Thesis

New hetaryldienes and their synthetic applications

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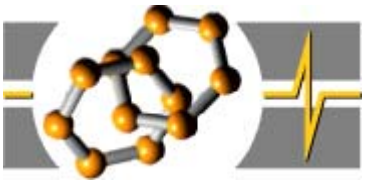

Chemical Research Center, Hungarian Academy of Sciences
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1. Introduction, aim of research

Our research group has been deeling with investigation of bridge-head nitrogen containing azolium salts and their reactivity for a long time. One of the most important finding in this area is the recognition of a synthetic method to hetaryldienes via ring closure reaction. Thus, a number of dienes bearing electron releasing groups at the end of the chain can be synthetized. This procedure was, however, limited to reactions of azolium salts with secondary amines so far.

The main target of the present work was elaboration novel methods allowing the synthesis of a wide group of *trans,trans*-hetaryldienes, and transformation of these derivatives to new polyhetaryl compounds. Our research activity was extended to other derivatives too, that can undergo ring closure reaction and can afford new hetaryl derivatives.

2. Experimental methods

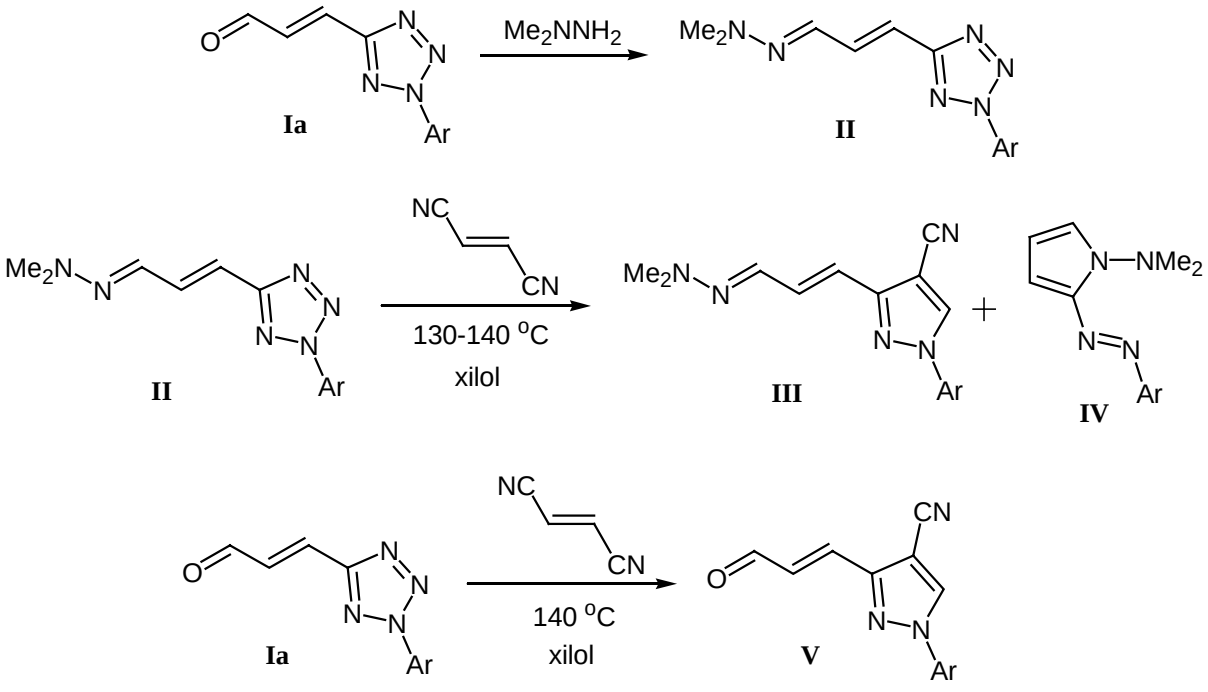
In the course of these studies well established preparative methods have been applied, purity of the compounds have been checked by TLC. The synthetized compounds have been purified by crystallization and column chromatography. Structure elucidation has been accomplished by ^{1}H, ^{13}C NMR, two dimensional NMR, IR and mass specrometry as well as by classical (elementary analysis) methods. The new derivatives have been characterized by their melting points in every case.

3. New scientific results

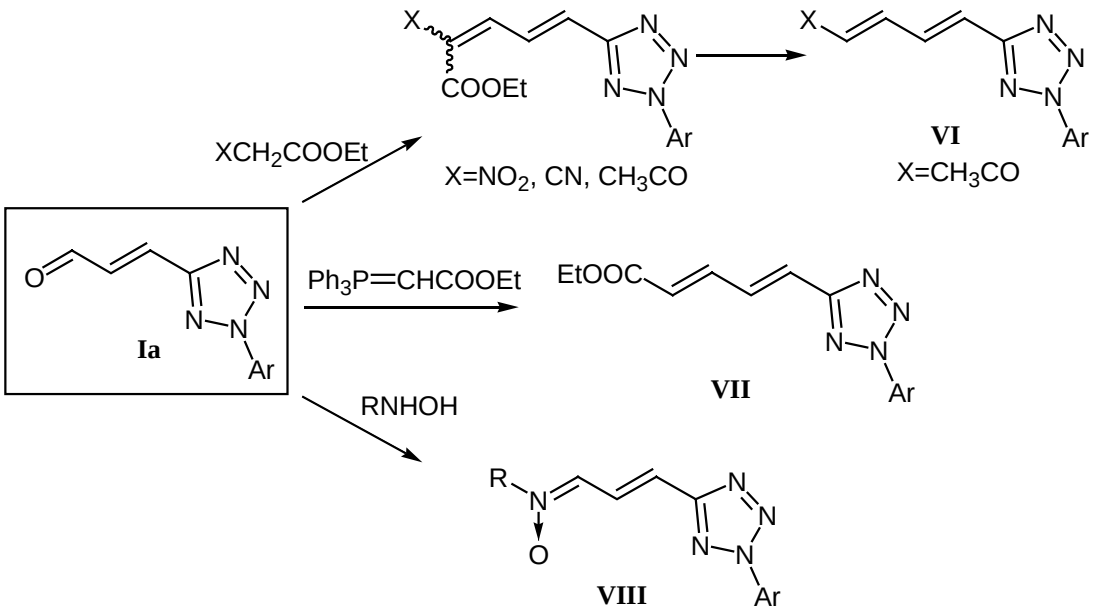
The new results are discussed – according to the structure of these theses – in three chapters.

3.1 Synthesis starting from tetrazolylacrolein

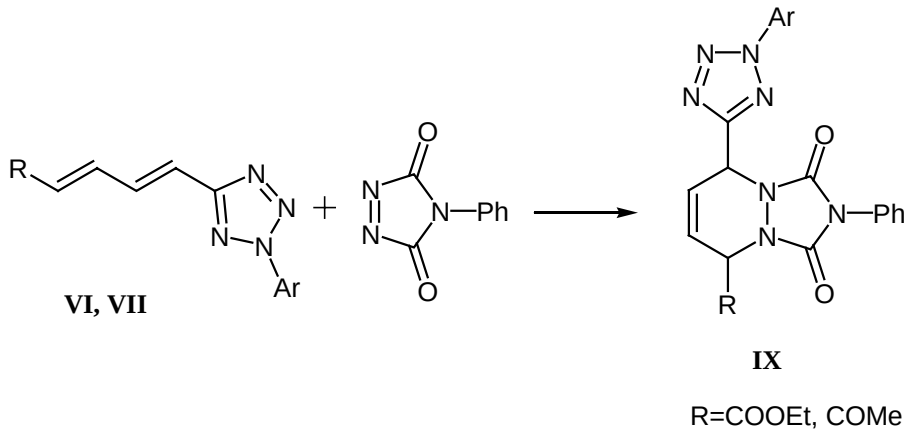
3.1.1 A synthetic pathway to tetrazolylacrolein (**Ia**) has been developed. The reaction of tetrazolylacrolein with *N*,*N*-dimethylhidrazine afforded hidrazone derivatives (**II**). This product in the presence of fumaronitrile underwent an unexpected transformation: instead of cycloaddition a ring transformation took place. Nitrogen elimination of the tetrazole ring afforded a dipolar intermediate which in reaction with fumaronitrile formed the pirazole derivative (**III**). The formation of pyrrole (**IV**) derivative in traces was also observed.

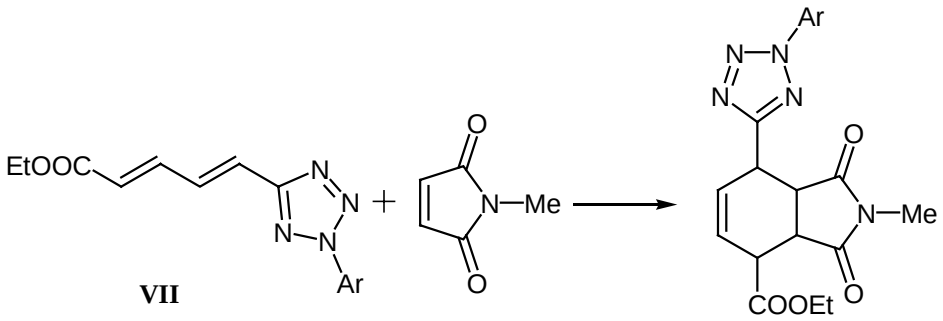


3.1.2 Starting from tetrazolylacrolein (**I**), *trans*,*trans* tetrazolyldienes (**VI**, **VII**) containig electron-withdrawing groups were synthetized by condensation and Wittig reactions. By the use of condensation reaction, nitrone derivatives (**VIII**) were also prepared from **I**.



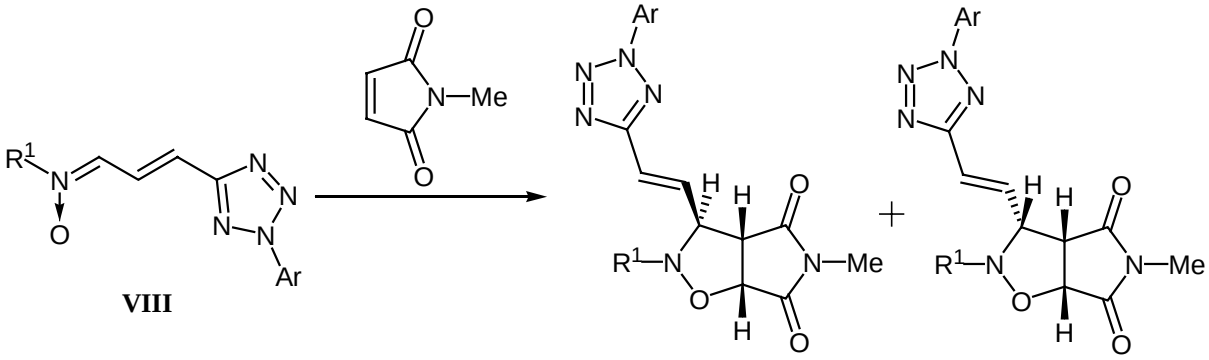
3.1.2.1 The synthetized dienes were examined in cycloadditions. We have found that even in the presence of electron-withdrawing substituents, these compound reacted as dienes of normal electron demand with *N*-phenyltriazoline dione, and **IX** was formed. The ester (**VII**) reacted with *N*-methylmaleimide under forced conditions (in ionic liquid) to form **X** cycloadduct.





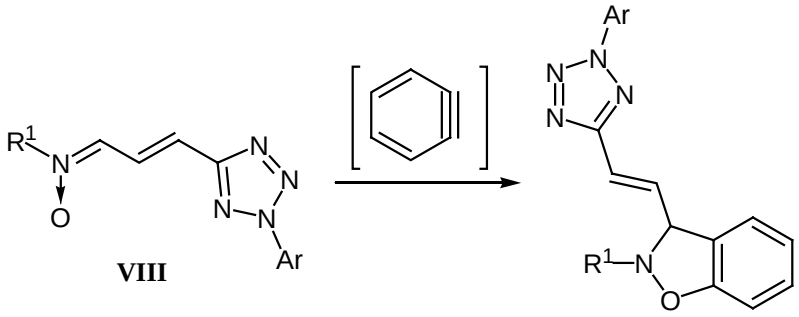
VII **X**

The two nitrone derivatives (**VIII**) can participate in 1,3-dipolar cycloadditions with *N*-methylmaleimide as a 1,3-dipole to yield **XI** and **XII** stereoisomers.



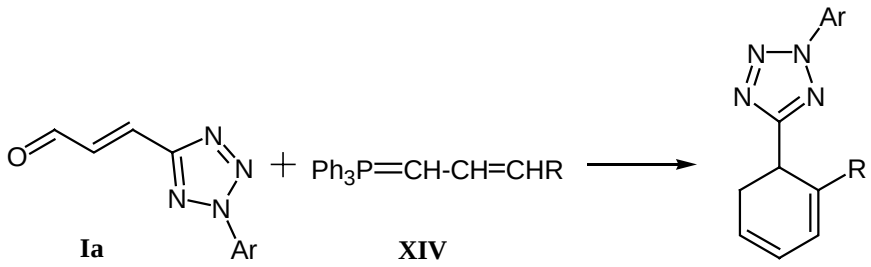
VIII **XI** **XII**

Further example for the 1,3-dipolar cycloaddition is the reaction of the nitrone with *in situ* generated dehydrobenzole to benzisoxazoline (**XIII**).



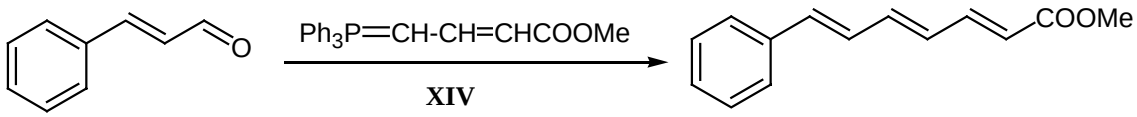
VIII **XIII**

3.1.3 Tetrazolylacroleins were reacted with stabilized phosphoranes (**XIV**) where instead of formation of triene derivatives, cyclohexadienes (**XV**) were isolated. The same reaction with cinnamic aldehyde gave the expected hexatriene derivative (**XVI**).



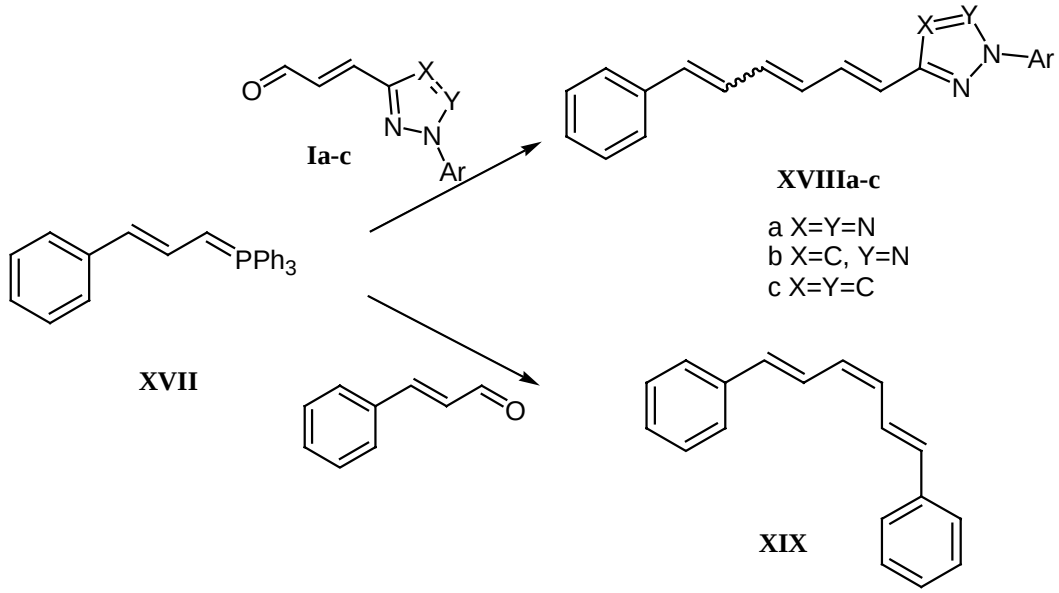
Ia **XIV** **XV**

R=CN, COOMe



XIV **XVI**

In the case of non-stabilized phosphorane (**XVII**) the regular Wittig reaction took place and triene derivatives (**XVIIIa-c**, **XIX**) were formed.



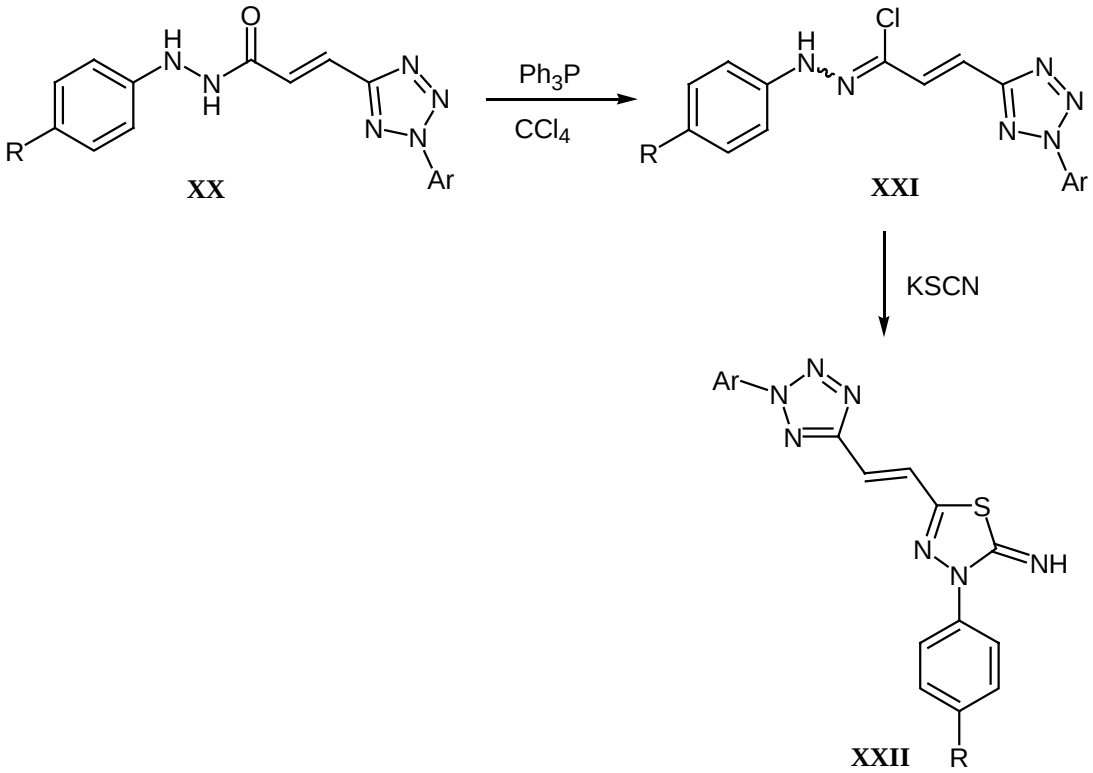
Ia-c **XVIIIa-c**

a X=Y=N
b X=C, Y=N
c X=Y=C

XVII **XIX**

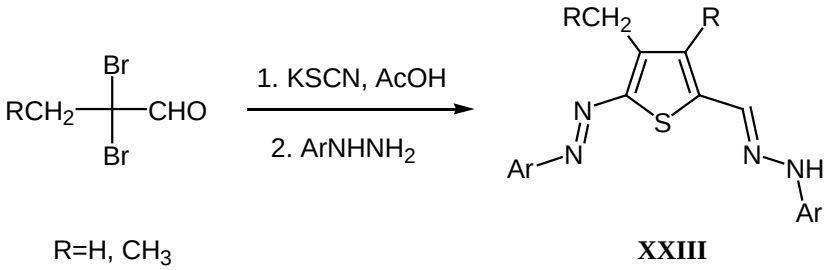
We have extended the reaction for triazolyl and pirazolylacroleins (**Ib**, **Ic**) and we have suggested a mechanism for the formation of cyclohexadiene derivatives.

3.1.4 Tetrazolylacrolein (**Ia**) was transformed with *N*-bromosuccinimide to acide bromide *in situ*, which could be converted to hidrazide (**XX**) by phehylhidrazine derivatives. Starting from the hidrazide a halogene-containing 1-azadiene was synthetized by application of the Appel reaction, which in the presence of potassium thiocyanate participated in ring closure reaction to yield 1,3,4-thiadiazoles (**XXII**).



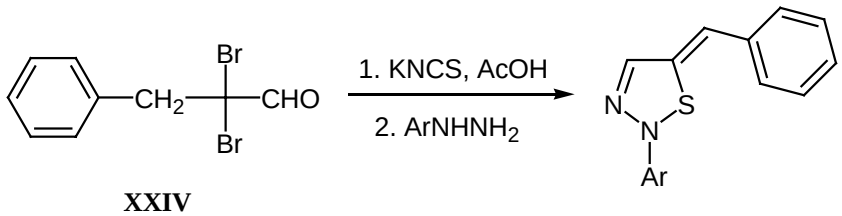
3.2 Investigations of extension of ring closure to new thiophenes

Investigation and extension of ring closure to new thiophenes was studied. Startig from 2,2-dibromopropionic aldehyde and 2,2-dibromobutiric aldehyde in the presence of potassium thiocyante and various phenyl hydrazines thiophene derivatives (**XXIII**) were formed in acetic acid.



In the course of extension of this reaction to 2,2-dibromodihyrocinnamic aldehyde (**XXIV**) a formation of 1,2,3-thiadiazole (**XXV**) was also observed.

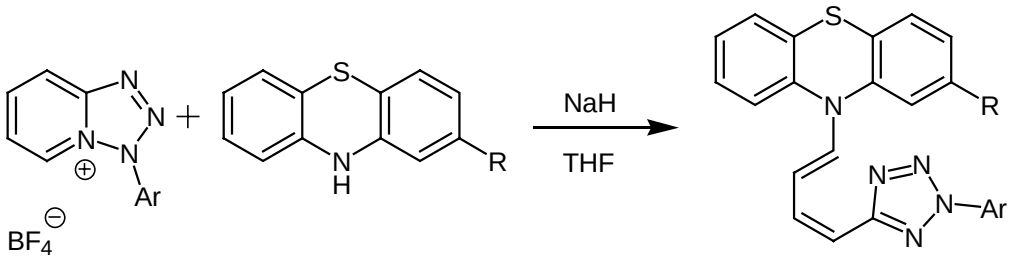
We have suggested a mechanism for the formation of the thiophene and 1,2,3-thiadiazole ring.



XXIV **XXV**

3.3 Synthesis of phenothiazinyldienes exerting reversal of multidrog resistance

New phenothiazinyldienes (**XXVII**) were sythetized by ring opening of tetrazolopiridinium salts (**XXVI**), and the biological activity was examined in co-operation. One of the new derivatives has a promising activity in the field of multidrug resistance inhibition.



XXVI **XXVII**

4. Published results

Publications:

1. I. Nagy, D. Kónya, Zs. Riedl, A. Kotschy, G. Timári, A. Messmer, Gy. Hajós; Synthesis and transformation of tetrazolylacroleins, *Tetrahedron* **59**, 7485-7489 (2003)

2. I. Nagy, Gy. Hajós, Zs. Riedl; New preparative route to hetaryldienes and azadienes, *Heterocycles* article in press

3. I. Nagy, Zs. Riedl, Gy. Hajós, N. Gyémánt, J. Molnár; Synthesis of new tetrazolylphenothiazines as potential multidrog resistance inhibitory compounds, *Arkivoc* vii 177-182 (2004)

Lectures, posters:

1. Ildikó Nagy, Zsuzsanna Riedl, György Hajós; Sythesis and transformation of hetaryldienes, IV. PhD Program, Mátraháza, 2001

2. Ildikó Nagy, Zsuzsanna Riedl, György Hajós; Sythesis and transformation of new *trans,trans* dienes, Hungarian Academy of Science, Annual meetig on Heterocyclic Chemistry 2002, Balatonszemes

3. Ildikó Nagy, György Hajós, Zsuzsanna Riedl; New synthesis from hetarylacroleins, V. PhD Program, Királyrét 2002

4. Ildikó Nagy, György Hajós, Zsuzsanna Riedl; New transformations of tetrazolylacroleins Chemical Research Center Annual meeting 2003

5. Ildikó Nagy, György Hajós, Zsuzsanna Riedl; New transformation of hetarylacroleins, Hungarian Academy of Science, Annual meeting on Heterocyclic Chemistry 2004, Balatonszemes

6. Ildikó Nagy, György Hajós, Zsuzsanna Riedl; New synthesis from hetarylacroleins, Annual meeting on Organic Chemistry 2001, Hajdúszoboszló

7. Ildikó Nagy, Zsuzsanna Riedl, György Hajós; Synthesis and transformation of new tetrazolylacroleins, 9th Blue Danube Symposium on Heterocyclic Chemistry 2002, Tatra, Slovakia

8. Ildikó Nagy, György Hajós, Zsuzsanna Riedl; New transformation of tetrazolylacroleins, Annual meeting on Organic Chemistry 2003, Hajdúszoboszló

9. Ildikó Nagy, György Hajós, Zsuzsanna Riedl; Synthesis and transformation of hetaryldienes, 10th Blue Danube Symposium on Heterocyclic Chemistry 2003, Bécs, Ausztria