleavage



The cleavage of the N(1), C(3) double bond occurs in two steps (scheme 4). In the first step aziridines are formed which may open on further reaction. 3-Phenyl-2H-azirines <u>2</u> combine under base catalysis[18] with alcohols or with sulfinic acids[19] to yield aziridines <u>10</u>, whereas in the reaction with benzoic acid at 80° [20] the primarily formed aziridine intermediate opens to give the benzamide <u>11</u>. The C,N double bond of 2H-azirines can also participate in cycloadditions. Thus, with heterocumulenes the formation of [2+2] as well as [2+2+2] cycloadducts and products thereof is observed.[21, 22] [2+4] Cycloadducts are formed with reactive dienes[23] and acyl heterocumulenes.[21] [2+3]-Cycloadditions which take place with 2H-azirines and dipolar compounds of the nitrilio-methanides type will be discussed later (see section 2.2.4).

Scheme 4

N(1)-C(3)-Cleavage



2. Preparative Photochemical Reactions of the 2H-Azirines

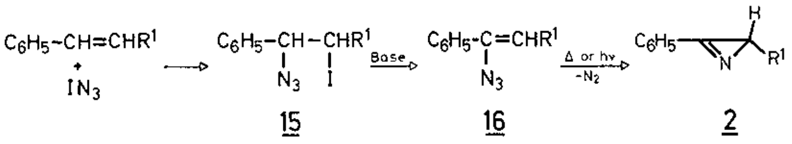
2.1 Syntheses of 2H-Azirines

Nowadays the 2H-azirines, required for the photoreactions to be discussed, are readily accessible and also available in greater quantities.[15]

3-Phenyl-2H-azirine (2a) can be prepared starting with styrene and iodine azide (see scheme 5). In an ionic addition, 1-azido-2-

iodo-1-phenylethane (15) is formed first which on treatment with bases (sodium isopropoxide, potassium t-butoxide) yields 1-azido-1-phenyl-ethene (16). Thermolysis or photolysis of this product gives, via the corresponding vinyl nitrene, 3-phenyl-2H-azirine (2a, overall yield 50-60%).[24,25] The azide 16a can also

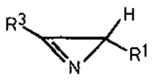
Scheme 5



a: $R^1 = H$ c: $R^1 = CH_3$ d: $R^1 = C_6H_5$

be synthesized by treatment of 1,2-dibromo-1-phenylethane with sodium azide and sodium hydroxide in dimethyl sulfoxide solution.[26] It may be mentioned that addition of bromine azide to styrene follows a radical pathway and yields 1-azido-2-bromo-2-phenylethane which after base-catalyzed elimination of HBr and photolysis of the corresponding 1-azido-2-phenylethene gives the unstable 2-phenyl-2H-azirine.[27]

The method briefly described in scheme 5 also allows the preparation of 2-methyl-3-phenyl-2H-azirine (2c)[25], 2,3-diphenyl-2H-azirine (2d)[25], 3-benzyl-2H-azirine (6a)[25], 2,3-dipropyl-2H-azirine (6b), and 9-azabicyclo[6.1.0]non-1-ene (6c).[25] Since some of the 2H-azirines are unstable, e.g., 2c or 6b,



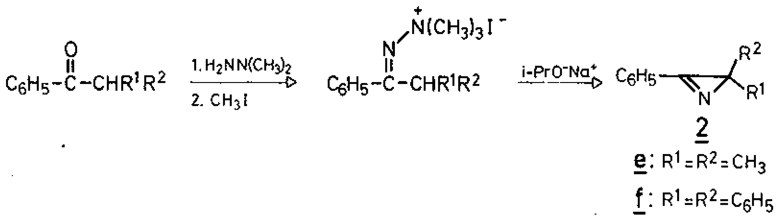
6

a: $R^1 = H, R^3 = C_6H_5CH_2$
b: $R^1 = R^3 = CH_3CH_2CH_2$
c: $R^1, R^3 = (CH_2)_6$

prolonged irradiation of the vinyl azides instead of the corresponding 2H-azirines offers an alternative method to generate the nitrilio-methanides.

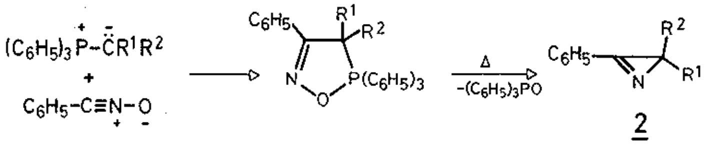
A further synthetic route leading to 2H-azirines is based on a modified Neber reaction.[15] For example, 2,2-dimethyl-3-phenyl-2H-azirine (2e)[16, 29] can be synthesized according to scheme 6. 2,2,3-Triphenyl-2H-azirine (2f) was prepared by a similar route.[30]

Scheme 6



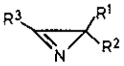
3-Aryl-2H-azirines 2 can also be obtained in good yields by reaction of alkylidene phosphoranes with nitrile oxides[31] (scheme 7).

Scheme 7



2H-Azirines crystallize as nearly colorless crystals or represent colourless liquids which can be distilled in vacuum. Characteristic UV maxima are given in table 1. 3-Aryl-2H-azirines 2 show in the IR spectrum $\tilde{\nu}_{C=N}$ at about 1740 cm^{-1}. This absorption appears at about 1770-1785 cm^{-1} in 3-alkyl-2H-azirines.[25]

Table 1. Absorption Maxima of 2H-Azirines in Ethanol

	λ max(ε)	Shoulders(ε)
$R^1=R^3=C_3H_7, R^2=H$ 6b	239 (237)	
$R^1=R^3=C_6H_5, R^2=H$ 2d	245 (23600)	285(1500), 305(1050)
$R^1=R^2=R^3=C_6H_5$ 2f	250 (24500)	285(1400), 310(1100)
$R^1=R^2=H, R^3=C_6H_5$ 2a	246 (13500)	280 (1700)
$R^1=R^2=CH_3, R^3=C_6H_5$ 2e	245 (15200)	277 (1500), 286 (1040)

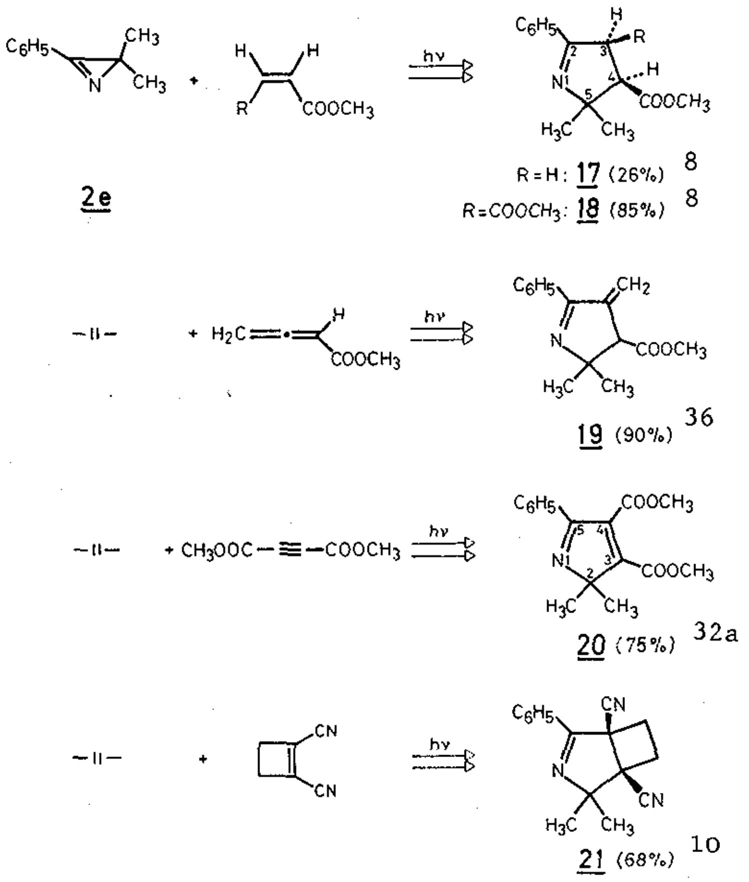
2.2 Irradiations

The irradiations of the 3-aryl-2H-azirines 2 are run with mercury high pressure lamps (125-700 W) and pyrex filters in inert solvents like benzene, cyclohexane, dimethoxyethane, acetonitrile, at 10-20° under nitrogen. The concentrations of the azirine solutions, usually employed, are 10^{-2} to 10^{-3} mol/l. The co-reactants are taken neat or in concentrations of ca. 10^{-1} to 10^{-3} mol/l. The irradiations of the 3-alkyl-2H-azirines are performed with vycor filters ($\lambda_{\text{transmittance}} > 240$ nm).

2.2.1 Reactions with Olefins and Acetylenes

Electron-deficient olefins like acrylic esters, acrylonitriles, fumaric and maleic esters and the corresponding dinitrile add mostly with high yields to the nitrilio-methanides, generated photochemically from different 2H-azirines, to form Δ^1-pyrro-

Scheme 8

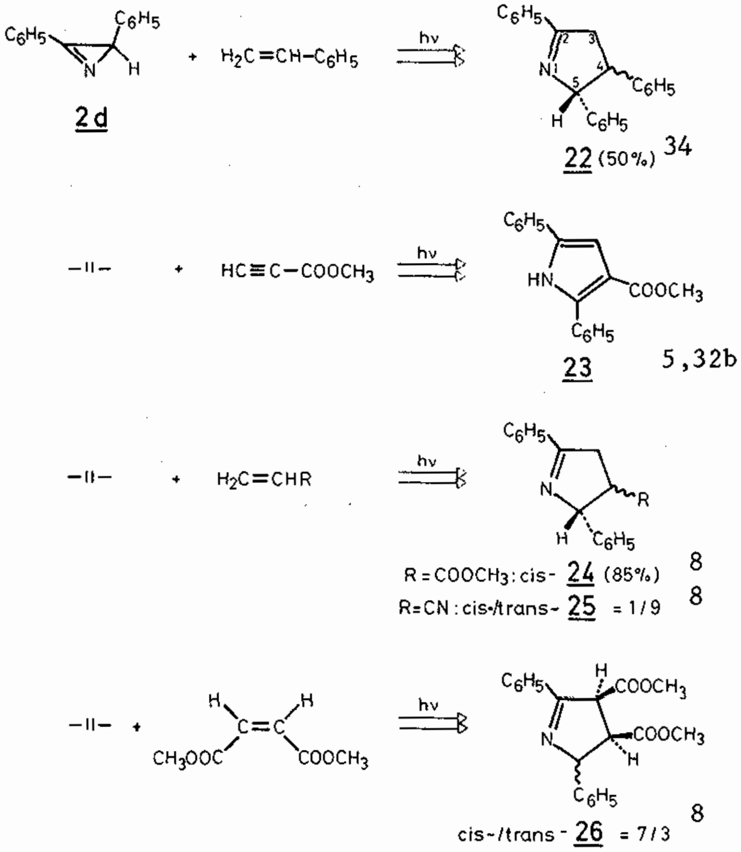


lines (see scheme 8 and 9). 1,2-Dicyanocyclobutene[33] and benzonitrilio-2-propanide form in 68% yield the bicyclic compound 21.[10] Similarly, styrenes[34] and vinylpyridines[35] react with the nitrilio-methanides 3. Whereas nonactivated olefins like 1-octene, cyclohexene[8] or the allene 3-methylbuta-1,2-diene[32b] fail to add to nitrilio-methanides, the strained norbornene or methyl allenecarboxylate[36] undergo the cycloaddition reaction with benzonitrilio-phenylmethanide (3d). Furthermore, 'push-pull' olefins which, however, contain an additional electron acceptor group behave similarly to acrylates. Diethyl ethoxymethylidene malonate as well as the dinitrile, for example, furnish with the azirine 2e the corresponding cycloadducts in 65 and 70% yields, respectively.[10]

Addition of acetylene derivatives, as, for example, dimethyl acetylenedicarboxylate, to benzonitrilio-methanides yields in the first step 2H-pyrroles which rearrange to pyrroles if C(2) is only monosubstituted (see schemes 8 and 9).
The cycloaddition of the electron-deficient olefins and the nitrilio-methanides 3 occurs, in general, regiospecifically as shown in scheme 2. The stereochemistry of the reaction with (E)- and (Z)-olefins corresponds, as a rule, to a concerted cycloaddition or follows the principle of least motion[37], i.e., derivatives of fumaric acid yield, with respect to position 3 and 4, trans substituted Δ^1-pyrrolines and those of maleic acid, the corresponding cis substituted compounds (see schemes 8 and 9).

The photolysis of 2H-azirines which, like 2,3-diphenyl-2H-azirine (2d), are monosubstituted at C(2), can lead to cis, trans-isomeric Δ^1-pyrrolines with respect to positions 4 and 5. Thus, while methyl acrylate gives pyrroline cis-24 as the main reaction product[8], acrylonitrile yields predominantly pyrroline trans-25 [8] (scheme 9). On the other hand, dimethyl maleate

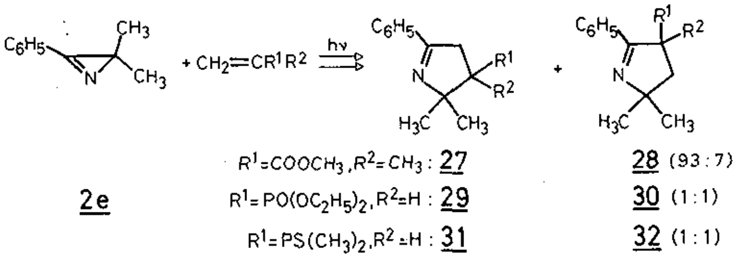
Scheme 9



and benzonitrilio-phenylmethanide (3d) furnish mainly the cis-isomer of the Δ^1-pyrroline 26.[8] The cycloaddition of other dipolarophiles also leads to the formation of stereoisomeric mixtures.

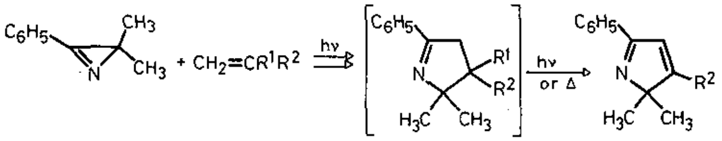
The regiospecificity of the olefin addition depends on the substitution of the double bond and on the nature of the activating group. Methyl acrylate and benzonitrilio-2-propanide (3e), for example, react regiospecifically in conformity with scheme 8. However, methyl α-methacrylate leads to a 93:7 mixture of the two isomeric Δ^1-pyrrolines 27 and 28 in high yield (see scheme 10).[35] The benzonitrilo-methanides generated from 2,2-dimethyl-3-(4-fluoro- and 4-methoxyphenyl)-2H-azirine, respectively, and methyl α-methacrylate undergo cycloaddition in the same manner to yield the corresponding isomeric Δ^1-pyrrolines (ratio of isomers 93:7).[35] α-Methylacrylonitrile exhibits a similar behaviour.[8] The regioselectivity is practically lost in the cycloaddition of benzonitrilio-2-propanide (3e) and diethyl vinyl phosphonate or dimethyl vinyl phosphine sulfide. The two isomers 29 and 30 as well as 31 and 32 are formed in equal amounts (scheme 10).[38,39] The addition reaction of benzonitrilio-phenylmethanide (3d) or benzonitrilio-ethanide (3e) and diethyl vinyl phosphonate also occurs exclusively in a regioselective manner.[38]

Scheme 10



The photoaddition of 3-phenyl-2H-azirines 2 to vinyl phosphonium salts (vinyl- and 2-propenyl-triphenyl phosphonium bromide) in acetonitrile solution[39,40] and to vinyl sulfones like phenyl vinyl sulfone[41] is accompanied by concomitant loss of the phosphorus and the sulfur containing substituent ($(C_6H_5)_3P \cdot HBr$ and $C_6H_5SO_2H$, respectively; see scheme 11) to yield the 2H-pyrroles 37-39. The mechanism of these reactions is still unknown. Presumably, the 'normal' intermediates 33-35 are formed in the first step. α-Ethoxyacrylonitrile and 2e behave similarly and form, by loss of acetic acid, the 2H-pyrrole 40 in a yield of 55%.[10,42]

Scheme 11



$R^1 = \overset{+}{P}(C_6H_5)_3Br^-, R^2{=}H$:	33	$-(C_6H_5)_3P \cdot HBr$	37 (40%)
$R^1 = \overset{+}{P}(C_6H_5)_3Br^-, R^2{=}CH_3$:	34	-"-	38 (26%)
$R^1 = SO_2C_6H_5, R^2{=}H$:	35	$-C_6H_5SO_2H$	39 (65%)
$R^1 = CN, R^2{=}OCOCH_3$:	36	$-CH_3COOH$	40 (55%)

2,2-Dimethyl-3-phenyl-2H-azirine (2e) produces on photolysis, in the presence of methyl phenylpropiolate, a 2:1 mixture of 4-ethoxycarbonyl-2,2-dimethyl-3,5-diphenyl- and 3-ethoxycarbonyl-2,2-dimethyl-4,5-diphenyl-2H-pyrrole.[39] A mixture of 2H-pyrroles is also obtained with 2e and methyl propiolate. 3-Methoxycarbonyl-2,2-dimethyl-5-phenyl-2H-pyrrole is the main product in this case.[32b]

The irradiation of 2-vinyl-3-phenyl-2H-azirines 41 leads to the formation of pyrroles of type 43.[43] Schematically, this reaction can be understood as an intramolecular addition of a benzonitrilio-methanide to an adjacent C,C double bond with inverse regiospecificity,* but it may be better regarded as an electro-

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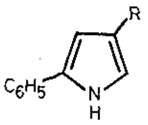
* The 'normal' addition to the C,C double bond would lead to the strained azetidine derivative i which on ring opening would give the isomeric pyrrole ii.

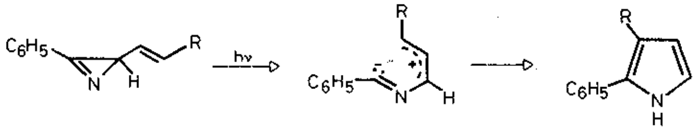
i



ii

cyclization of a species which is isoconjugate with the cyclopentadienyl cation (see scheme 12).

Scheme 12



41 42 43

The electrocyclization can be completely suppressed in the presence of an external dipolarophile in excess. Thus, the photolysis of a mixture of 41 (R = $COOCH_3$) and surplus methyl acrylate furnishes the expected [3+2] cycloadduct of type 18. The pyrrole 43 is not formed under this condition.[43]

Electrocyclizations seem to play a role also in the photolysis of 2-vinyl-3-phenyl-2H-azirines of type 44 which are arylated at C(2'). The formation of the benzoazepines 47 can be formulated as mentioned in scheme 13 [44, 45] (cf. the photo-induced rearrangements of compound 62 and 64 in the following section).*

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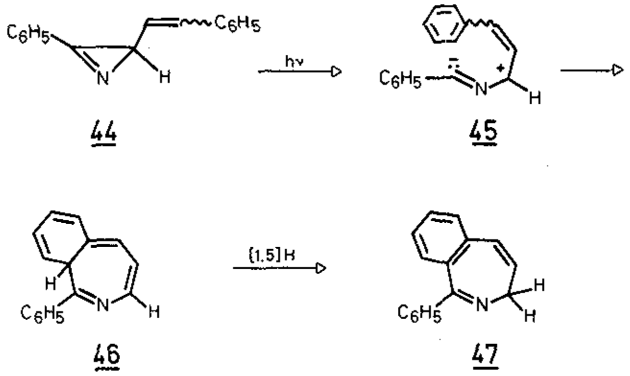
* It can be expected that pericyclizations in systems with a 1,3-dipolar substructure take place rapidly (cf. for example, the pericyclizations of ionic systems[46]).

Scheme 13



Normal intramolecular cycloaddition occurring via the expected nitrilio-methanide, interceptable, for example, by methyl trifluoroacetate, are shown by 2-allyl-2H-azirines of type 48, 49 which give the bicyclic compounds 50 and 51,* respectively.[44, 47] Further irradiation transforms the stronger absorbing 50 into 51.[47b] The isomeric 2H-azirines 48 and 49 cannot be interconverted photochemically.

It is of interest to notice that irradiation of 2-phenyl-3-(2-phenylvinyl)-2H-azirine (52)[48], which is isomeric with 44, does not lead to an intramolecular cyclization product. This would represent a strained seven-membered cyclic ketimine. In the presence of acrylonitrile a 3,5:1 mixture of the Δ^1-pyrrolines cis- and trans-53 is formed in a yield of 78% (scheme 15).[49]

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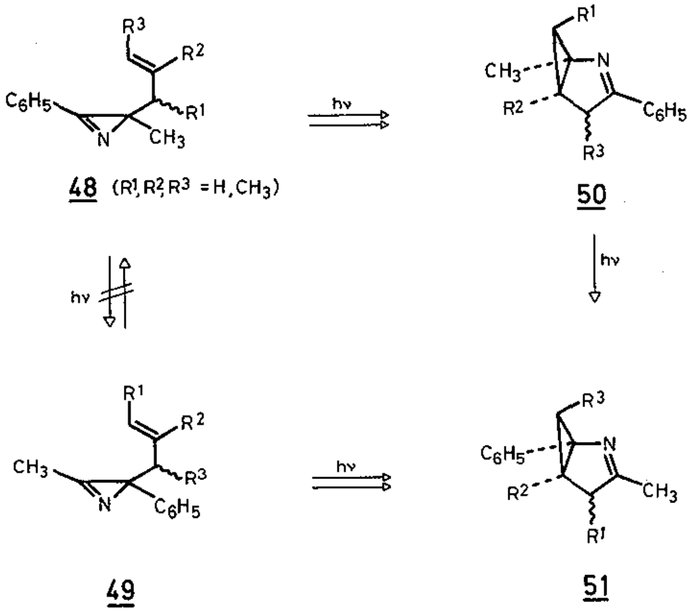
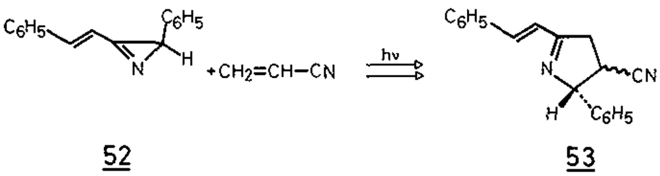
* The endo-compound with $R^1=R^2=H$, $R^3=CH_3$ rearranges at room temperature to the thermodynamically more stable exo-isomer.[47] On warming or on standing for longer periods in the presence of air both isomers form pyridines.

Scheme 14



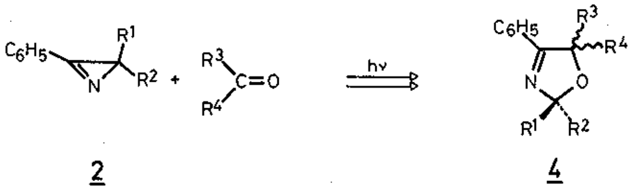
Scheme 15



2.2.2 Reactions with Aldehydes and Ketones

Aliphatic and aromatic aldehydes react smoothly with the photochemically generated benzonitrilio-methanides to form 3-oxazoline derivatives 4 (R^4=H) exclusively (preparative yields 30-80%)[2, 6, 34] (see scheme 16). The 2H-azirines 2c and 2d, which are monosubstituted at C(2), produce cis, trans-isomeric 3-oxazolines. In general, the cis-isomers predominate in a ratio of 2:1 to 4:1.

Scheme 16



The addition of ketones to the benzonitrilio-methanides is, as a rule, much more sluggish. Even though benzonitrilio-2-propanide (3e) combines with practically all ketones in good yield to furnish 5,5-disubstituted 3-oxazolines 4 [50], the yields drop sharply to 20-40% when benzonitrilio-phenylmethanide (3d) or -ethanide (3c) and acetone are used.[34,50] On the other hand, ketones with electron-attracting groups like trifluoromethyl[50], ethoxycarbonyl[50], nitrile[50] or phosphonate [38] in α-position react well also with benzonitrilio-methanides such as mentioned above. Again, the 2H-azirines 2c and 2d react with unsymmetrical ketones to form mixtures of cis, trans-isomers.* It may be mentioned that both carbonyl groups of hexa-2,5-dione react with benzonitrilio-2-propanide (3e).

Cyclic ketones would be expected to give spiro-3-oxazolines. Indeed, irradiation of 2H-azirine 2e and cyclohexanone result in the formation of 2,2-dimethyl-5,5-pentamethylene-4-phenyl-3-oxazoline in excellent yields.[50] The photochemical behaviour

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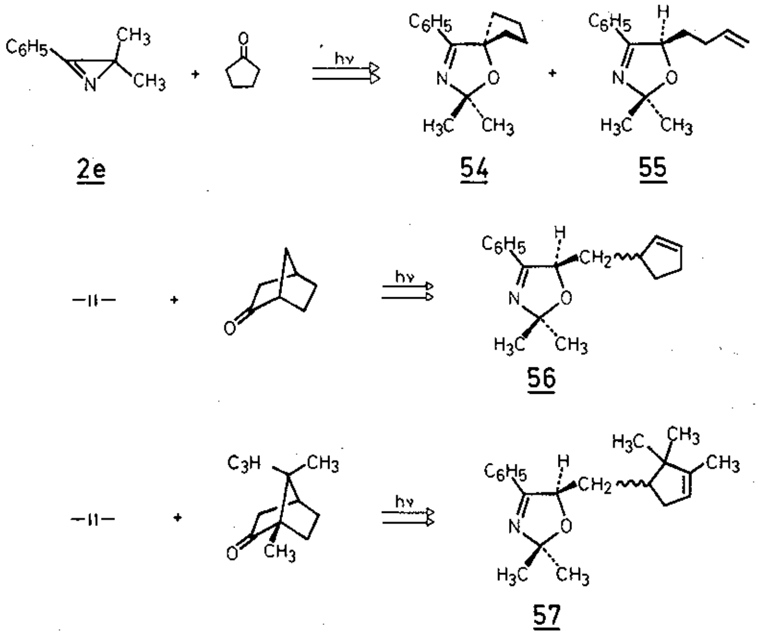
* It is to be expected that the isomer which carries the substituent at C(2) in a cis relation to the larger substituent at C(5) preponderates.

of 2e and cyclopentanone is more complex (scheme 17). When 2e is irradiated and cyclopentanone slowly added, the expected spiro-3-oxazoline 54 is the main product. However, when the cyclopentanone is irradiated first and the irradiation then continued in the presence of 2e, the sole product is 2,2-dimethyl-5-(3-butenyl)-4-phenyl-3-oxazoline (55).[50] Thus, under the latter conditions cyclopentanone reacts first by Norrish I-type cleavage and H-transfer to yield 4-pentenal. This aldehyde reacts faster with benzonitrilio-2-propanide (3e) than does the cyclic ketone still present, so that only 55 is formed. Norcamphor and camphor react with 2e under photolytic conditions exclusively after Norrish I-type cleavage to (2-cyclopentenyl)acetaldehyde

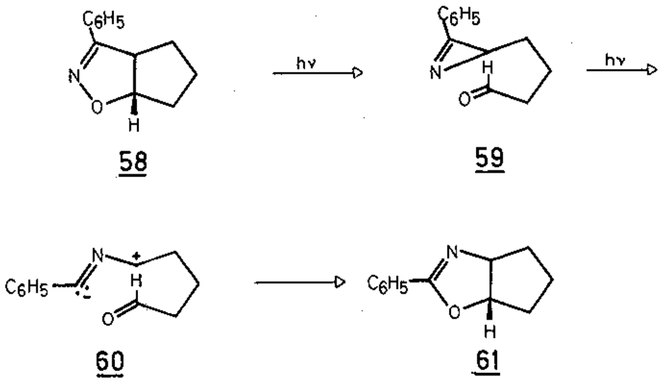
Scheme 17



and (2,2,3-trimethyl-3-cyclopentenyl)acetaldehyde, respectively, to produce subsequently 3-oxazolines 56 and 57, respectively (scheme 17).[50]

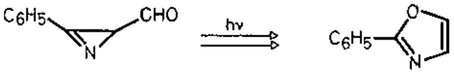
The direction of addition can be reversed when the 1,3-dipole reacts intramolecularly with an aldehyde group. Thus, irradiation of cis-3-phenyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (58) which reacts presumably via 59 ⟶ 60 leads to an isomeric compound as main product which could be characterized as the bicyclic 3-oxazoline 61 (scheme 18).[50] It can be argued that steric strain is responsible for the reversal of the mode of addition in this case.

Scheme 18



A reversal is also observed in the irradiation of 2-formyl-3-phenyl-2H-azirine (62) (scheme 19) which leads to the oxazole 63 [43, 44] (see also [51]). However, as already discussed in section 2.2.1 (scheme 12), this reaction can be better explained as electrocyclization.

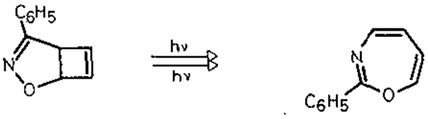
Scheme 19



62 63

Reactions which are comparable with those of 58 → 60 (scheme 18) and 45 → 46 (scheme 13), appear also to be responsible for the photochemical isomerization of the bicyclic isoxazoline 64 into the oxazepine 65 [52] (scheme 20).

Scheme 20



64 65

2.2.3 Reactions with α,ß-Unsaturated Carbonyl Compounds and 1,4-Quinones

The question arises as to whether the C,C or the C,O double bond of the compounds mentioned in the title react preferentially with benzonitrilio-2-propanide (3e). The results so far obtained, suggest that an aldehyde function reacts as fast as an olefin group, but both react faster than a ketone group.[42] Steric hindrance by increasing substitution at the olefinic part may alter this order. The α,ß-unsaturated cyclic ketones cyclo-2-pentenone, cyclo-2-hexenone and cyclo-2-heptenone, for example, add to benzonitrilio-2-propanide (3e) in good yields exclusively at the C,C double bond. The regiospecificity, as observed with activated olefins (section 2.2.1) and carbonyl systems (section

2.2.2), is preserved. Some typical data are collected in table 2.

2,3-Diphenyl- and 2-methyl-3-phenyl-2H-azirine (2d and 2c, respectively) can also be made to react with phosphorus-containing α,β-unsaturated carbonyl compounds.[39] The phosphonate 66 and the phosphonium salt 67 furnish with benzonitrilio-phenylmethanide (3d) only the C,C addition product whereas with the

Table 2. Cycloaddition of Benzonitrilio-2-propanide (3e) to α,β-Unsaturated Carbonyl Compounds

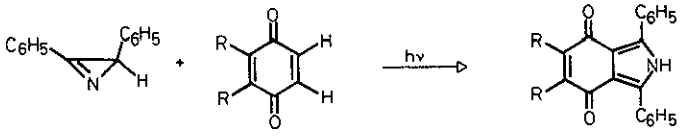
α,β-unsaturated Carbonyl Compounds	% C=C a) Addition	% C=O a) Addition	C=C/C=O
$CH_2 = CH-CHO$	39	46	0,92 b)
$CH_3-CH = CH-CHO$	-	84	-
$C_2H_5O-CH = C(CH_3)-CHO$	-	93	-
$CH_2 = CH-COCH_3$	73	-	-
$(CH_3)_2C = CH-COCH_3$	3	30	0,18 b)
$(C_2H_5)_2OP-CH = CH-COCH_3$ 66	41	31	1,35
$Br^-(C_6H_5)_3\overset{+}{P}-CH = CH-COCH_3$ 67	-	59	-
$(CH_3)_2C = CH-COPO(OCH_3)_2$ 68	-	80	-

a) Yields of isolated material. b) Ratio determined gas-chromatographically.

corresponding 2-propanide 3e both addition types are observed (see table 2). On the other hand, 3e and 67 give only the corresponding 3-oxazoline derivative. This is also true for the phosphonate 68 which on irradiation with the 2H-azirines 2c-e forms only the oxazolines.

As expected, 1,4-quinones react with the C,C double bond. So far, defined products, namely isoindolediones 69 [53] (scheme 21) have resulted only from 2,3-diphenyl-2H-azirine (2d). To obtain the diones 69, positions 5,6 in the quinones have to be unoccupied. The same applies to positions 2,3 in naphthoquinones.

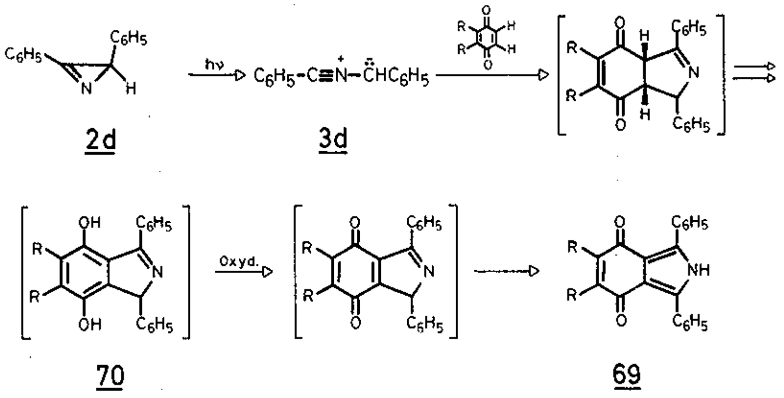
Scheme 21



2d R = H,CH_3,OCH_3 69 (33-43%)

In a more detailed investigation it was ascertained that the formation of the isoindolediones takes place in a sequence of steps as shown in scheme 22.[53] The intermediate benzonitriliophenyl-methanide (3d) add to the unsubstituted C,C double bond of the quinone whereby another intermediate, presumably 70, absorbing at short wavelength, is formed. This species is oxidized by oxygen to yield the strongly coloured dione 69. The relative slowness of the transformation 70 $\Rightarrow$ 69 permits a nearly complete photoreaction of the 2H-azirine 2d, or else, the strongly absorbing product 69 would hinder a total photolysis of 2d.

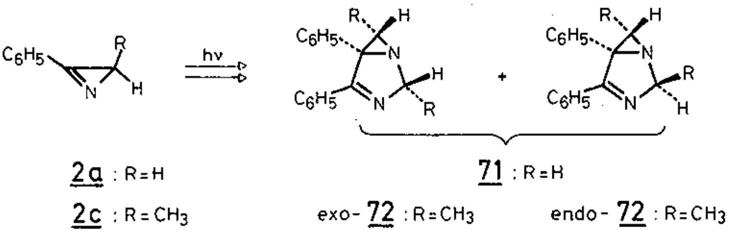
Scheme 22



2.2.4 Reactions with Imines

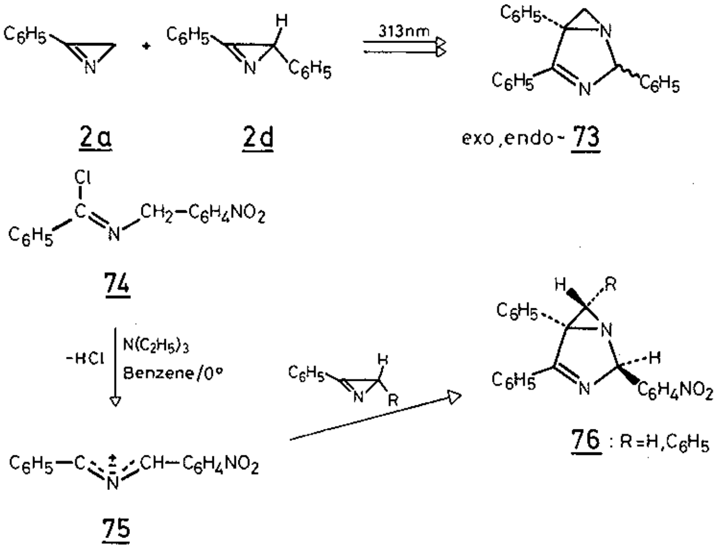
Normally, imines like benzylidene-methylamine do not react with benzonitrilio-methanides. The situation changes if one considers the strained C,N double bond in the 2H-azirines themselves. In this case, 4,5-diphenyl-1,3-diazabicyclo[3.1.0]hex-3-enes are obtained in moderate yields. Thus, irradiation of 3-phenyl-2H-azirine (2a) without dipolarophile, results in the formation of the bicyclic compound 71 $^{54-56}$ (scheme 23) and 2-methyl-3-phenyl-2H-azirine (2c) forms under the same conditions a mixture of 2-exo, 6-exo- and 2-endo, 6-exo-68 in a ratio of 3-2:1.^{34,55,57}

Scheme 23



Similar bimolecular adducts are observed with 2,3-diphenyl-2H-azirine (2d)[55,56,58], 2,2-dimethyl-3-phenyl-2H-azirine (2e)[34,59,60], and 2-β-naphthyl-2H-azirine.[56] When a mixture of 3-phenyl-(2a) and 2,3-diphenyl-2H-azirine (2d) is irradiated in such a way that only 2d is excited (313 nm light), the sole products are 2-exo- and 2-endo-2,4,5-triphenyl-1,3-diazabicyclo [3.1.0]-hex-3-ene (exo- and endo-73)[34,57] (see scheme 24). On the other hand, it was shown that benzonitrilio-p-nitrophenylmethanide (75), generated chemically by HCl elimination from N-(p-nitrobenzyl)-benzimidoylchloride (74), adds likewise to 2a and 2d with formation of the bicyclic compounds 76 [61] (scheme 24). It may be mentioned that bicyclic compounds of type 71, 72, 73 or 76 can easily be prepared starting with 2-acylaziridines, aldehydes and ammonia[56,62], since they represent bicyclic amidals.

Scheme 24



As is the case with other aziridines, isoelectronic with 2-vinylaziridines[63-65] (cf. also [66,67]), 1,3-diazabicyclo[3.1.0]hex-3-enes undergo reversible ring opening of the three-membered ring, either thermally or photochemically, whereby azomethinio-methanides are formed. These intermediates can react further by (reversible*) ring opening of the five-membered ring to form 2,5-diaza-1,3,5-hexatrienes** (formal head-head dimers of benzonitrilio-methanides). In the presence of dipolarophiles such as diethyl fumarate, the azomethinio-methanides can also be trapped by a cycloaddition. Further trapping reactions are observed in the presence of methanol.[34,57] An additional interesting transformation is observed with 1,3-diazabicyclo[3.1.0]hex-3-enes of type 76 carrying an H-atom at C(2). Subjected to base catalysis they form pyrimidines under dehydrogenation.[61,62]

In conclusion, it may be mentioned that, on irradiation, 2-phenyliminomethyl-3-phenyl-2H-azirine reacts in an analogous manner as the corresponding formyl and vinyl derivatives already discussed (see schemes 19 and 12, respectively), i.e., 1,2-diphenylimidazole is formed intramolecularly.

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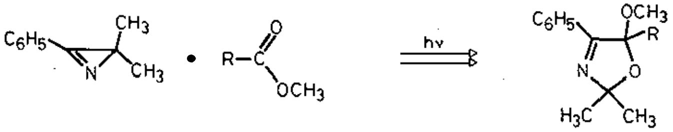
* Cf. [68,69] ** As will be shown in section 3.3 benzonitrilio-methanides can also form directly in a thermal reaction 2,5-diaza-hexa-1,3,5-trienes.

2.2.5 Reactions with Esters, Chlorides and Anhydrides of Carboxylic Acids

Esters of carboxylic acids which are 'activated' by electron-attracting groups in the acyl or alkyl part, react with the photochemically generated benzonitrilio-methanides of type 3 to produce 5-alkoxy-3-oxazolines 77 (scheme 25) in 20-80% yields.[7] The addition to the carbonyl group occurs with the same regiospecificity as observed with aldehyde and ketone functions in intermolecular reactions. Esters which are not sufficiently activated like methyl acetate or benzoate do not undergo the addition reactions.

Scheme 25

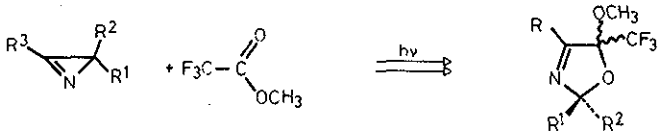


2e 77

R = CF_3	82%
CH_2F	74%
CH_2Cl	70%
CH_2Br	46%
$COOCH_3$	66%
CH_2CF_3	27%
CN (ethyl ester)	30%

A sufficient activation of the acyl part is obtained by introduction of at least one α-halogen atom (F, Cl, Br). Methyl trifluoroacetate proved to be by far the most reactive ester. It reacts with the dipolar intermediates obtained upon irradiation of all types of 2H-azirines, including those produced from aliphatic 2H-azirines.[28,70] An acyl activation can also be attained by introducing a methoxycarbonyl (e.g. dimethyl oxalate[7]) or a nitrile group (e.g. ethyl cyanoformate[9]). The latter ester forms with benzonitrilio-phenylmethanide (3d) a cycloaddition product involving the nitrile group too (cf. section 2.2.6). Some representative examples of cycloadditions of activated esters with benzonitrilio-2-propanide (3e) are depicted in scheme 25; for reactions with other nitrilio-methanides see scheme 26.

Scheme 26



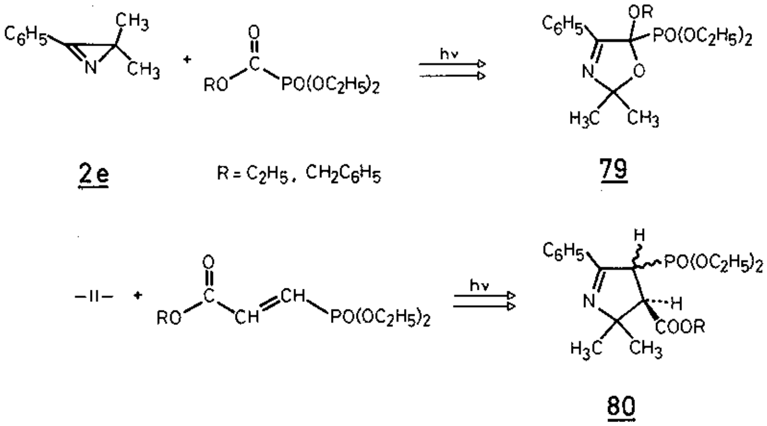
78

2a: $R^1=R^2=H$, $R^3=C_6H_5$	36%
2c: $R^1=CH_3$, $R^2=H$, $R^3=C_6H_5$	80%
2d: $R^1=R^3=C_6H_5$, $R^2=H$	77%
2f: $R^1=R^2=R^3=C_6H_5$	61%
6a: $R^1=R^2=H$, $R^3=CH_2C_6H_5$	60%
6b: $R^1=R^3=CH_2CH_2CH_3$, $R^2=H$	65%
6c: $R^1,R^3=(CH_2)_6$, $R^2=H$	60%

Cycloadditions with 2H-azirines which are monosubstituted at C(2) result in the formation of trans, cis-mixtures of the 5-alkoxy-3-oxazolines 78 in a ratio of 1.5-1.7.[7,28,70] The structure of trans-5-methoxy-5-trifluoromethyl-2,4-diphenyl-3-oxazoline (78, R^1=R^3=C_6H_5, R^2=H), the irradiation product of 2,3-diphenyl-2H-azirine (2d)/methyl trifluoroacetate, was proven by an X-ray analysis.[7]

An ester carbonyl group is also activated by the diethyl phosphonate residue. The photo-induced reaction of 2,2-dimethyl-3-phenyl-2H-azirine (2e) with diethyl ethoxycarbonyl or benzyloxycarbonyl phosphonate leads to the formation of the corresponding diethyl 5-alkoxy-2,2-dimethyl-4-phenyl-3-oxazolin-5-yl phosphonate 79 (scheme 27) in over 90% yield.[38,39] The addition of benzonitrilio-2-propanide (3e) again obeys the expected regiospecificity. It is remarkable that the addition to vinylogous alkoxycarbonyl phosphonates (see scheme 27) takes place only at the C,C-double bond[39] (cf. the corresponding additions to acrylates, section 2.2.1).

Scheme 27



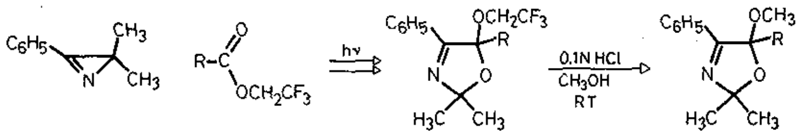
2e

79

80

The activation of carboxylic esters, exerted by the alkyl part, can best be achieved by an esterification of the corresponding acids with 2,2,2-trifluoroethanol. Trifluoroethyl acetate or caprylate, for example, add to benzonitrilio-2-propanide (3e) forming the oxazolines 81a or 81b in 65 and 37% yields, respectively (scheme 28).[7] A further advantage of the trifluoroethoxy moiety is its easy exchangeability in the 5-trifluoroethoxy-3-oxazolines 81 under acidic conditions with other alkoxy groups (scheme 28). This procedure allows the preparation of other 5-alkoxyoxazolines which are not accessible by the direct route of cycloaddition to benzonitrilio-2-propanide (3e) (see scheme 28, compound 77 ($R=CH_3$)).

Scheme 28



2e

81a : $R=CH_3$

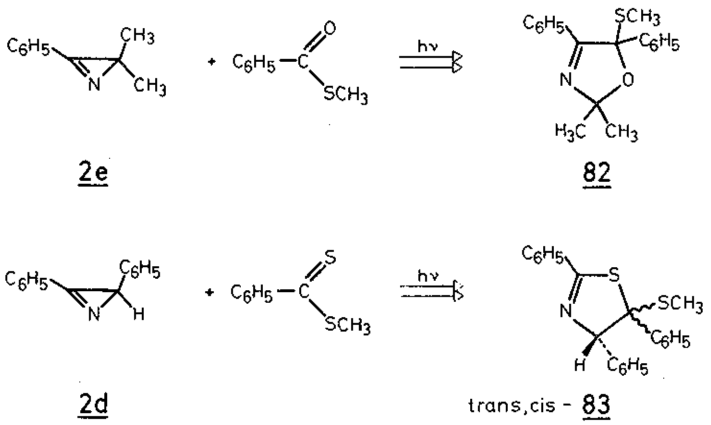
81b : $R=(CH_2)_5CH_3$

77 ($R=CH_3$)

A cycloaddition, involving the ester carbonyl group also occurs, though in lower yields, with benzonitrilio-2-propanide (3e) and phenyl, vinyl or propargyl acetate. On the other hand, acetol acetate reacts only with its keto group.[7]

S-Methyl thiobenzoate and benzonitrilio-2-propanide (3e) combine by participation of the carbonyl group with the same regiospecificity as observed with the esters so far discussed (scheme 29).[7]

Scheme 29

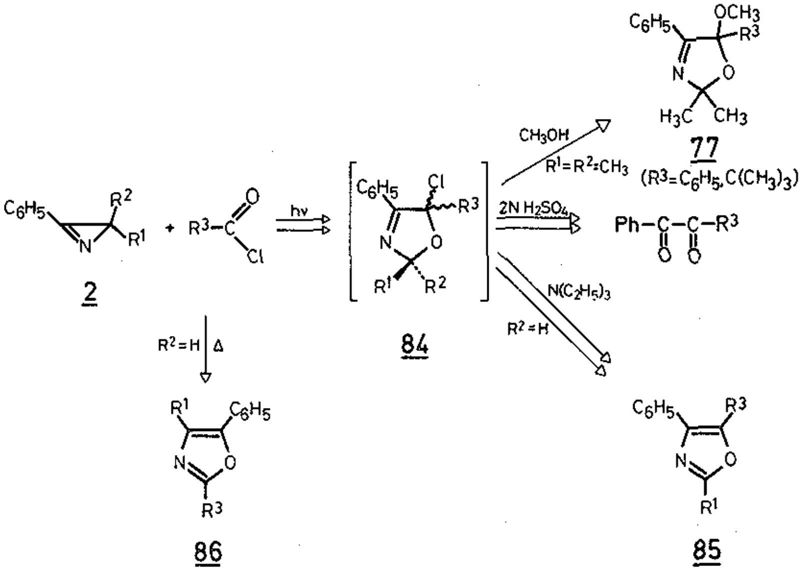


In contrast to this, the reaction of methyl dithiobenzoate and benzonitrilio-phenylmethanide (3d), generated photochemically, takes place at the thiocarbonyl group with the inverse regiospecificity (cf. also [71]), i.e., a mixture of trans- and cis-5-methylthio-2,4,5-triphenyl-2-thiazoline (trans- and cis-83; scheme 29) is obtained.

It should be mentioned that cycloadditions of carboxylic esters and dipolarophiles have so far not been described. Concerning reactions of benzonitrilio-2-propanide (3e) and acetoacetate or cyanoacetate see section 2.2.8.

As expected, cycloadditions are also observed between photochemically generated benzonitrilio-methanides and acyl chlorides[72] (cf. also[73]). The primarily formed cycloadducts, i.e., 5-chloro-4-phenyl-3-oxazolines of type 84 (see scheme 30), are labile and could not be isolated directly. The 5-chloro substituent, however, can easily be exchanged by an alkoxyl group. Thus, irradiation of 2,2-dimethyl-3-phenyl-2H-azirine (2e) in the presence of benzoyl or pivaloyl chloride produces, after addition of methanol, the corresponding 5-methoxy-3-oxazolines 77 ($R=C_6H_5,(CH_3)C$) in 20-30% isolated yields (scheme 30). Consequently, this procedure

Scheme 30

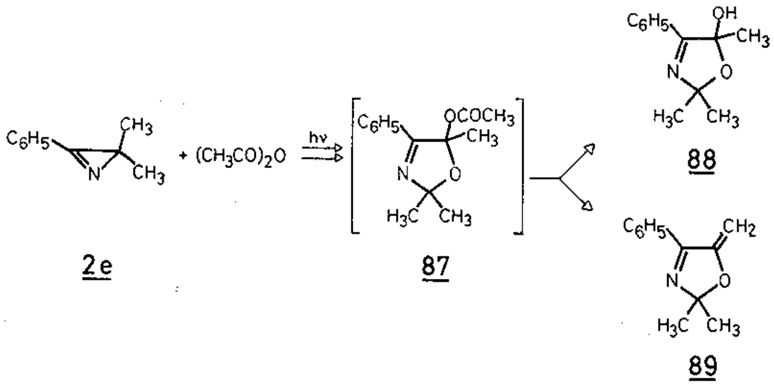


offers a further possibility for the preparation of 5-alkoxy-3-oxazolines which are not accessible directly (see above). The acid-catalyzed hydrolysis of the primary cycloadducts 84 yields 1,2-diketones (see scheme 30).

Cycloadducts 84, which are monosubstituted at C(2), on treatment with tertiary amines like triethylamine, undergo a 1,4-elimination of HCl and form oxazoles of type 85 in moderate yields. In this connection, it should be noted that 2H-azirines and acyl chlorides react, on heating, under elimination of HCl, to yield the isomeric oxazoles 86 (scheme 30).[20]

A similar photoreaction as observed with 2H-azirines and acyl chlorides also takes place with anhydrides. Co-irradiation of 2H-azirine 2e and acetic anhydride, for example, furnishes, after work-up, via the non-isolable intermediate 87, the two 3-oxazolines 88 and 89 in 51% and 25% yields, respectively[72] (see scheme 31). Both compounds are presumable formed via the corresponding carbenium ion. Oxazoline 89 is generated as the sole product when 2e is irradiated in the presence of ketene (see section 2.2.7).

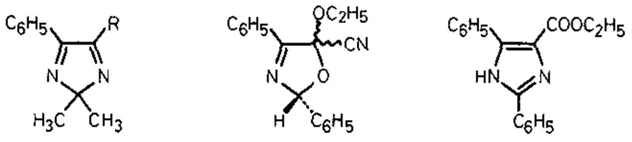
Scheme 31



2.2.6 Reactions with Nitriles

Whereas 'non-activated' nitriles such as acetonitrile or benzonitrile do not show a tendency for cycloaddition with benzonitrilio-2-propanide (3e), 'activated' nitriles add to 3e to give 2H-imidazole derivatives 90 (scheme 32). Nitriles which react in this way are fluoroacetonitrile, trichloroacetonitrile, 4-trifluoromethylbenzonitrile, 2- and 4-cyanopyridine,[10] for example. Ethyl cyanoformate and benzonitrilio-phenylmethanide (3d) form a mixture of the 3-oxazoline 91 (30%) and the imidazole 92 (14%)[9] (scheme 32).

Scheme 32



90 91 92

2.2.7 Reactions with Heterocumulenes

Decidedly, the most interesting reaction in this series is represented by the photoinduced combination of 3-aryl- or 3-benzyl-2H-azirines* and carbon dioxide[2,4,28,30,59,70,74] observed in Zurich. This reaction, carried out by passing a finely dispersed carbon dioxide stream through a benzene solution of the 2H-azirine during irradiation, results in the formation of 3-oxazolin-5-ones 93 in mostly good yields. Scheme 33 contains a few examples. Reactive intermediates are again the nitrilio-

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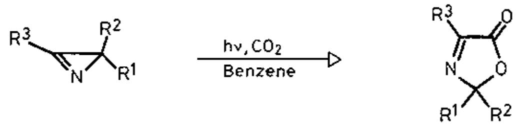
* 2H-Azirines, substituted with aliphatic groups, fail to give this reaction. Presumably, the 3-oxazolines, to be expected, are photolytically unstable under the conditions of irradiation (mercury high pressure lamp and Vycor filter or mercury low pressure lamp) which have to be employed in this case.[28]

Scheme 33



2d : $R^1 = R^3 = C_6H_5, R^2 = H$ — **93a** (65%)

2e : $R^1 = R^2 = CH_3, R^3 = C_6H_5$ — **93b** (84%)

6a : $R^1 = R^2 = H, R^3 = CH_2C_6H_5$ — **93c** (40%)

methanides* which react with carbon dioxide in the same regiospecific manner as known from the other carbonyl compounds (see section 2.2.2 and 2.2.5).

The synthetic potential for the formation of 3-oxazolin-5-ones was hitherto restricted to special cases. Thus, reaction of C-phenylglycine and trifluoroacetic anhydride yields 4-phenyl-2-trifluoromethyl-3-oxazolin-5-one and alkylation of 4-isopropyl-2-phenyl-2-oxazolin-5-one with acrylonitrile (Michael type addition) leads to the formation of 2-(β-cyanoethyl)-4-isopropyl-2-phenyl-3-oxazolin-5-one.[78] Very recently, 2,2-disubstituted 3-oxazolin-5-ones were made available by a reaction sequence detailed in scheme 34.[79]

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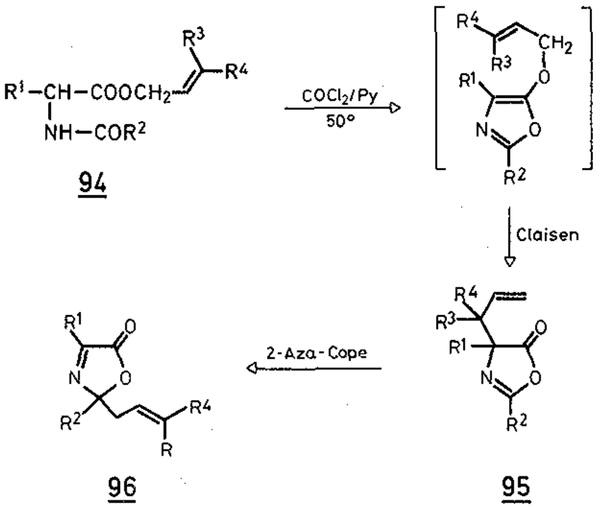
* The first known example of the reaction of a 1,3 dipolar intermediate and carbon dioxide was observed with a benzonitrilio-amide[75] (cf. also [76,77]).

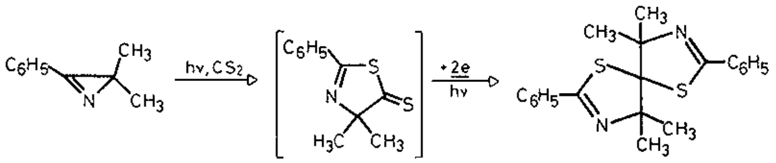
Scheme 34



The carbon dioxide cycloaddition with the photochemically generated nitrilio-methanides is reversible[4,28,74]: Irradiation of the 3-oxazolin-5-ones with 250-350 nm light gives back the corresponding nitrilio-methanides (quantum yield 0,30 [74]) which can be trapped by dipolarophiles in the usual way. Thus, 3-oxazolin-5-ones can be regarded as a further source for nitrilio-methanides whereby the photolysis of those 3-oxazolin-5-ones 96 is of interest which can be synthetized in a ground state reaction

When 2,2-dimethyl-3-phenyl-2H-azirine (2e) is irradiated in the presence of carbon disulfide, a 2:1 adduct, 5,5-spirobis-(4,4-dimethyl-2-phenyl-2-thiazoline) (98), is isolated.[74] Undoubtedly, a 1:1 adduct, the dithiolactone 97 is the intermediate in this reaction (see scheme 35; cf.[80]). It should be mentioned that no defined products were obtained from 2e and carbon oxysulfide.

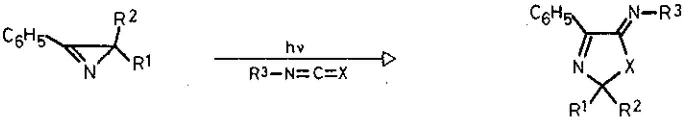
Scheme 35



2e 97 98

Photoreactions are also observed between 3-phenyl-2-azirines 2 and carbodiimides, isocyanates, as well as isothiocyanates (scheme 36).[59] The isocyanates and their thio analogues react with the C,O and C,S double bond, respectively and not with the C,N double bond. The structure of the cycloadducts is based, among other data, on their ^{13}C-NMR spectra. A chemical proof is given by the hydrolysis of the 5-imino-3-oxazoline 99a to the 3-oxazolin-5-one 93b (see scheme 33).

Scheme 36



2 99

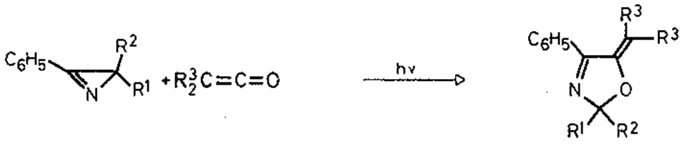
e: $R^1=R^2=CH_3$	$R^3=CH_3$, X=O	a	(53%)
	$R^3=C_6H_5$, X=O	b	(51%)
	$R^3=CH_3$, X=S	c	(45%)
	$R^3=C_6H_5$, X=S	d	(12%)
	R^3=o-$CH_3C_6H_4$, X=N-o-$CH_3C_6H_4$	e	(29%)
d: $R^1=C_6H_5$, R^2=H	$R^3=C_6H_5$, X=O	f	(45%)
	$R^3=C_6H_5$, X=S	g	(20%)[a]
	R^3=o-$CH_3C_6H_4$, X=N-o-$CH_3C_6H_4$	h	(33%)[b]

---

[a] The corresponding 5-anilino-thiazole was isolated. [b] The corresponding 5-(o-toluidino)-imidazole was isolated.

Ketenes can as well be regarded as heterocumulenes and, indeed, a facile reaction is observed between benzonitrilio-methanides and the C,O double bond of ketenes (see scheme 37).[81,*] The

Scheme 37



2 100

a:	R^1=R^2=H	R^3=C_6H_5	a (25%)
c:	R^1=CH_3, R^2=H	R^3=C_6H_5	b (30%)
d:	R^1=C_6H_5, R^2=H	R^3=C_6H_5	c (50%)
		R^3=H	d (18%)
e:	R^1=R^2=CH_3	R^3=C_6H_5	e (49%)
		R^3=H	89 (20%)

ketenes can be replaced by their precursors, the α-diazoketones and instead of 2H-azirines, their photochemical equivalents, the azido-ethenes can be used. Thus, it is even possible to co-irradiate α-diazoketone and azidoethenes. 1-Azido-1-phenylpropane and azibenzil, for example, form the 5-diphenylmethylidene-3-oxazoline 100b in about 30% yield.

As already mentioned, 2,2-dimethyl-5-methylene-4-phenyl-3-oxazoline (89) is also generated when the irradiated mixture of

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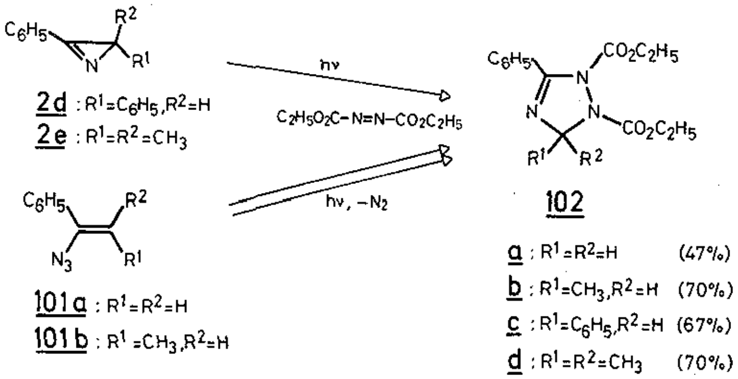
* Completely different cycloadducts are formed in the thermal reaction of 2H-azirines and ketenes.[82]

2e and acetic anhydride is worked up (cf. section 2.2.5).

2.2.8 Reactions with Diethyl Azodicarboxylate

The C,N double bond in diethyl azodicarboxylate is also able to add the benzonitrilio-methanides 3, produced photochemically from 3-phenyl-2H-azirines or their precursors, whereby 1,2-diethoxycarbonyl-Δ^3-1,2,4-triazolines 102 are generated.[83] Examples are sketched in scheme 38. The yields of the Δ^3-1,2,4-triazolines 102 are in the order of 50-70%.

Scheme 38

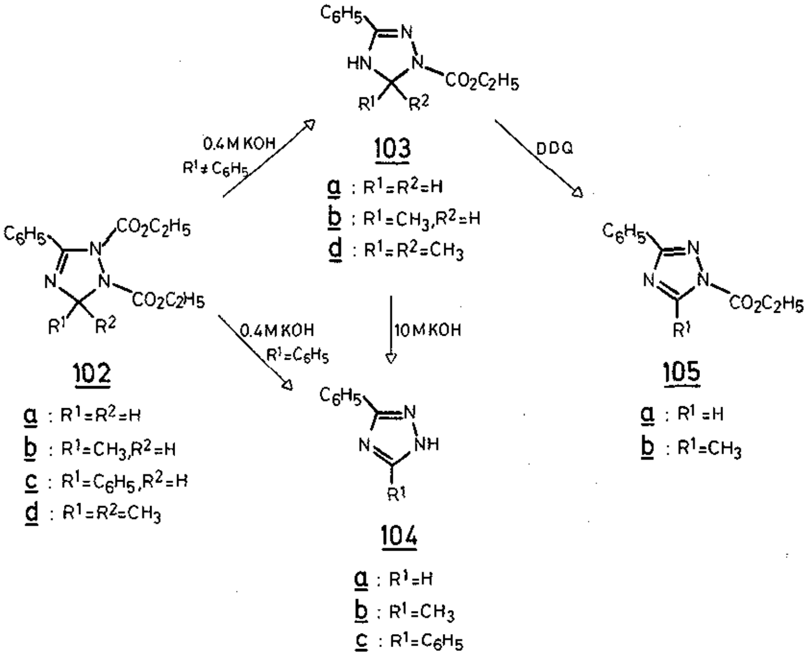


Treatment of the Δ^3-1,2,4-triazolines 102a-c with 10 N potash lye leads to saponification and decarboxylation under formation of the triazoles 104 a-c (scheme 39). Under milder conditions (0,4 N KOH) only the ethoxycarbonyl group in position 2 is saponified and subsequently decarboxylated whereby the Δ^2-1,2,4-triazolines 103 a, b, d are produced.

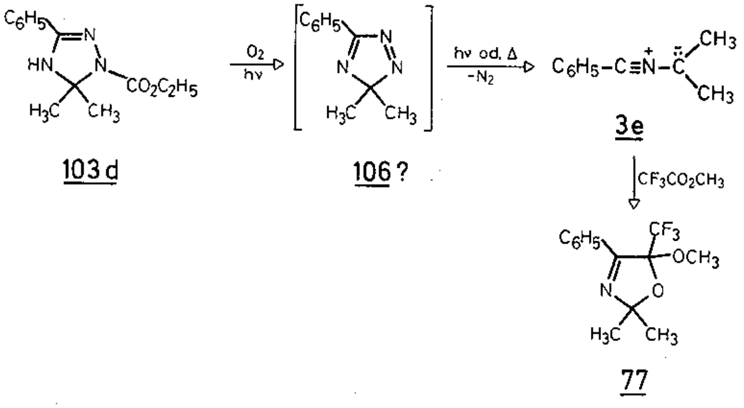
Triazolines 103 with R^2=H, which can also be synthesized by another route (cf. [83]), are dehydrogenated by 2,3-dichloro-

5,6-dicyanoquinone (DDQ) to yield 1-ethoxycarbonyl-1,2,4-triazoles 105. When the Δ^2-triazoline 103d is irradiated in the presence of oxygen, benzonitrilio-2-propanide (3e) is formed which can be trapped by methyl trifluoroacetate to yield the 3-oxazoline 77 (scheme 40), already described in section 2.2.5 (see scheme 25; R = CF_3). The mechanism of this oxidative photodegradation is presently unknown. A possible intermediate could be 5,5-dimethyl-3-phenyl-1,2,4-triazole (106), a representative of the so far unexplored class of 5H-1,2,4-triazoles.

Scheme 39



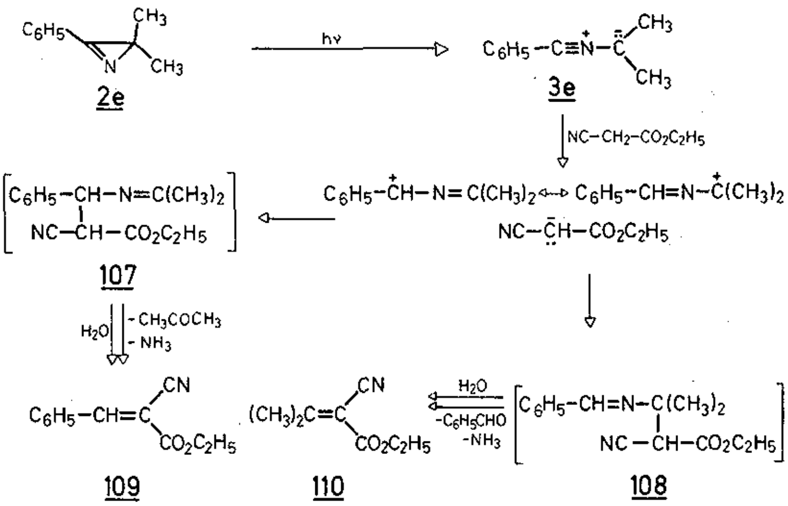
Scheme 40



2.2.9 Reactions with Alcohols and C,H Acidic Compounds

A reversible protonation of p-nitrobenzonitrilio-phenylmethanide and benzonitrilio-p-nitrophenylmethanide, respectively, by triethylammonium chloride was already postulated earlier to explain the equilibration of both methanides.[84] The easy protonation of benzonitrilio-methanides follows from the observation that irradiation of a benzene solution of 2,2-dimethyl-3-phenyl-2H-azirine (2e) in the presence of surplus ethyl cyanoacetate leads neither to a cycloadduct including the nitrile group (see section 2.2.6) nor to a cycloadduct with the carbonyl group of the ester part (see section 2.2.5). Instead, ethyl 2-cyanocinnamate (109) and ethyl isopropylidene-cyanoacetate (110) are obtained after work-up in 30% preparative yields in each case.[7] The formation of these products is traced in scheme 41. The crucial point is the protonation of the benzonitrilio-methanide 3e at the C-atom of the nitrile part by ethyl cyanoacetate. The resulting mesomeric carbenium ion combines now with the counterion at the former nitrile carbon leading to the intermediate

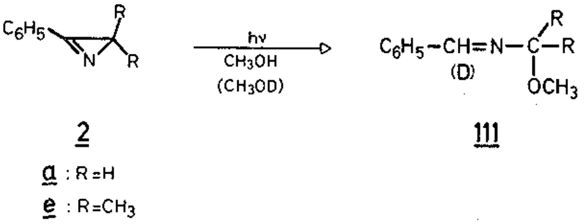
Scheme 41



107 which, during work-up (hydrolizing conditions), loses acetone and ammonia to give ethyl 2-cyanocinnamate (109). On the other hand, combination of the cyanoacetate anion with the tertiary carbenium centre leads, during work-up, to the loss of benzaldehyde and ammonia whereby ethyl isopropylidene-cyanoacetate (110) is generated. The fact that both products 109 and 110 are formed excludes a concerted cycloaddition of the cyanoacetate, involving the C,H bond, and the benzonitrilio-2-propanide (3e).

Irradiation of 2,2-dimethyl-3-phenyl-2H-azirine (2e) in methanol or O-d-methanol produces in an almost quantitative yield the aminoacetat 111 (scheme 42).[85] In this case the nucleophile combines only with the tertiary carbenium centre. A similar reaction is observed when 3-phenyl-2H-azirine (2a) is irradiated in methanol or O-d-methanol. The fact that the protonated intermediate of 3a and 3e (from 2a and 2e, respectively) shows the

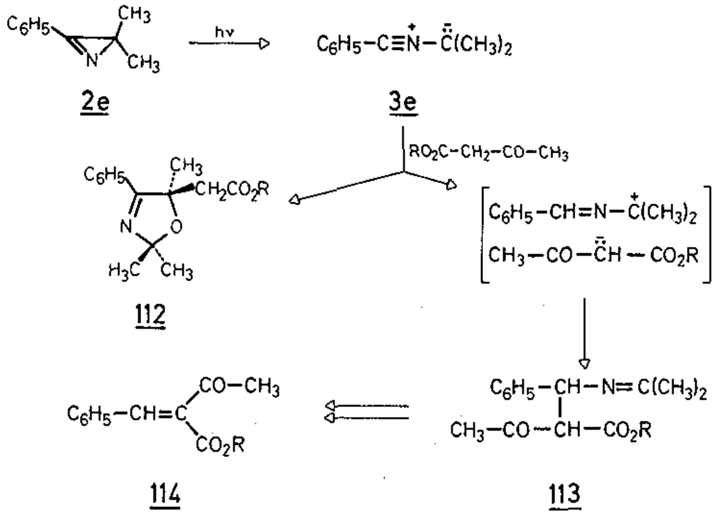
Scheme 42



same regiospecificity in the addition reaction with the nucleophile, although the carbenium center changes from a schematically primary to a tertiary one, might be attributed to thermodynamic control (formation of a conjugated phenylimine system instead of an isolated imine system). The enhanced nucleophilicity of the cyanoacetate anion shifts the addition reaction in the direction of a kinetic control.

The irradiation of 2H-azirine 2e in the presence of ethyl acetoacetate is of interest since in this case the cycloaddition of the nitrilio-methanide 3e and the keto group competes with the protonation of 3e by acetoacetate. The latter reaction results finally, via the intermediate 113 and hydrolysis, in the formation of ethyl benzylidene acetoacetate (114) (scheme 43).[50] The ratio of the cycloadduct 112 and the benzylidene ester 114 amounts to about 3:1. Thus, in the case of ethyl acetoacetate and 3e, cycloaddition and protonation followed by combination of the ion pair occur with similar speed. It should be mentioned that in benzene solution at 33° the amount of the enol form of ethyl acetoacetate is 16%.

Scheme 43



Benzonitrilio-phenylmethanide (3d), generated from 2,3-diphenyl-2H-azirine (2d), exhibits a similar behaviour as 3e. Irradiation of 2d in the presence of malonodinitrile yields, via (α-benzylideneaminobenzyl)malonodinitrile as intermediate, benzylidene-malonodinitrile.[50] Likewise, trifluoroacetamide gives the amidal N-(α-benzylideneaminobenzyl)trifluoroacetamide,[50] methanol the aminoacetal α-benzylideneamino-α-methoxytoluene,[85] and benzyl mercaptan the amino-thioacetal α-benzylideneamino-dibenzylsulfide.[85]

3. General and Mechanistic Considerations

3.1 The Photolysis of 2H-Azirines

It is known that simple imines, which show an n,π^* absorption ($\varepsilon \approx 100$) in the 235 nm region, do not react, in general, with other partners since their excited state is deactivated mainly by (E)/(Z) isomerization.[5,86] Naturally, this mode of deactivation cannot occur in 2H-azirines. It is probable that the first excited n,π^* singlet state of the 2H-azirines is responsible for the photolysis of the C(2), C(3) bond since the photoreaction of 3-phenyl-2H-azirines can neither be sensitized by ketones nor quenched by piperylene.[56,74,87,88] Quantum yields of 0.8 [56], 0.36 [74], and 0.4 [87] were determined by the Stern-Volmer technique for the photolysis of 2,3-diphenyl-(2d), 2,2-dimethyl-(2e), and 2-naphthyl-2H-azirin, respectively, in hydrocarbon solvents at room temperature. The quantum yields are independent of the wavelength employed. Fig. 1 shows the UV-spectrum of 2,3-diphenyl-2H-azirine (2d) together with that of the corresponding benzo-

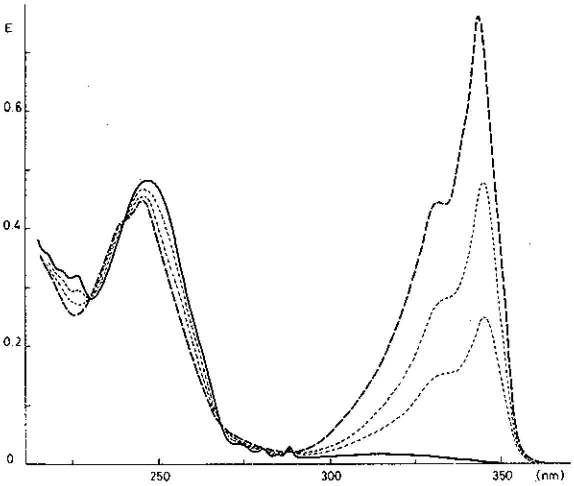


Fig. 1. Rearrangement of 2,3-diphenyl-2H-azirine (2d) into benzonitrilio-phenylmethanide (3d) by irradiation with 255 nm light in a DMBP matrix at -196°.

——— UV -Spectrum of azirine 2d.

------ UV -Spectra during irradiation.

— — — UV -Spectrum of benzonitrilio-phenylmethanide (3d).

nitrilio-phenylmethanide (3d) as obtained by irradiation of 2d with 255 nm light in a DMBP (2,2-dimethylbutane/pentane 8:3) matrix at -196°. The quantum yield directly measured for the transformation 2d $\longrightarrow$ 3d is 0.78 [89] which is in good agreement with the value given above. The nitrilio-methanide 3d is stable in the dark at -196°. Irradiation of the latter at -196° with 345 nm light, which practically excludes excitation of the azirine 2d, allows the nearly quantitative re-formation of 2d [30,89] (Fig. 2) with a quantum yield of 0.15.[89] Low temperature photolysis can also be used for the formation of other nitrilio-

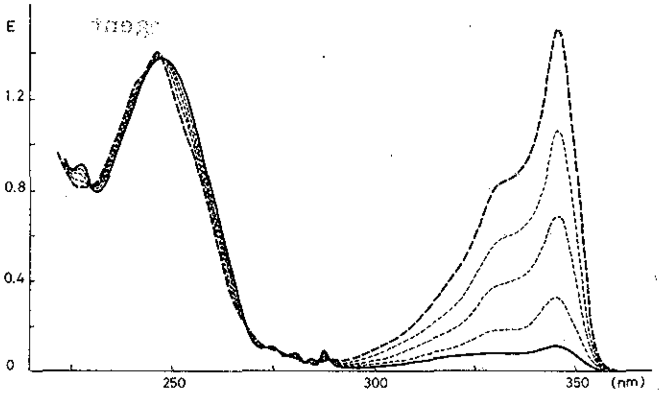


Fig. 2. Rearrangement of benzonitrilio-phenylmethanide (3d) into 2,3-diphenyl-2H-azirine (2d) by irradiation with 345 nm light in a DMBP matrix at -196°.

– – – UV -Spectrum before irradiation, corresponding 70% 3d and 30% 2d.

------ UV -Spectra during irradiation.

—— UV -Spectrum after irradiation, corresponding 5% 3d and 90% 2d.

methanides. Benzonitrilio-2-propanide (3e) is characterized by a UV maximum at 277 nm and the purely aliphatic butyronitrilio-1-butanide by a maximum at 280 nm (-196°, DMBP matrix).[28,89]

The dipolar species 3d can also be generated in the presence of methyl trifluoroacetate at -196° in the DMBP matrix. Its stability is unaffected by the presence of methyl trifluoroacetate at -196°. On warming to -160° the absorption of 3d vanishes and after work-up a mixture of the stereoisomeric 5-methoxy-2,4-diphenyl-3-oxazolines cis-78 and trans-78 is obtained. This experiment demonstrates that in its ground state, benzonitrilio-phenylmethanide (3d) reacts fast with the trapping agent when the glass softens (about -160°).[30,89]

The transformation n,π^*-azirine $\longrightarrow$ nitrilio-methanide can be regarded as an electrocyclic ring opening[51,74,90] in analogy to the reaction cyclopropyl cation $\longrightarrow$ allyl cation. This means that the reversibility 2H-azirine $\rightleftarrows$ nitrilio-methanide is only 'allowed' photochemically in agreement with the experiment. The opening of the C(2),C(3) bond in the 2H-azirines can also be compared with the α-cleavage of ketones (Norrish-I type reaction); this contention is supported by *ab initio calculations*.[88]

3.2 Other Accesses of Nitrilio-Methanides

Beside the photochemical formation of nitrilio-methanides from 3-oxazolin-5-ones 93* (quantum yield for the transformation of

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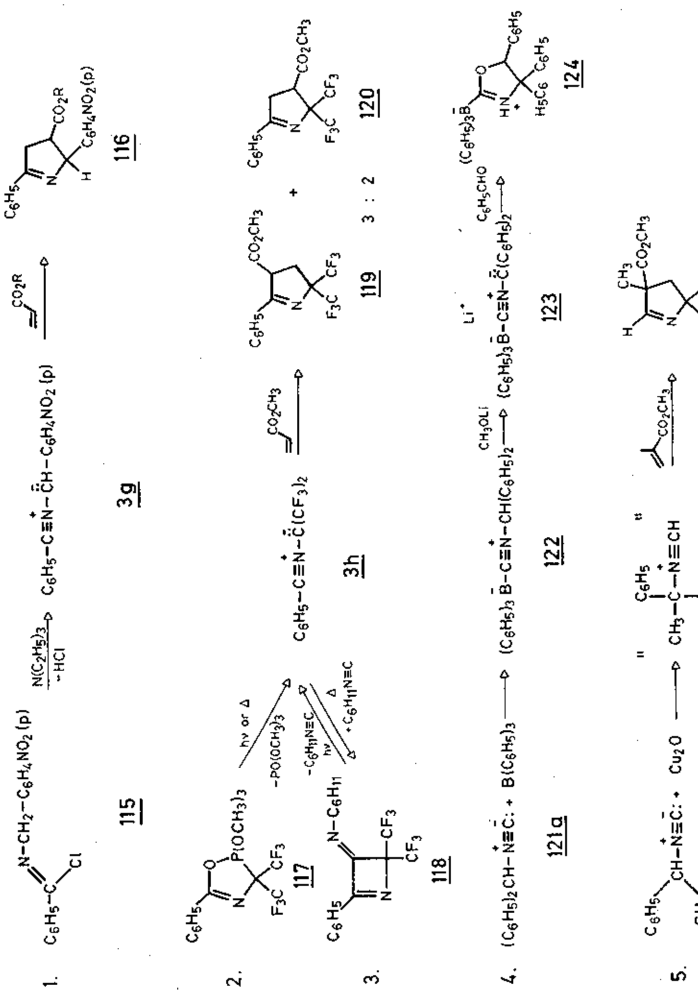
* Some 3-oxazolin-5-ones seem to lose carbon dioxide also thermally (120-200°) under formation of nitrilio-methanides (cf. [92]).

Scheme 44


1.
115
3g
116
2.
117
3.
118
3h
119
120
3 : 2
4.
121a
122
123
124
5.
121b
125
126

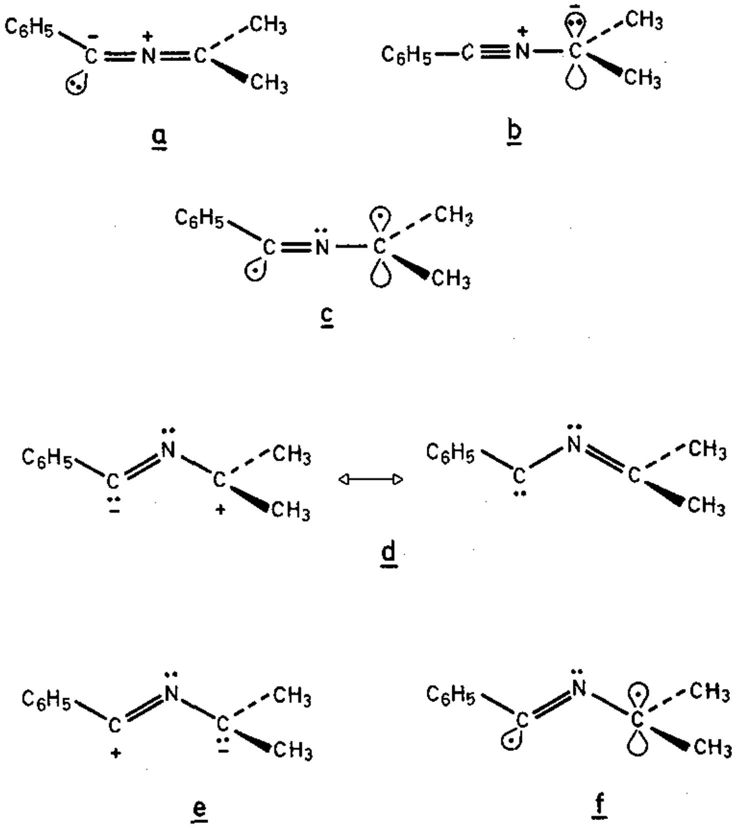
2,2-dimethyl-3-phenyl-3-oxazolin-5-one (93b) into benzonitrilio-2-propanide (3e) = 0.30 [74] and 1-ethoxycarbonyl-5,5-dimethyl-3-phenyl- Δ^2-1,2,4-triazoline in the presence of oxygen, already mentioned in section 2.2.7 and 2.2.8, respectively, several other photochemical and thermal methods for their generation are known. These methods are summarized in scheme 44.

The Huisgen procedure (1) seems to be restricted to imidoyl chlorides which bear nitrophenyl[93] or two trifluoromethyl substituents[94]. Procedures (2) and (3) so far investigated, generate nitrilio-methanides which are substituted by alkyl or aryl groups at the nitrile-C atom and principally by two trifluoromethyl groups at the methane-C atom.[94,95] Only boron containing nitrilio-methanides are obtainable using procedure (4).[96] The products formed by procedure (5) point to the occurrence of dipolaroid intermediates. The isonitriles employed possess at the α-position at least one H-atom and an activating phenyl or ethoxycarbonyl group.[97] In comparison with the procedures given in scheme 44, the photochemical generation of nitrilio-methanides from 2H-azirines has the two following crucial advantages: a) The choice of the nitrilio-methanides is practically unrestricted; b) No side-products are formed by the generation of the dipolar species.

3.3 Properties of the Nitrilio-Methanides

Assuming that a priori such structures of nitrilio-methanides which dispose of the highest numbers of bonds are the most favourable the dipolar allenyl-like structure a and the dipolar propargyl-like structure b* can be constructed (scheme 45). Both formulae require a stretched dipolar species. The structures a

Scheme 45



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* It may be mentioned in this context that the heats of formation of allene and propyne are very similar (ΔH_f^o = + 45,5 and 44,4kcal/mol, respectively).[98]

and b are supplemented by the stretched singlet σ,π diradical structure c.[88] Thus, the nitrilio-methanides can be regarded as particles with partial zwitter ionic and partial diradical character.[88] The bent allyl cation structure d results when the CNC angle in a is reduced. It contains a smaller number of formal bonds (3 in contrast to 4 in a). Structure d should have singlet carbenoid character. Bending in structure b shifts its character towards the allyl anion form e.

The fact that fumaric and maleic esters add stereospecifically to nitrilio-methanides[8] is in agreement with a concerted process, i.e. a [3+2] cycloaddition reaction.[99] Also in this case it seems reasonable to assume that the transition state arises from a parallel plane approach of dipolar species and reactant.[99-101] A reaction path which includes cyclopropane type intermediates, formed by [1+2] cycloaddition of the carbenoid from d and, for example, an electron-deficient olefin, seems to be ruled out: The necessary subsequent N-cyclopropylimine → 1-pyrroline rearrangement requires temperatures $> 80^{o}$[102] whereas the cycloaddition of nitrilio-methanides and electron-deficient olefins occurs already at temperatues $< 20^{o}$.

Investigations carried out so far indicate that only dipolarophils with an electron-deficient X=Y group undergo cycloaddition reaction with nitrilio-methanides. As previously mentioned, reactions are also observed with norbornene but not with normal olefins or allenes. However, the possibility exists that unactivated double bonds add intramolecularly to nitrilio-ylides as shown in scheme 14.

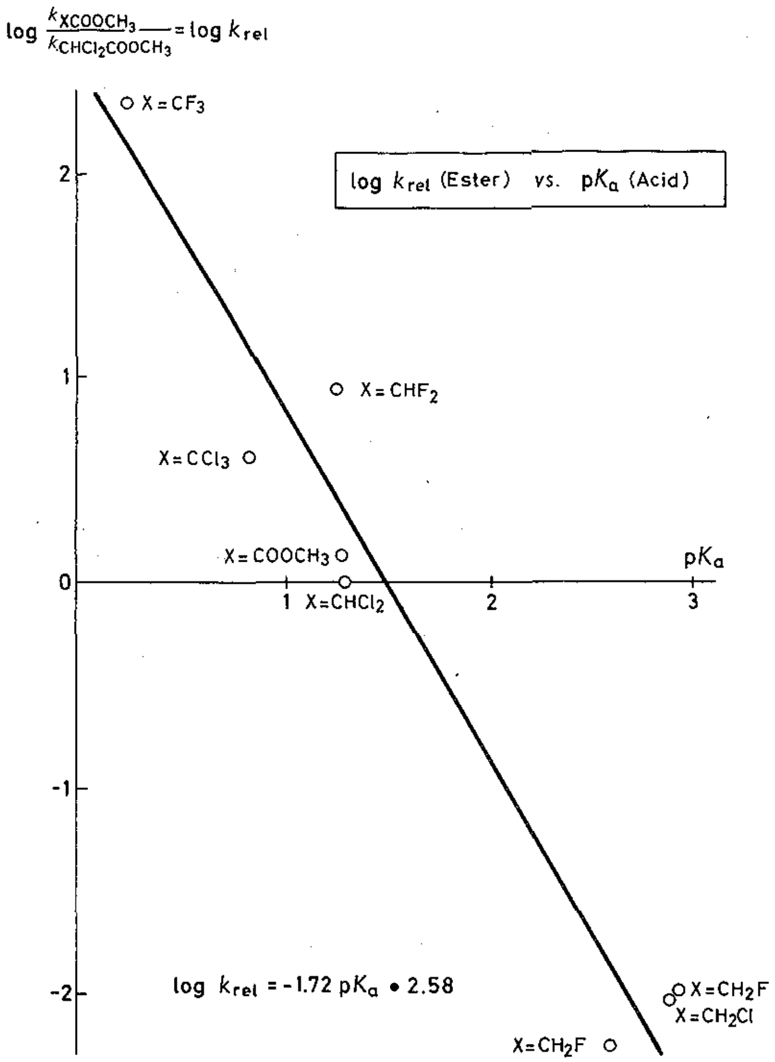
It can be assumed that in this case the presumed intermediate benzonitrilio-methanides derived from 48 or 49 undergoes for entropic reasons the intramolecular [3+2] cycloaddition which can also be considered as the homo-variant of the electrocyclization process 42 → 43 (cf. scheme 12).*

It is evident from the preceding sections that the dipolarophils show large differences with respect to their reactivity towards nitrilio-methanides. Carbonyl compounds follow, in general, the order: aldehydes, carbon dioxide $\rangle$ ketones $\rangle\rangle$ normal carboxylic esters. For methyl carboxylates, activated in the acyl part, relative reactivity orders (k_{rel}[methyl dichloroacetate] = 1.00) with respect to benzonitrilio-2-propanide (3e) were established (see figure 3). A practicable correlation (r = 0.97; 'satisfying' according to Jaffé[103]) is found between the log k_{rel} of the addition reactions and the pK_a's of the acids of the corresponding methyl esters: $\log k_{rel} = -1{,}72\ pK_a + 2{,}58$. According to this correlation methyl acetate should have a log k_{rel} of -5,60 and methyl benzoate of -4,60. This means that these esters should add to 3e by a factor of about 1000 more slowly than mono-halogenated

---

* Because of the lability of the C(1), C(5) bond in 50 and 51 not only the expected 4-exo but also some of the 4-endo product is obtained.[47] — The alternative [3+2]addition mode would lead to strained 2-aza-bicyclo[2.1.1]hex-2-enes which could give the observed products by a [1,3]C-shift.

Figure 3. Correlation between the log k_{rel} of the addition reactions of benzonitrilio-2-propanide (3e) to methylesters and the pK_a's of the acids of the corresponding methyl esters.



methyl acetates. Thus, these cycloadditions cannot compete with the addition of 3e to 2,2-dimethyl-3-phenyl-2H-azirine (2e) (see section 2.2.4). It can be supposed that methyl carboxylates of acids with $pK_a < 3.5$ will add to 3e. The pK_a-values of aliphatic carboxylic acids RCOOH correlate according to Taft[104] by the following equation: $pK_a(CH_3COOH) - pK_a(RCOOH) = 1.721\ \sigma^*$ (σ^* = polar substituent constant). The above given correlation can, therefore, also be formulated as : $\log k_{rel} = 2.06\ \sigma^* - 4.11$ ($r = 0.96$) which again gives a 'satisfying' result. The ρ-value of +2.06, which is greater than that for the ionisation of carboxylic acids ($\rho = +1.72$), points to the fact that the transition state of the [2+3] cycloaddition is strongly polarized.
The nitrilio-methanides 3 (scheme 2) behave with respect to the dipolarophils as nucleophilic reactants*). A model of the addition of nitrilio-methanides to carbonyl compounds which also reflects the steric interactions in the transition state is given in figure 4. On steric grounds the 1,3-dipolar reactant has to adopt transoid conformation (i.e., the bulkier substituent at the methanide C-atom is located trans to the phenyl group at the nitrile C-atom). The addition of carbonyl dipolarophils results preferentially in such a way that the smaller group at the carbonyl C-atom occupies a cisoid position with respect to the phenyl group at the nitrile C-atom (smallest steric interaction).

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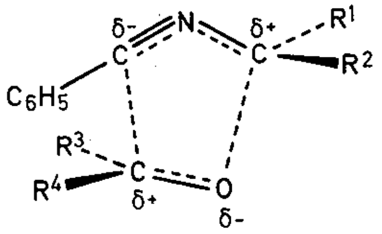
*) Several Hammett correlations for the addition of 1,3-dipolar species to suitable substrates have been reported; the ρ-values vary between -0.9 and +1.3 (cf.[7] and literature cited therein as well as [105].

Figure 4. Possible transition state for cycloadditions of nitrilio-methanides to carbonyl compounds.



3a: $R^1=R^2=H$

3c: $R^1=CH_3$, $R^2=H$

3d: $R^1=Ph$, $R^2=H$

3e: $R^1=R^2=CH_3$

Esters: R^3=Alkyl; $R^4=OCH_3$

Aldehydes: R^3=Alkyl, Aryl; R^4=H

Ketones: $R^3 > R^4$

The rate of addition of nitrilio-methanides to olefins increases with the decrease in the electron density of the olefin[56]. Dimethyl fumarate or fumarodinitrile, for example, add 525 times and 1180 times, respectively, faster to benzonitrilio-phenylmethanide (3d) than does methyl acrylate (k_{rel} = 1.0). The absolute reaction rate of the latter dipolarophile and 3d at 25° can be estimated to be about $7.6 \cdot 10^8\ M^{-1}s^{-1}$ (see subsequent explanations).[89] The addition rates depend strongly on steric factors. Thus, methyl methacrylate reacts 18 times and methyl crotonate 160 times slower than the reference ester whereas dimethyl maleate shows nearly the same reactivity as the reference ester*).

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*) The log k_{rel} values show with respect to the ionisation potentials of the dipolarophils a similar dependence as found for cycloadditions with phenyl azides[105, 106] and benzonitrile oxides[107].

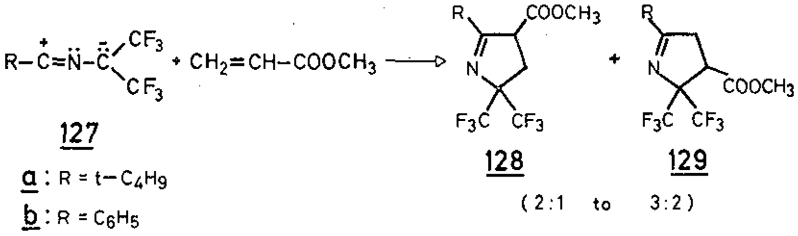
The regiospecificity and regioselectivity is the same as for the carbonyl compounds (see figure 4). On the basis of this model the given order of reactivity can be understood: The interaction of the phenyl group with the substituent at the electron-deficient C-atom plays the prominent role.

Exceptions to this rule are known (see section 2.2.1). The observation that methyl α-methacrylate and α-methacrylonitrile react with benzonitrilio-methanide (3a) or benzonitrilio-2-propanide (3e) to yield beside the 'expected' also the 'unexpected' cycloadducts in ratios of 6:4 and 93:7, respectively, can be understood as the result of destabilization (by the α-methyl group) due to a developing negative charge at the α-carbon of the olefins of the strongly polar transition state of the [3+2] cycloaddition (see preceding part).

The inferior regioselectivity in the cycloaddition with propiolic esters (see section 2.2.1) can be attributed to the fact that an alkoxycarbonyl group is not able to stabilize electronically an adjacent negative charge induced by two electrons occupying a sp^2-type orbital in the transition state. As already mentioned (section 2.2.1) vinyl phosphonates and vinyl phosphine sulfides give cycloadducts in a ratio of 1:1. It is of interest to note that 4-fluoro- or 4-methoxybenzonitrilio-2-propanide with methyl α-methacrylate yield the two possible cycloadducts in exactly the same ratio (93:7) as the unsubstituted benzonitrilio-2-propanide (3e)[35].

Inductive effects exerted by substituents in the nitrilio-methanides can also have a dominant influence on the direction of addition, as already shown in the case of the cycloadditions of nitrilio-hexafluoro-2-propanides irrespective of the mode of generation (cf. scheme 44, methods 1,2 and 3, resp.). t-Butyronitrilio- or benzonitrilio-hexafluoro-2-propanide (127a, b) and methyl acrylate yield predominantly products with inverse regioselectivity[94,95a] (scheme 46) as compared with the reactions shown in scheme 8. The same is true for the cycloaddition reaction with acrylonitrile or methyl propiolate. Aldehydes and ketones form the inverse cycloadducts almost exclusively.[95b] In contrast, ethyl pyruvate does not react regiospecifically.[95b] The nitrilio-methanide resonance structure can be regarded as the preferred 'reactive form' of these hexafluoro derivatives.*)

Scheme 46



Reactions which lead to the formation of nitrilio-amide or nitrilio-methanide intermediates are often accompanied by dimers of the dipolar species or subsequent products of the dimers (cf.[89] and

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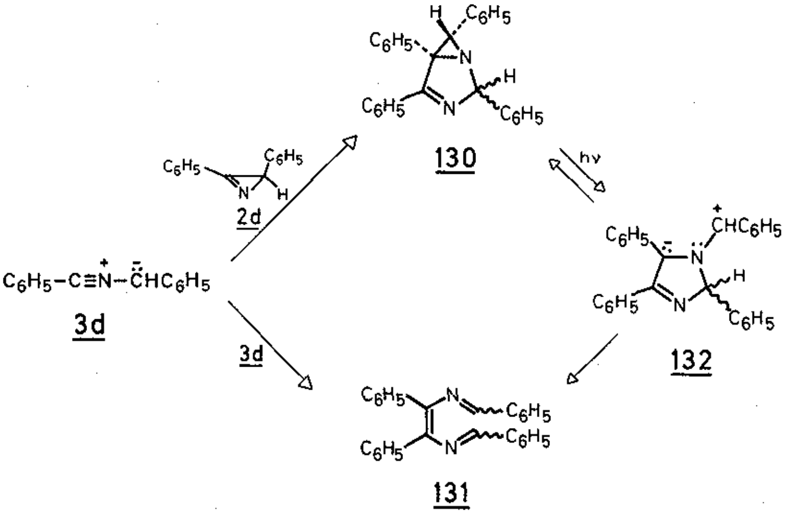
*) This statement is corroborated by the observation that 127b and alcohols yield alkyl N-(hexafluoro-isopropyl)-benzimidates[94] (cf. section 2.2.9).

literature cited therein). The dimer 130 of benzonitriliomethanide (3d) can be formed when 2,3-diphenyl-2H-azirine (2d) is irradiated. It represents the cycloadduct of 3d and 2d as demonstrated in section 2.2.4. Further irradiation of the dimer 130 transforms it into 1,3,4,6-tetraphenyl-2,5-diaza-1,3,5-hexatriene 131 [89], the formal head-to-head dimer of the dipolar species 3d (see scheme 47). Low temperature irradiation of 2d gives almost quantitatively benzonitrilio-phenylmethanide (3d). On warming the solution of 3d in DMBP glass to -160° a quantitative dimerization of 3d to yield the hexatriene 131 takes place. The bicyclic derivative 130 cannot be an intermediate under

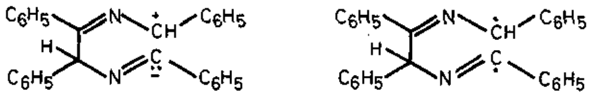
Scheme 47



these conditions. The bicycle 130 irradiated at -196° in DMBP glass forms a cherry red dipolar intermediate 132 (λ_{max} 520 nm) (cf. also [63,64]) which isomerizes only at -120° to yield the hexatriene 131. The dimerization reaction 3d → 131 can also be accomplished at room temperature: Irradiation of a solution of 2d (DMBP, $\sim 20^{\circ}$) with 350 nm-light of high intensity which does not excite the bicyclic material 130 leads to a relatively high photo-stationary concentration of 3d. The formation of 131 under these conditions can be attributed almost exclusively to the dimerization of 3d. By irradiation with 350 nm-light of low intensity the stationary concentration of 3d is also low, so that the cycloaddition of 3d and 2d to give 130 predominates.[89]

By flash photolysis experiments of solutions of 2d in cyclohexane at room temperature the disappearance of formed 3d could be followed directly by UV spectroscopy: At high concentrations of 3d ($c \gg 10^{-7}$ M) the dipolar species disappears with second order kinetics and a specific rate constant $k = 5 \cdot 10^{7}\ M^{-1}s^{-1}$. At low concentations of 3d ($c < 10^{-7}$ M) it vanishes with pseudo-first order kinetics (reaction 3d + 2d ⟶ 130). The specific pseudo-first order rate constant is $1 \cdot 10^{4}\ M^{-1}s^{-1}$. It is probable that 131 is formed by head-to-head reaction of two molecules of the dipolar intermediate in the biradicaloid or carbenoid form. At the moment, however, it cannot be excluded that a head-to-tail dimerization of 3d occurs to yield 133 (of dipolar or diradical nature, scheme 48) which is transformed into 131 by a subsequent H-shift.

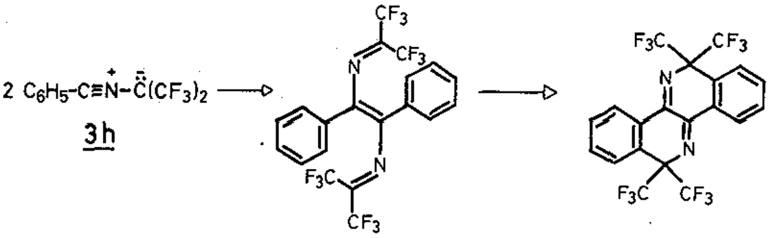
Scheme 48



133

A head-to-head dimerization is also observed with benzonitriliohexafluoro-2-propanides (generated at 140° according to method 2, scheme 44). The primary coupling product 134 cyclizes followed by 1,5 H-shift and dehydrogenation by oxygen to yield compounds of type 135 (scheme 49).[108]

Scheme 49



3h 134 135

4. Concluding Remarks

The photolysis of 2H-azirines, especially that of 3-aryl-2H-azirines, furnishes intermediates of the nitrilio-methanide type which react with numerous electron-deficient alkenes or alkynes as well as carbonyl compounds, including carbon dioxide and activated esters, to yield a variety of five-membered heterocycles. The good availability of 3-aryl-2H-azirines confers preparative interest to this reaction sequence, especially since it can be run on a larger scale.[109] The mechanistic aspects of the photoreaction and of the cycloaddition of the dipolar species could be studied in greater detail.

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