New Applications of Organic Azides in Syntheses of Sulfur- and Nitrogen-Containing Heterocycles

G. MLOSTOŃ

Department of Organic and Applied Chemistry, University of Lódź, PL-90136 Lódź

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Organic azides are versatile reagents, well known as useful tools in organic synthesis and their chemistry was thoroughly reviewed in the past [1—3]. Selected reactions of azides with general importance are summarized in Fig. 1 and [2 + 3]-dipolar cycloadditions of the dipole $RN{=}N^{+}{=}N^{-}$ may be pointed out as the most important transformations. Numerous reports indicated that [2 + 3]-cycloadducts with dipolarophiles A = B are rather unstable compounds and frequently show tendency to eliminate nitrogen or rearrange to isomeric aminodiazo compounds [1].

In early eighties, *Huisgen et al.* found out that thiocarbonyl compounds, especially thioketones, are "superdipolarophilic" and react with 1,3-dipoles such as diphenyldiazomethane, thiobenzophenone *S*-methylide or nitrones much faster than tetracyanoethylene

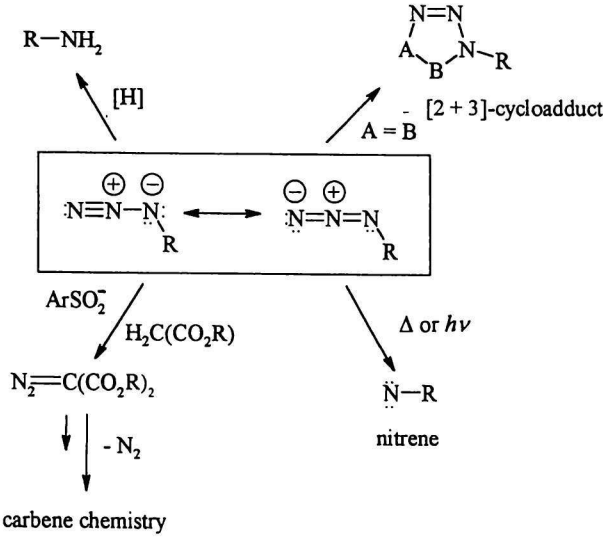
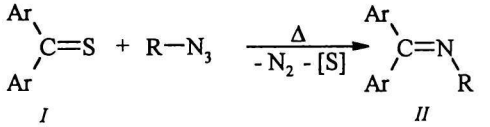
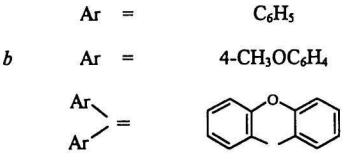


Fig. 1. Applications of azides in important procedures of organic synthesis.



R = C_6H_5; $C_6H_5CH_2$
$C_6H_5SO_2$; α-naphthyl



Scheme 1

(TCNE) or dimethyl acetylenedicarboxylate (DMAD) [4]. In spite of a large number of ethylenic dipolarophiles A = B tested in [2 + 3]-cycloadditions with azides, reactions with heterodipolarophiles were only scarcely described until the recent time. Carbonyl group was shown to be completely inert in reactions with azides but their sulfur analogues evolved nitrogen when heated in solutions containing an azide [5]. From the historical point of view, *Schönberg* published the first paper reporting reactions of aromatic thioketones *I* with phenyl, benzyl, and benzenesulfonyl azides [5] (Scheme 1). Corresponding imines *II* resulting from extrusion of nitrogen and sulfur were found to be the only products of these reactions. Similar results were described by *Guziec et al.* almost 50 years later; heating of sterically crowded cycloaliphatic thioketones *III* (analogous selones were also involved in the study) with phenyl azide dissolved in benzene, gave *N*-phenyl-substituted imines of type *IV* (Scheme 2) [6].

Reaction mechanisms proposed by both *Schönberg* and *Guziec*, pointed out a possible first step involving

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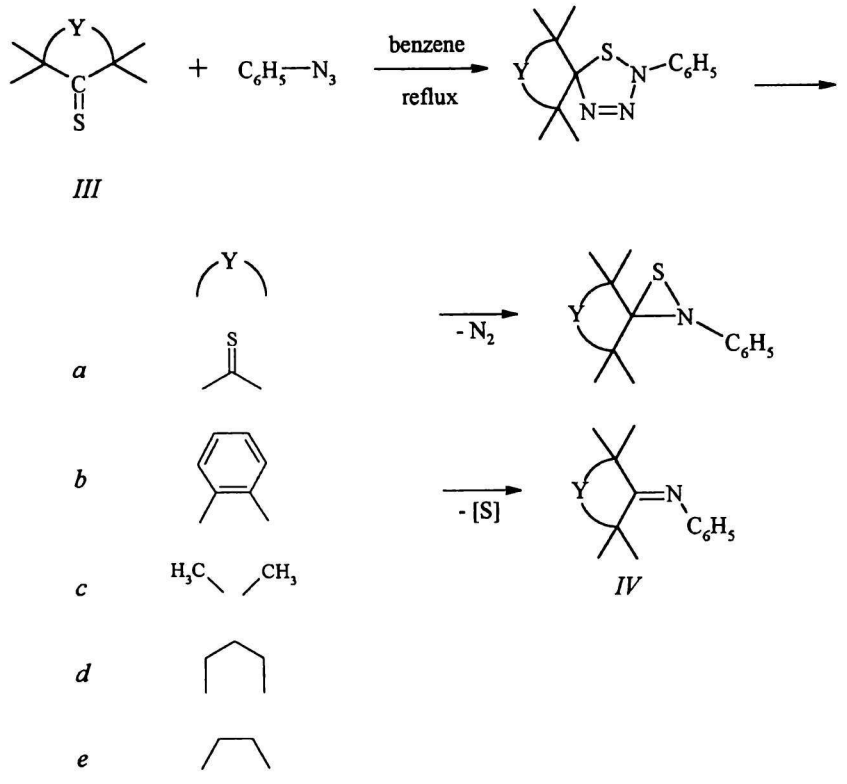
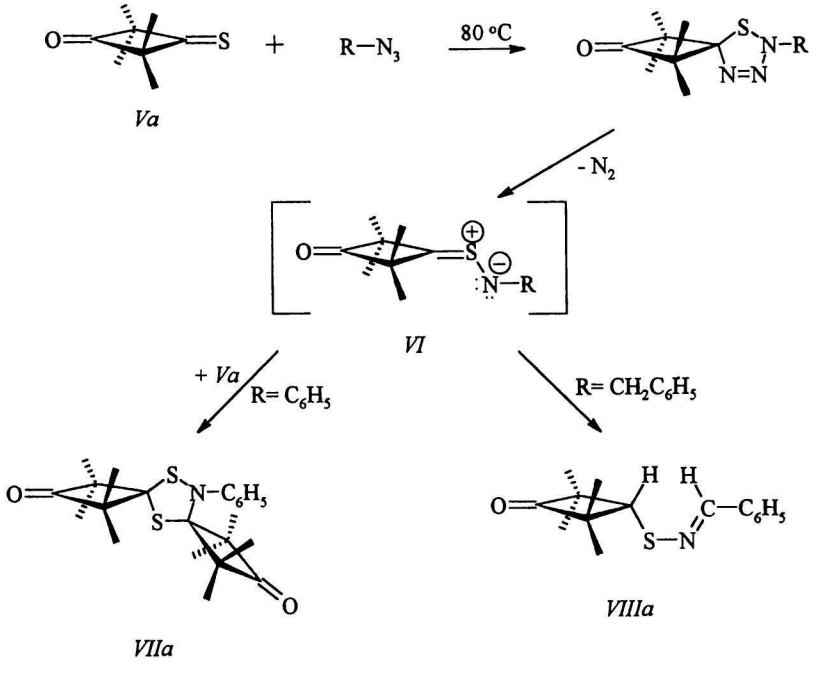


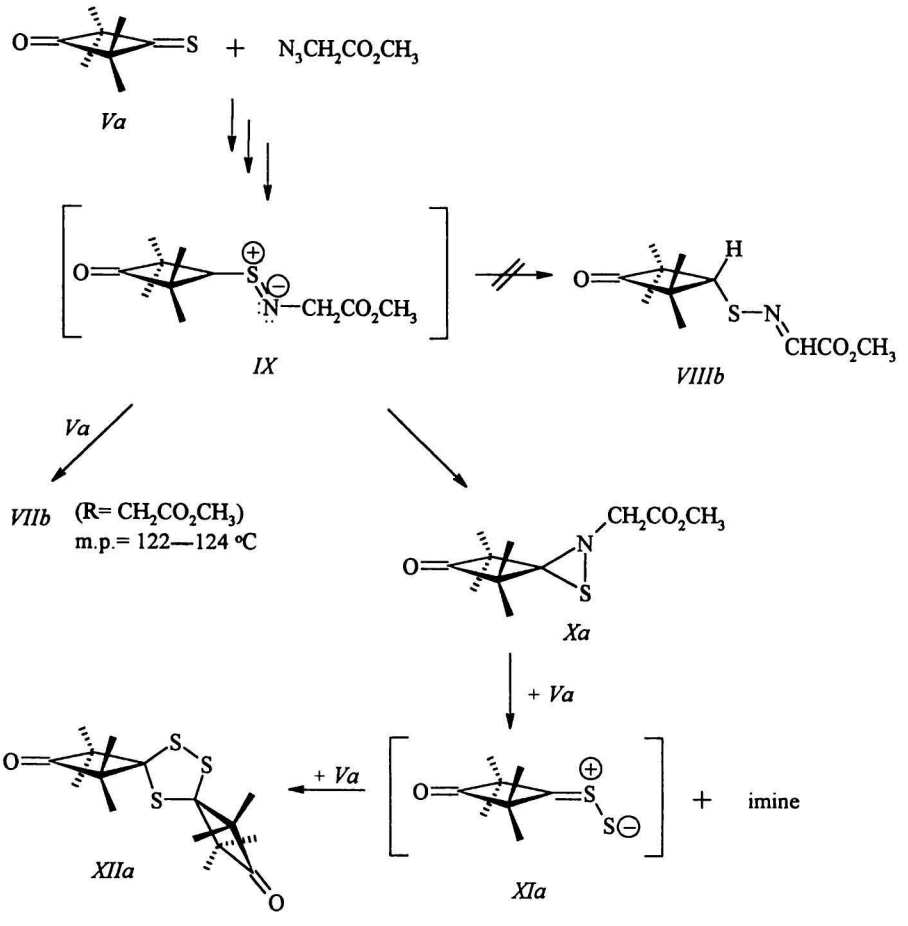
Scheme 2



Scheme 3

[2 + 3]-dipolar cycloaddition of the azide dipole with thiocarbonyl group. In addition, *Schönberg* [5] suggested another possible route involving nitrene species generated by thermal decomposition of azide. This suggestion does not find any support in later studies which showed that aryl azides are stable enough under reaction conditions and do not decompose with nitrogen evolution under 120 °C [3].

2,2,4,4-Tetramethyl-3-thioxocyclobutanone (*Va*) was exploited in numerous [2 + 3]-dipolar cycloadditions with diazoalkanes and other 1,3-dipoles [7—9] but its reactions with azides have not been studied un-



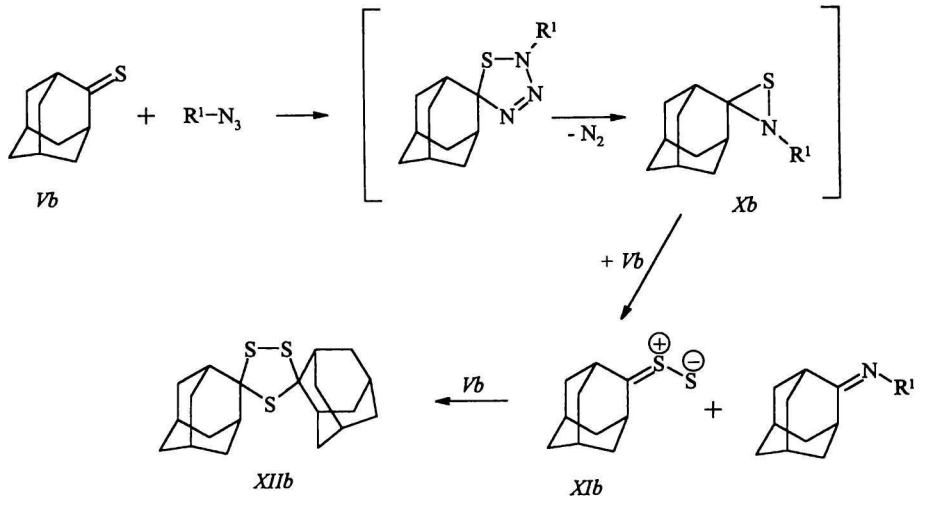
Scheme 4

til recent time. Unlike reactive diazo compounds which add to *Va* even at low temperature [7], conversions of this sterically encumbered thioketone with azides required enhanced temperatures and heating at 80 °C was found to give reasonable reaction times. In a preliminary experiment with phenyl azide, gasometrical control of the amount of evolved nitrogen indicated that the first period of reaction finished after evolution of *ca.* 50 % of the expected volume [10]. Separation of the reaction mixture afforded di-*spiro*-1,4,2-dithiazolidine *VIIa* as the major product. Mechanism of its formation was explained as a result of the reaction of intermediate *S*-imide of type *VI* (R = C_6H_5) with another molecule of unchanged thioketone.

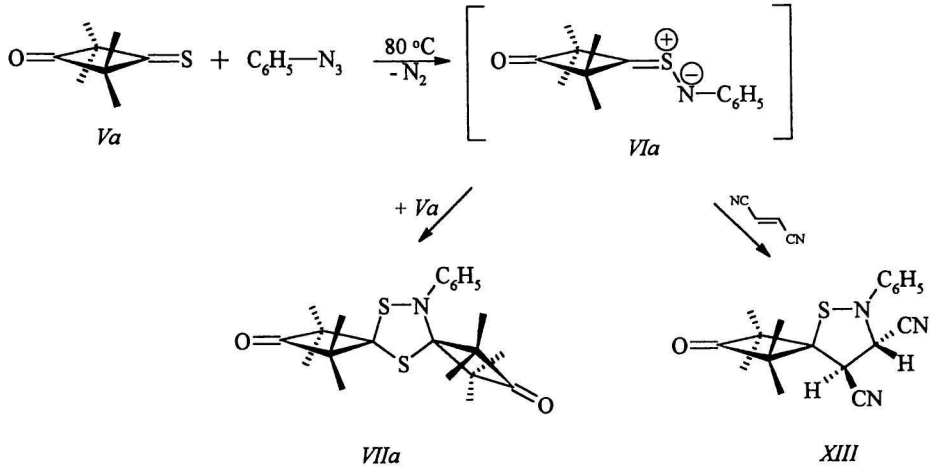
Existence of thione *S*-imides *VI* as key intermediates after elimination of nitrogen from the primary cycloadduct of azides with thioketones found further support in results obtained with *Va* and benzyl azide (Scheme 3). In this case derivative of thiooxime of type *VIII* arisen from sigmatropic 1,4-[H]-migration in the intermediate *S*-imides, was obtained as a major component of the reaction mixture [11]. Competitive reaction course involving trapping of the molecule of *Va* with *VI* (R = $C_6H_5CH_2$) led to formation of *N*-benzyl-substituted derivatives of type *VII*.

On the other hand, heating of *Va* dissolved in an excess of methyl azidoacetate did not provide the expected product of sigmatropic hydrogen migration *VIIIb* (Scheme 4); instead, a corresponding [2 + 3]-cycloadduct *VIIb* (R = $CH_2CO_2CH_3$) and di-*spiro*-1,2,4-trithiolane *XIIa* were isolated after chromatographic work-up of the reaction mixture [12]. This observation indicated that reactivity of the intermediate *S*-imide *IX* strongly depends on the substitution pattern. Unlike aromatic or aliphatic substituents, (methoxycarbonyl)methyl group must accelerate ring closure of the transient *S*-imide to give unstable thiaziridine *Xa* which is believed to transfer sulfur atom to the thiocarbonyl group similarly to thiiranes described recently by *Huisgen* and *Rapp* [13]. The thione *S*-sulfide *XIa* is a new, *in situ* generated intermediate which like other species of this type easily traps *Va* to produce 1,2,4-trithiolane *XIIa*.

When adamantanethione (*Vb*) replaced 2,2,4,4-tetramethyl-3-thioxocyclobutanone (*Va*) in the reactions with azides (Scheme 5), di-*spiro*-1,2,4-trithiolane *XIIb*, along with *N*-substituted imines of adamantanone were the only products separated from the mixtures after nitrogen evolution was complete [14]. The route leading to *XIIb*, similar to those presented



Scheme 5



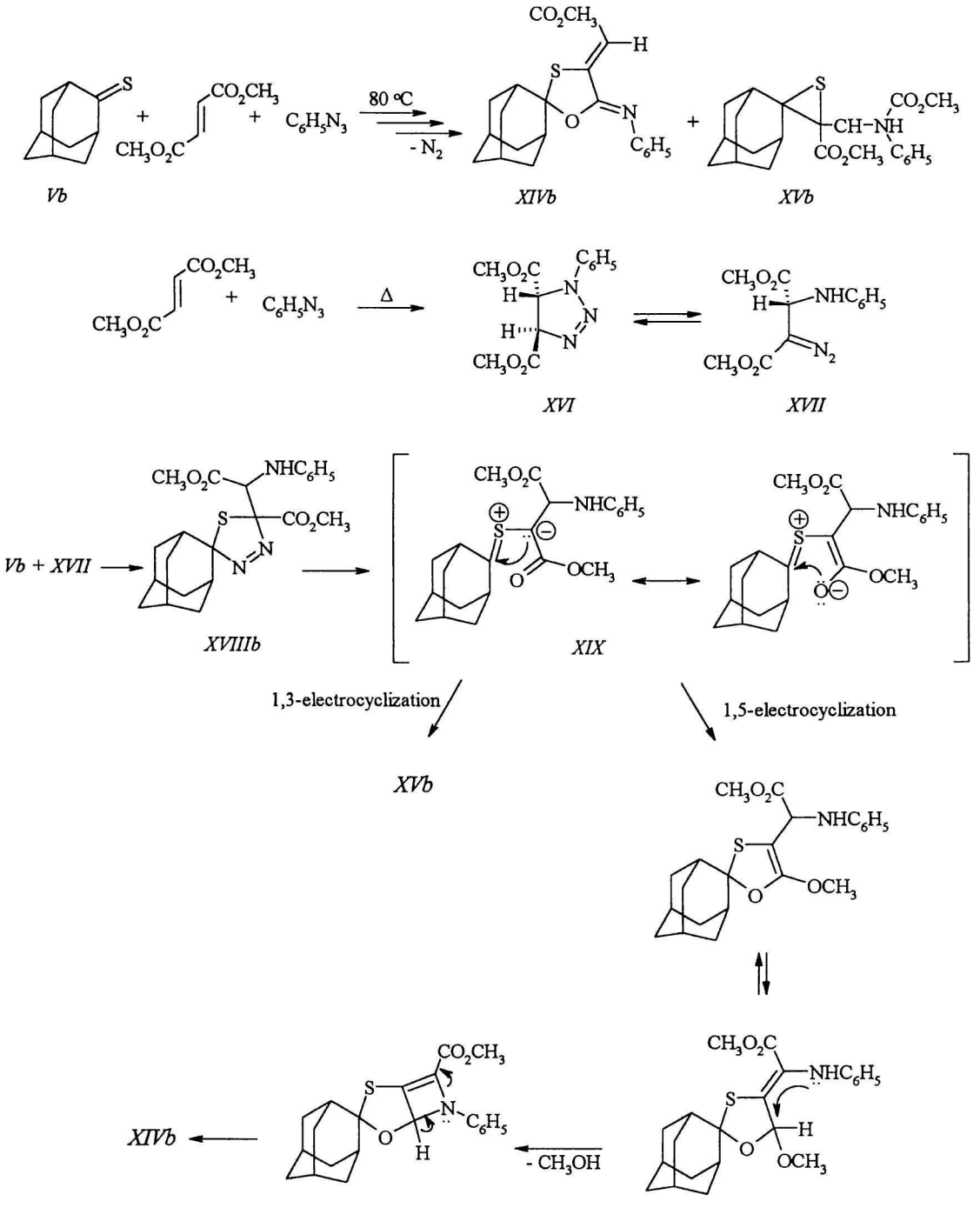
Scheme 6

in Scheme 4 for the formation of *XIIa*, involves the transfer of the sulfur atom from unstable thiaziridine *Xb* to the thiocarbonyl group and a subsequent addition of reactive thione *S*-sulfide *XIb* to a next molecule of *Vb*.

Successful attempts were made to trap the postulated thione *S*-imide *VIa* with other dipolarophiles than the parent thioketone *Va* (Scheme 6). In a three-component experiment with *Va* and fumaronitrile dissolved in an excess of phenyl azide, almost equal molar amounts of [2 + 3]-cycloaddition products of the intermediate *VIa* with *Va* or fumaronitrile, respectively, were isolated [15]. This result showed that *VIa* is able to react with both thione *Va* and fumaronitrile with similar rates. The X-ray study of crystalline 1,2-thiazolidine *XIII* confirmed unchanged *trans*-configuration of both cyano groups in the final product. This geometry in the cycloadduct is a clear evidence for one-step, concerted [2 + 3]-cycloaddition of *VIa* with electron-poor fumaronitrile.

Completely different results were observed when in the three-component reactions with *Va* or *Vb*, fumaronitrile was replaced by methyl fumarate. In both cases, derivatives of *spiro*-1,3-oxathiol *XIVa, XIVb* were isolated as major products and their structures were confirmed by means of X-ray crystallography; minor products were identified as thiiranes *XVa, XVb* or their desulfurized analogues [15, 16].

A plausible explanation of the mechanistic pathway is based on an earlier observation by *Huisgen et al.* that phenyl azide reacts easily with methyl fumarate to give an unstable 1,2,3-triazoline *XVI* which spontaneously isomerizes even at room temperature to give aminodiazo compound *XVII* [17]. [2 + 3]-Cycloadditions of diazo compounds with cycloaliphatic thiones are well documented and it is known that Δ^3-1,3,4-thiadiazolines (2,5-dihydro-1,3,4-thiadiazoles) are primary reaction products which relatively easily eliminate nitrogen to generate reactive thiocarbonyl ylides [7, 18, 19]. Diazo compound *XVII* produces after addition to adamantanethione (*Vb*) corresponding Δ^3-1,3,4-thiadiazoline



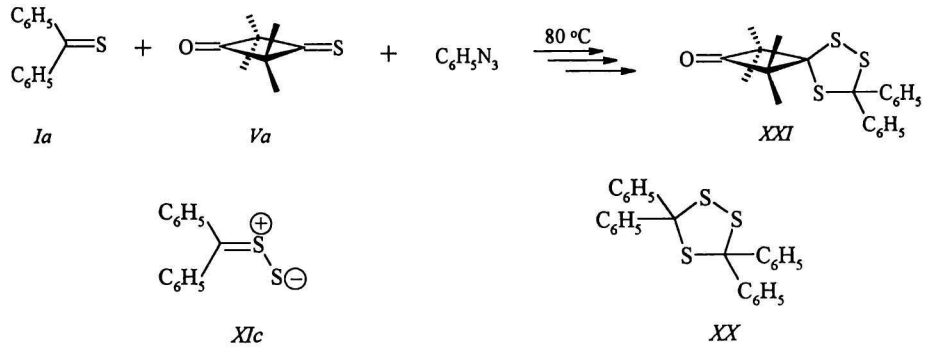
Scheme 7

XVIIIb which extrudes nitrogen and thiocarbonyl ylide *XIX* appears as a new intermediate. Like other carbonyl-substituted species of this type, it undergoes 1,5-electrocyclization to form skeleton of the 1,3-oxathiol ring [18]. Due to the presence of reactive amino and ester groups, cascade of reactions involving methanol elimination, azetine ring closure, and ring opening to an azadiene system, leads finally to *XIVb*.

1,5-Electrocyclization in the molecule of intermediate *XIX*, shown in Scheme 7, competes with 1,3-ring closure which is a typical reaction for thiocarbonyl ylides in the absence of suitable dipolarophiles [18]; this is the route leading to the formation of thiirane *XVb*.

Similar three-component reaction with *Va* and methyl fumarate dissolved in phenyl azide at 80 °C, resulted in the formation of respective products *XIVa* and *XVa*, derivatives of 2,2,4,4-tetramethylcyclobutanone [15].

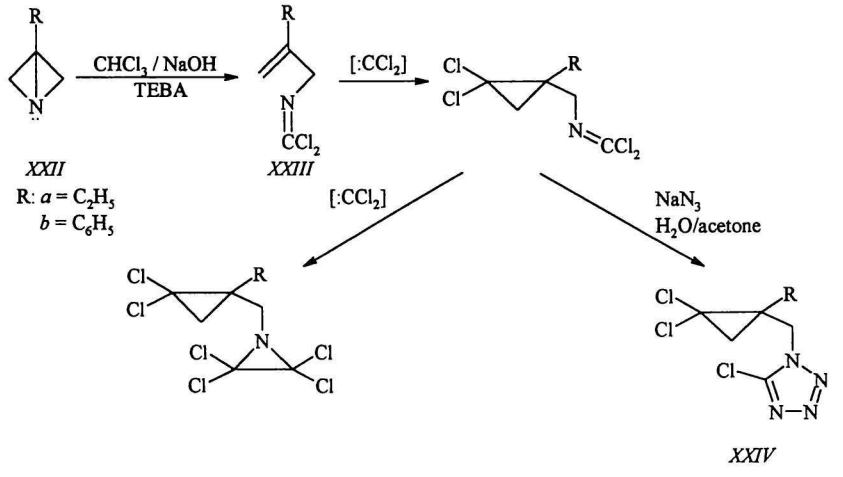
Aromatic thioketones react with azides faster than



Ia *Va* *XXI*

XIc *XX*

Scheme 8



XXII
R: *a* = C_2H_5
b = C_6H_5

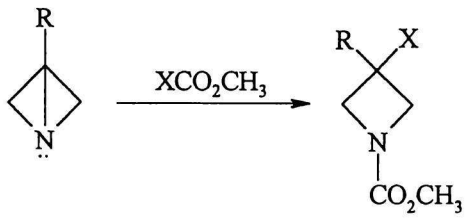
XXIII *XXIV*

Scheme 9

their cycloaliphatic analogues and for systems of this type no case was reported when unstable intermediates such as thione *S*-imide, thiaziridine or thione *S*-sulfide could be trapped. Results from our laboratory confirmed earlier observation by *Schönberg* [5] that the only products of two-component reaction of thiobenzophenone (*Ia*) with phenyl azide were benzophenone *N*-phenylimine and elemental sulfur. However, heating the three-component reaction mixture consisting of *Ia* and sterically crowded thioketone *Va* dissolved in phenyl azide, resulted in isolation of mixed *spiro*-1,2,4-trithiolane *XXI* [20] (Scheme 8). Crucial role in the formation of 1,2,4-trithiolanes play thiocarbonyl *S*-sulfides *XIa* and/or *XIc* which are generated *in situ* after transportation of the sulfur atom from intermediate thiaziridine to either cycloaliphatic or aromatic thione (*cf.* with the mechanism presented in Scheme 5). Further reaction of species *XI* with a thioketone results in formation of 1,2,4-trithiolane derivatives. Postulated tetraphenyl-substituted product *XX* is thermally unstable [13] and under conditions of the reaction decomposes completely to give again blue *Ia* and its *S*-sulfide *XIc*. On the other hand, interaction of *XIc* with *Va* affords thermally more stable, mixed 1,2,4-trithiolane *XXI* which was isolated and its structure was confirmed by means of spectroscopic methods. Details of the structure of a similar 1,2,4-trithiolane, derivative of bis(4-methoxy)thiobenzophenone were established using X-ray diffraction analysis [20].

Sterically congested azabicyclo[1.1.0]butanes with general formula *XXII* are relatively easily available based on published procedures [21—23]. The presence of nitrogen atom and the strain energy of the bicyclo[1.1.0]butane ring lend its derivatives remarkable reactivity towards electron-deficient (electrophilic) reagents. Additions of some reagents of type HX (X = Cl, F, OH) across the N-1—C-3 bond were previously reported [22—24] and they are believed to proceed through the same intermediate of the type of 3-azetidinium carbocation [25].

Recently, reactions of *XXIIb* with dichlorocarbene were described and *gem*-dichloro-1,4-azadiene *XXIII* was shown to be the primary product of the ring opening (Scheme 9) [26]. Longer reaction times and step-by-step addition to both olefinic and imine double bonds afforded final products containing both cyclopropane and aziridine rings. For identification of the oily [(2,2-dichlorocyclopropyl)methyl](dichloromethylene)imines they were treated with sodium azide in acetone/water solution and thus they were successfully converted into crystalline tetrazole derivatives *XXIV*.



XXII *XXVa, XXVb*

Yields = 79 – 90 %

XXV	X
a	Cl
b	N_3

Scheme 10

In order to elucidate the mechanistic pathway of these reactions, assumption was made that like other electrophiles, dichlorocarbene adds to the free electron pair of the nitrogen atom to produce nitrogen ylide which is subsequently stabilized by a cascade of reactions, resulting finally in the ring opening and formation of 1,4-azadiene derivatives. The same mechanism has recently been proposed by *Moss et al.* who described reactions of 3-ethylazabicyclo[1.1.0]butane with chloro(phenyl)carbene in low-temperature matrices [27].

Esters of both chloro- and azidoformic acids were shown to add easily across N-1—C-3 bond in azabicyclo[1.1.0]butanes to afford azetidine-1-carboxylic acid derivatives of type *XXV* in high yields (Scheme 10). Methyl chloroformate was found to react faster, however, its reaction with *XXIIb* was complete after 1 day at ambient temperature whereas similar reaction with azidoformate was finished only after 4 days [28].

Thermolysis of methyl 3-azido-3-phenylazetidine-1-carboxylate (*XXVb*) was studied at 350 °C (flash vacuum thermolysis) and corresponding derivative of 2,5-dihydroimidazolecarboxylic acid *XXVI* was the main product found in the reaction mixture [29] (Scheme 11). Ring enlargement results from the intramolecular insertion of nitrene generated after decomposition of the azide group; unstable aziridine derivative may be a putative intermediate.

Unlike azidoformates, tosyl azide did not react with azabicyclobutane *XXIIa* and reacted very slowly with *XXIIb* at room temperature. However, slow reaction (7 days) of *XXIIb* with equimolar amount of tosyl azide dissolved in chloroform afforded after chromatographic separation two crystalline products which were identified as 1:1 and 1:2 adducts *XXVII* and *XXVIIIa* (R = C_6H_5), respectively [28] (Scheme 12). The structure of the "dimeric" products *XXVIIIa* was confirmed by means of X-ray crystallography [30].

Recent results obtained with tosyl azide and an excess of 3-ethylazabicyclo[1.1.0]butane (*XXIIa*) at 80 °C showed that in this case reaction mixture consisted of oligomeric products, the highest one being hexameric (*XXVIIIe*, R = C_2H_5) [30]. All adducts were chromatographically separated and identified by means of spectroscopic methods. These results showed that organic azides add to azabicyclo[1.1.0]butanes with different rates and the reaction of intermediate carbocations with azide anion competes with nucleophilic approach of azabicyclo[1.1.0]butane molecule which results in prolongation of the chain formed by azetidine rings [31].

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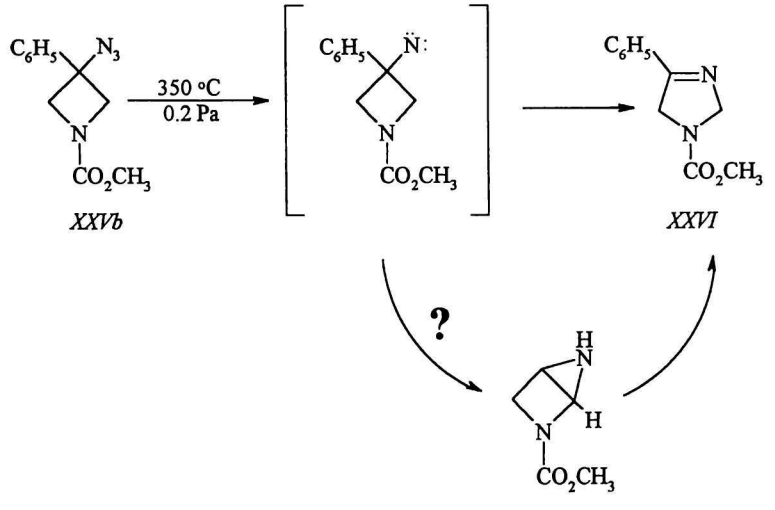
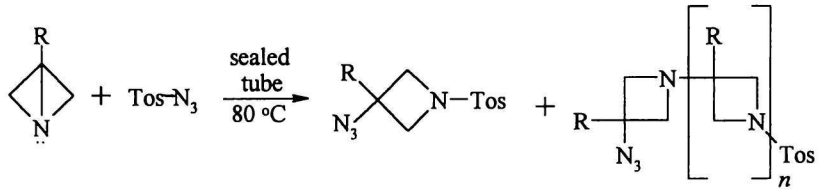


Scheme 11



XXIIa, XXIIb *XXVII* *XXVIII*

R . *a* = C_2H_5; *b* = C_6H_5

XXVIII

a—e	*n* = 1—5	R = C_2H_5
f—h	*n* = 1—3	R = C_6H_5

Scheme 12

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