SYNTHESIS AND TRANSFORMATIONS OF α-AZIDO-KETONES

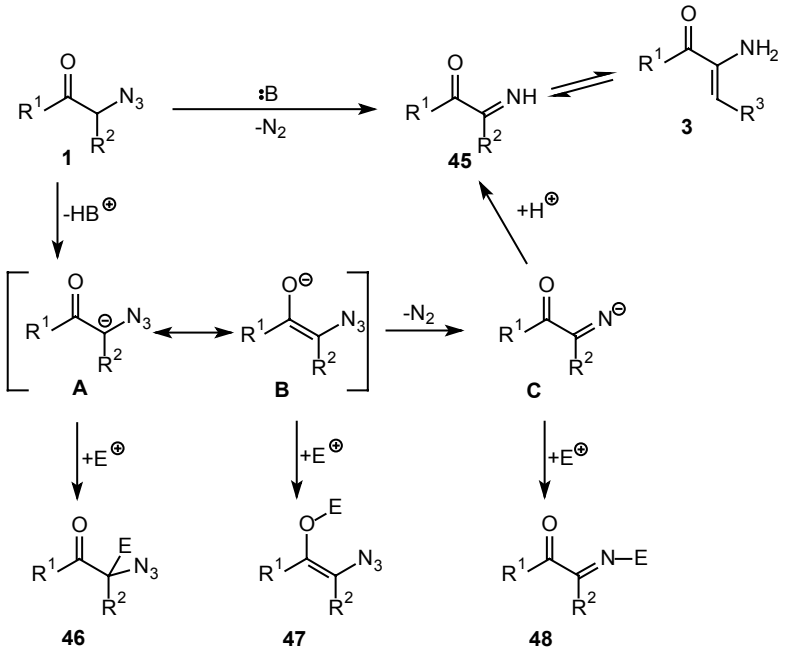
Juhászné Tóth Éva

Supervisor:
Dr. Patonay Tamás

University of Debrecen
Debrecen, 2002.

1. Introduction and Aim of the Dissertation

α-Azido ketones **1** with at least one α-hydrogen atom have been found to be highly base-sensitive and to undergo loss of nitrogen from carbanion **A**, followed by protonation of imino anion **C** to give imine **45**[1]. This reaction has limited synthetic value unless the α-imino ketone **45** has β-hydrogen and thus, it is able to tautomerize to an α-amino enone **3**. This sequence has been utilized for the synthesis of α-amino cyclic enones, heterocyclic enones, and acyclic enamines which have a functional group in the position β capable of conjugation with the enone moiety.



A key feature of this scenario is the assumption that three different anionic intermediates (**A, B, C**) can be trapped by electrophiles to give products **46-48**. However, just a few reports have appeared on the use of some of these intermediates as nucleophiles.

Patonay and Hoffman have demonstrated that anions **A** and **C** generated from azides **1** by treatment with amines can be trapped with aldehydes or ketones to yield 2-azido-3-hydroxy ketones **53** or 2,5-dihydro-5-hydroxyoxazoles **55** depending on the conditions and techniques. Some examples of the synthetic utility of 2-azido-3-hydroxy ketones **53** was also presented; these valuable 1,2,3-trifunctionalized synthons can be transformed easily and selectively in many ways, even without using protecting groups.

[1] Numbering of compounds refers to ones used in the dissertation

In continuation of their work we wished to optimize the reaction conditions and to extend the base-catalyzed reactions of α-azido ketones **1** to different electrophiles. Moreover, our further goal was to study the possible transformations of the products obtained in the coupling reactions.

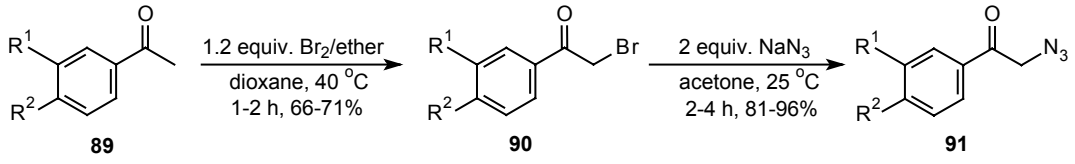
2. Applied Methods

In our synthetic work we have applied macro-, semimicro- and micro methods of modern synthetic organic chemistry. Reactions were monitored by thin-layer chromatography. Reaction mixtures were purified by column chromatograpy. Products were identified by classical analitical methods (elemental analysis, melting point) and spectroscopic (IR, MS, ^{1}H-,^{13}C-NMR) tools. In some cases relative configuration of compounds was determined by X-ray crystallography.

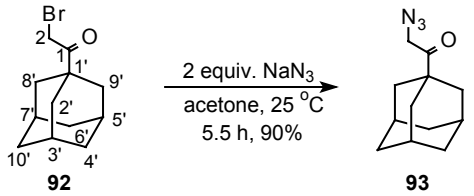
3. New Results of the Dissertation

3.1. Synthesis and Mass Spectrometry of α-Azido Ketones

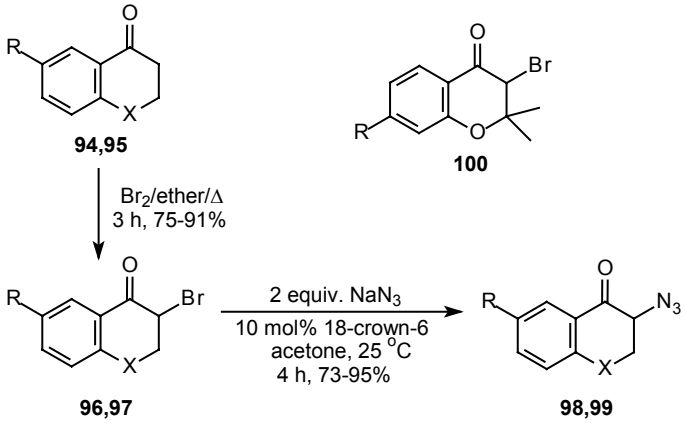
Our starting material α-azido ketones were synthetized by nucleophilic substitution of α-bromo or α-nosyloxy ketones. We have established that acetone can be used advantageously in the transformation of phenacyl bromides **90** with sodium azide to afford the corresponding azides **91** in excellent yields (81-96%). Using the same reaction conditions we have also managed to prepare the 1-(1-adamantyl)-2-azidoethan-1-one (**93**) in very good yield (90%).



89-91	a	b	c	d	e	f	g
R^1	H	H	H	H	H	H	MeO
R^2	H	MeO	F	Cl	NO_2	Ph	H



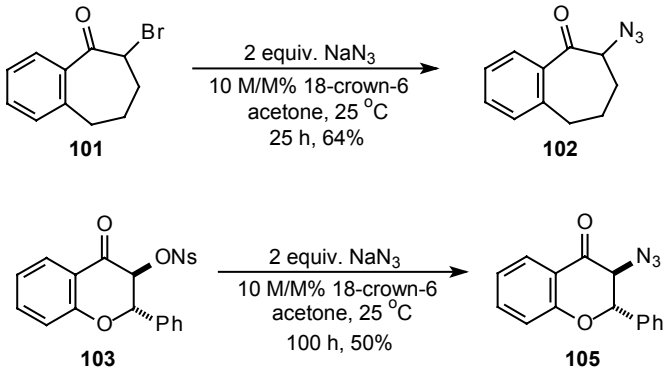
However, it was found that the reaction between sodium azide and 3-bromochromanones **96** due to the steric hindrance of the S_N2 displacement took place very slowly in acetone, and considerable amount of secondary products was also detected. In the presence of 10 mol% of 18-crown-6 phase-transfer catalyst, the reaction was accelerated due to the higher concentration of azide ions and 3-azidochromanones **98** were obtained in good to excellent yields (73-95%). Even the very sensitive 3-azido-1-thiochromanone (**99a**) became available in modest yield (26%) by this methodology.



94-102	a	b	d	h
R	H	MeO	Cl	Me

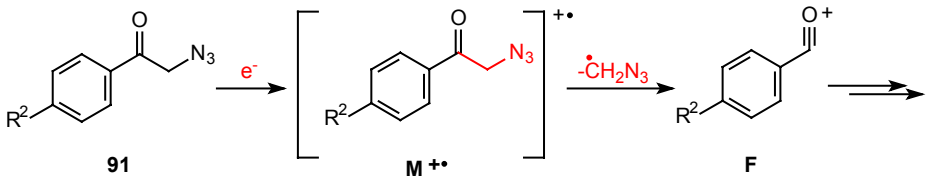
	94,96,98	95,97,99
X	O	S

Earlier attempts to prepare azides **98** and **99a** by nucleophilic substitution of 3-bromochromanones **96** and 3-bromo-1-thiochromanone **97a** in more polar solvents such as DMF, DMSO, alcohols and their mixtures with water failed to give any azides, affording only 3-aminochromones and -1-thiochromones. Thus, our methodology has notable synthetic value. The use of crown ethers in combination with acetone as solvent allowed us to synthetize 2-azidobenzosuberone (**102**) and *trans*-3-azidoflavanone (**105**) in good yields, as well.



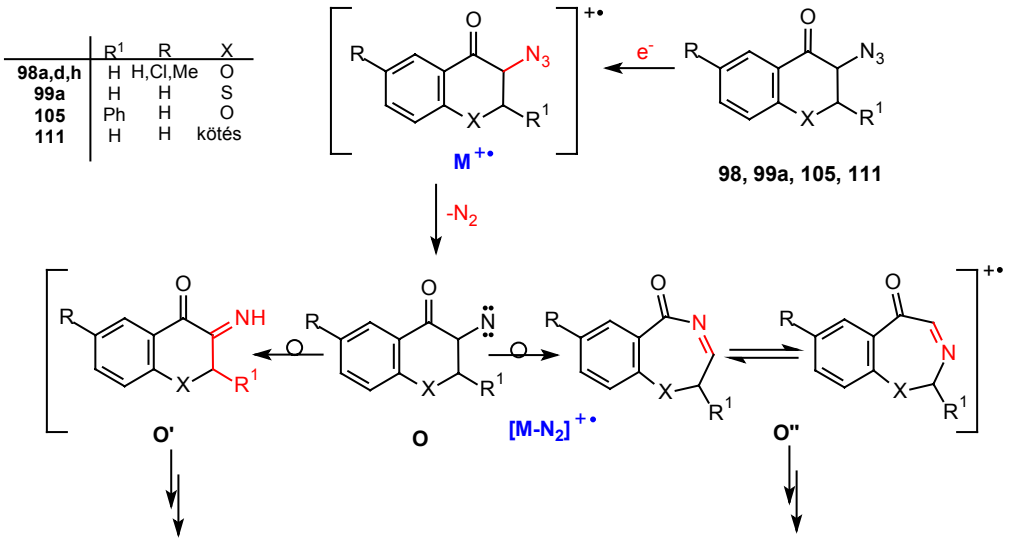
Previously, azide **105** had been prepared in poor yield by quenching the reaction between *trans*-3-mesyloxyflavanone and sodium azide in DMF at low conversion.[5a] On the other hand, when 3-bromo-2,2-dimethylchromanones **100a**,**b** were treated with sodium azide under the standard conditions, no reaction was observed, even after longer periods or at elevated temperatures. The lack of the reaction could be explained in terms of the steric hindrance exerted by the axial methyl group in the position β on the rear-side attack of the nucleophile at C-3. This has so far been the only observed limitation of our new method.

We also studied the mass spectrometric behaviour of phenacyl azides **91** and α-azidobenzo(hetera)cyclanones **98, 99a, 105, 111** in details. No molecular ion peak was observed in the EI mass spectra of azides **91** with the exception of 2-azido-4′-methoxyacetophenone (**91b**), the relative abundance of $M^{+\bullet}$ was very low, in this particular case, too. The base peak was at m/z = M-$CH_2N_3^+$ in all cases.



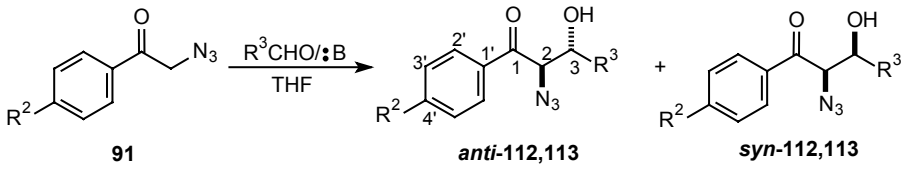
91	a	b	c	d	e
R^2	H	MeO	F	Cl	NO_2

In the spectra of cyclic azides **98, 99a, 111** (except azide **105**) the molecular ion peaks were observable. Their fragmentation started with loss of nitrogen that is typical of azides.



3.2. Base-Induced Coupling of α-Azido Ketones with Aldehydes: An Easy Route to 2-Azido-3-hydroxy Ketones, 2-Acylaziridines, and 2-Acylspiroaziridines

With substituted phenacyl azides and α-azidobenzo(hetera)cyclanones in our hands, we systematically investigated their reactions with aldehydes. The 2-azido-4′-substituted-acetophenones **91a-e** were treated with acetaldehyde and propionaldehyde under the optimized conditions [8.0 equiv. of electrophile, 0.08 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)] and the corresponding aldol products *syn*- and *anti*-**112a-e** and **113a,d** were obtained in moderate to good yields (30-82%).

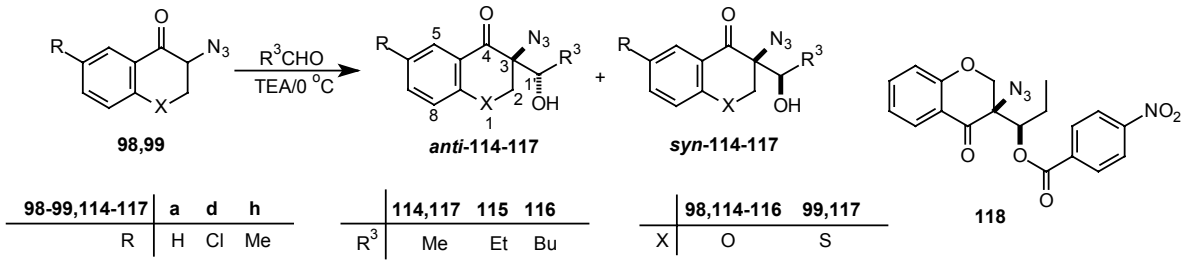


91, 112-113	a	b	c	d	e
R^2	H	MeO	F	Cl	NO_2

	112	113
R^3	Me	Et

The assignment of *syn* and *anti* stereochemistry of **112** and **113** was made on the basis of the coupling constants of the methine protons at C-2 and C-3. A low diastereoselectivity (0-32% *de*) with a *syn* preference was observed in the formation of products **112** and **113**. Incorporation of electron-withdrawing substituents, particularly the nitro group, into position 4′ resulted in a significant decrease in the yield.

Analogous treatment of 3-azidochromanones **98a,d,h** and 3-azido-1-thiochromanone (**99a**) with high excess of aliphatic aldehydes in the presence of 1.0 equiv. of triethylamine afforded the desired 3-azido-3-(1-hydroxyalkyl)chromanones **114a, 115a,d,h, 116a** and 3-azido-3-(1-hydroxyethyl)-1-thiochromanone **117a** in good (60-74%) yields.

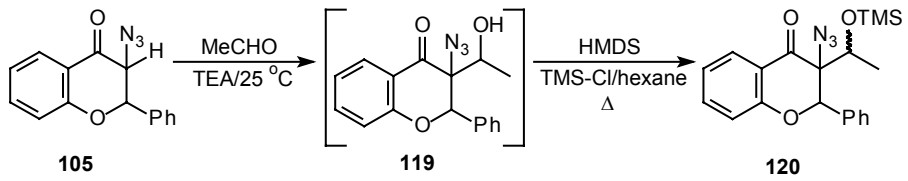


98-99,114-117	a	d	h
R	H	Cl	Me

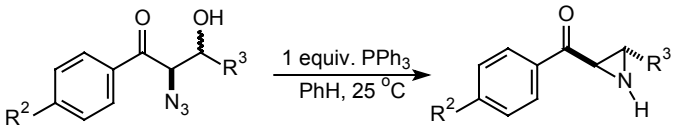
	114,117	115	116
R^3	Me	Et	Bu

	98,114-116	99,117
X	O	S

Products **114-117** were isolated as mixtures of *syn* and *anti* diastereomers. The assignment of *syn* and *anti* stereochemistry was deduced from the X-ray analysis of the *p*-nitrobenzoate **118** derived from *syn*-**115a** which allowed us to assign the isomers in the whole series on the basis of the characteristic differences in their NMR spectra. A low diastereoselectivity with *syn* preference was observed in most cases, the d.e. values varied between 12 and 16% for products **114a, 115a, 115d, 115h**. However, the selectivity depended significantly on steric factors. 1,2-Azido alcohol **116a** with a longer alkyl chain and aldol product **117a** with a more distorted heterocycle afforded higher *syn*/*anti* ratios (34 and 56% *de*, respectively). Treatment of *trans*-3-azidoflavanone (**105**) with acetaldehyde yielded the anticipated but highly unstable product **119** which could be isolated in the form of the protected derivative **120**.



These results clearly show the generality of this new C–C bond-forming reaction for both aliphatic and cyclic α-azido ketones. 2-Azido-3-hydroxy ketones available from the reaction between various α-azido ketones and aldehydes are useful trifunctionalized synthons. Treatment of 1,2-azido alcohols **112a-e** and **113a** with triphenylphosphine (TPP) in benzene solution yielded the corresponding *trans*-aziridines **121a-d** and **122a** in poor (3.1-32%) yields.

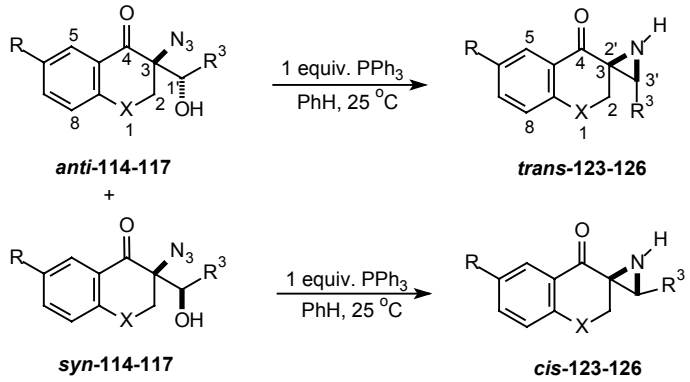


***syn,anti*-112,113** **trans-121,122**

112-113, 121-122	a	b	c	d	e
R^2	H	MeO	F	Cl	NO_2

	112,121	113,122
R^3	Me	Et

Our method was the first report on the synthesis of 1-unsubstituted-2-acylaziridines. A marked substituent effect was also observed. The presence of an electron-withdrawing substitutent in position 4′ significantly reduced the yield of the ring-closure, the nitro derivative **121e** was unavailable in this way. However, much better (32-63%) yields were achieved by the analogous treatment of *syn*- and *anti*-3-azido-3-(1-hydroxyalkyl)chromanones and -1-thiochromanone **114a, 115a,d,h, 116a** and **117a**, which afforded the desired *cis*- and *trans*-aziridines **123a, 124a,d,h, 125a** and **126a**. The relative configuration of the aziridine rings were determined by 2D $\{^1H\}$-^1H NOE measurements. This type of spiroaziridines was almost unknown in the literature, the only synthesis reported by Piva based on the photoinduced cyclization of a 2-aminocyclohexenone derivative. Examination of the stereochemical outcome of the cyclization showed that the reaction was completely diastereospecific and diastereoselective in accordance with some earlier findings and the proposed mechanism.



***anti*-114-117** ***trans*-123-126**

***syn*-114-117** ***cis*-123-126**

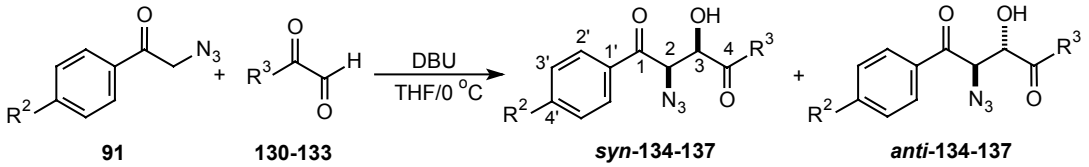
114-117, 123-126	a	d	h
R^2	H	Cl	Me

	114,123,126	115,124	116,125
R^3	Me	Et	Bu

	114-116, 123-125	117,126
X	O	S

3.3. Base-Induced Coupling of α-Azido Ketones with α-Oxo Aldehydes and α-Oxo Esters: Synthesis of 2-Azido-3-hydroxy-1,4-diones, 3-Azido-4-oxo-butenoates and their Transformation into 5-Substituted 3-Acylizoxazoles, and Trisubstituted 2*H*-Azirines

To demonstrate that not only simple aldehydes or ketones but more complex carbonyl compounds can also be used as electrophiles, we extended our experiments to α-oxo aldehydes and α-oxo esters. When 2-azido-4′-substituted-acetophenones **91a-d** were treated with various arylglyoxal hydrates **130-132** and *tert*-butylglyoxal hydrate (**133**) in the presence of catalytic amounts of DBU, 2-azido-3-hydroxy-1,4-diketones **134a-d, 135b, 136b, 137b** were obtained in moderate to good yields (52-84%).



91 **130-133** ***syn*-134-137** ***anti*-134-137**

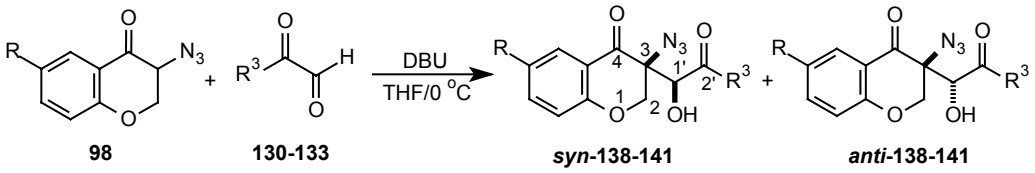
91, 134-137	**a**	**b**	**c**	**d**
R^2	H	MeO	F	Cl

	130,134	**131,135**	**132,136**	**133,137**
R^3	Ph	4-MeO-C_6H_4	4-Cl-C_6H_4	tBu

The electronic effect of R groups in position 4′ has no influence on the conversion and yield of the C–C bond-forming reaction. Moreover, both aryl- and alkylglyoxals gave moderate-to-good yields, indicating the generality of the coupling reaction. Adducts **134-137** were isolated as mixtures of *syn* and *anti* isomers in all cases. The assignment of *syn* and *anti* relative configuration was made from the determination of the stereochemistry of *syn*-**134b** by X-ray analysis which allowed us to assign the isomers in the whole series on the basis of their characteristic spectral differences. A moderate-to-good diastereoselectivity (52-74% *de*) with *syn* preference was observed in the formation of products **134-137**. These *de* values were markedly higher than the selectivities found in the reactions between azido ketones **91** and simple aldehydes. On the other hand, excellent regioselectivity between the formyl and oxo carbonyl groups was observed in favor of the former, as azides **134-137** being formed exclusively and no other aldol products being detected in the reaction mixtures. This selectivity could be explained in terms of the higher electrophilicity and the smaller steric hindrance of the formyl group.

We also studied the coupling reactions of cyclic systems. Analogous reactions between 3-azidochromanones **98a,d,h** and α-oxo aldehydes **130-133** in the presence of

catalytic amounts of DBU afforded the desired 3-azido-3-(1-hydroxy-2-oxoalkyl)-4-chromanones **138a,d,h 139h, 140h** and **141h** in high (usually > 80%) yields. These yields were significantly higher than those found in treatment of the acyclic substrates **91**. This observation may be explained in terms of the lack of α-hydrogen in the α-azido ketone unit, and hence, the absence of *retro*-aldol cleavage.

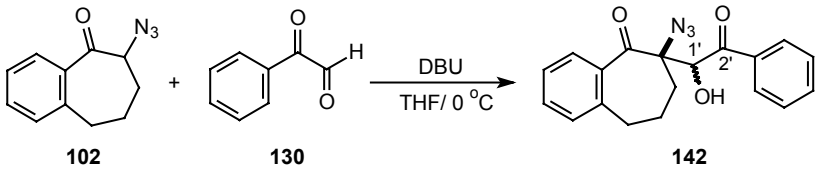


98, 138-141	a	d	h
R	H	Cl	Me

	130,138	131,139	132,140	133,141
R^3	Ph	4-MeO-C_6H_4	4-Cl-C_6H_4	tBu

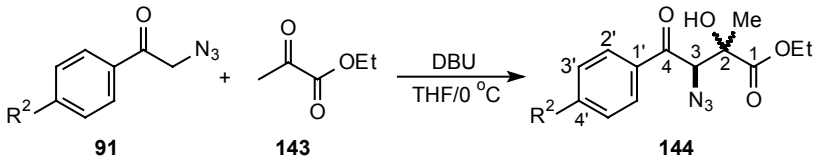
Again, azido alcohols **138-141** were isolated as mixtures of *syn* and *anti* diastereomers. The relative configuration of the diastereomers was assigned by crystallography. The minor component of **138h** proved to be *anti* isomer on the basis of X-ray analysis. With the stereochemistry of the *syn*/*anti*-**138h** pair established, we were able to assign the isomers in the whole series on the basis of their characteristic spectral differences. As before, *syn* preference was found to be characteristic for the coupling reaction but diastereoselectivity was considerably lower (16-34% *de*) than in the case of acyclic azides **91**. These figures are quite similar to the values and preference observed previously in the reactions between 3-azidochromanones **98** and simple aldehydes. The reaction between azide **98h** and *tert*-butylglyoxal hydrate (**133**) gave a different stereochemical outcome as a weak *anti* preference (8% *de*) was observed.

We have also extended our experiments to another cyclic substrate, 2-azidobenzosuberone (**102**). When azide **102** was treated with phenylglyoxal hydrate (**130**) under our standard conditions, 2-azido-2-(1-hydroxy-2-oxo-2-phenylethyl)benzosuberone (**142**) was obtained in 86% yield, although the conversion was only 54%. It is very likely that higher flexibility of the seven-member ring results in a higher steric hindrance in the attack of the intermediate carbanion on the carbonyl centre and, hence, lowers the efficiency of the coupling reaction.



102 **130** **142**

To extend the range of electrophiles we have also investigated the base-induced reaction of phenacyl azides **91** and α-oxo esters. When azides **91a-c** were treated with ethyl pyruvate (**143**) as a model electrophile in the presence of DBU considerable amounts of the coupled products **144** were detected (TLC and ^{1}H NMR) but attempts to isolate these compounds by column chromatography failed.



91 **143** **144**

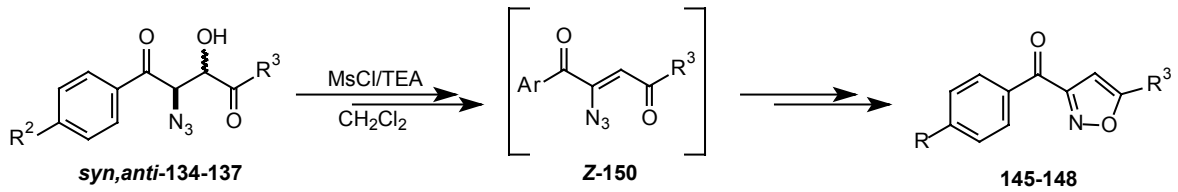
91,144	**a**	**b**	**c**
R^2	H	MeO	F

Since chromatography of the crude product afforded the starting material **91** in high amount, it is very likely that the instability of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates **144** can be explained in terms of their increased capability for decomposing in a *retro*-aldol cleavage due to the increased steric interactions around the quaternary C-2 atom. The only stable product, ethyl 3-azido-2-hydroxy-4-(4-methoxyphenyl)-2-methyl-4-oxobutanoate (**144b**), was isolated in 69% yield, which proves the efficiency and the usefulness of the coupling with α-oxo esters.

2-Azido-3-hydroxy-1,4-diones and 3-azido-2-hydroxy-4-oxobutanoates, available from reactions between α-azido ketones and various α-oxo aldehydes or α-oxo esters, are useful 1,2,3,4-tetrafunctionalized synthons. Their different functionalities allow selective manipulations, even without the use of any protecting groups. Out of the many possible applications we investigated their transformation into vinyl azides in detail. Our planned strategy was to convert the hydroxyl group of adducts **134-137** and **144** into a good leaving group by mesylation.

Treatment of *syn*,*anti*-1-aryl-2-azido-3-hydroxy-1,4-diones **134a-d, 135b, 136b, 137b** and *syn*-**134b** with a slight excess (1.2 equiv.) of mesyl chloride (MsCl) and 2.4 equiv. of

TEA in dry dichloromethane resulted in the formation of the corresponding 3-aroyl-5-substitutedisoxazoles **145a-d, 146b, 147b** and **148b** in moderate yield (23-63%).

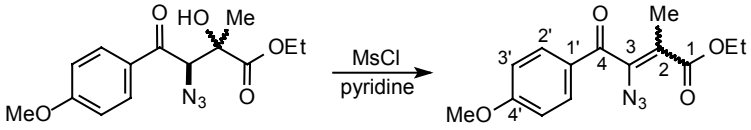


***syn,anti*-134-137** **Z-150** **145-148**

134-137, 145-148	a	b	c	d
R^2	H	MeO	F	Cl

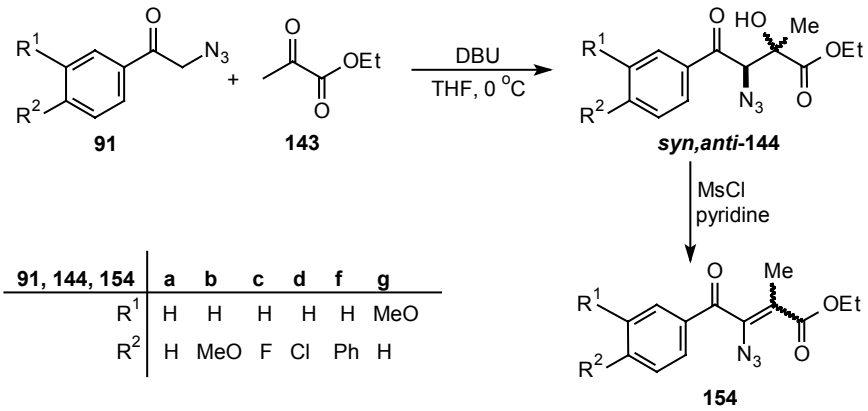
	134,145	135,146	136,147	137,148
R^3	Ph	4-MeO-C_6H_4	4-Cl-C_6H_4	tBu

This reaction offers a new entry to the field of 3,5-disubstituted isoxazoles. Products **145-148** were identified by their spectral characteristics, microanalysis and chemical corroboration. Formation of isoxazoles can be explained by the intermediacy of (*Z*)-β-azido-α,β-unsaturated ketones (*Z*)-**150** which are highly unstable and give isoxazoles at room temperatures, presumably *via* the corresponding nitrenes **151**. Further support for the intermediacy of vinyl azides (*Z*)-**150** was provided by the analogous treatment of pyruvate adduct **144b** with MsCl in dry pyridine which resulted in the formation of ethyl 3-azido-4-(4-methoxyphenyl)-2-methyl-4-oxo-2-butenoate (**154b**). This latter compound was inevitably stable due to the lack of the β-azido-α,β-unsaturated ketone unit.



144b **154b**

The observed stability of azide **154b** prompted us to develop a methodology for the synthesis of this family of compounds. Direct mesylation of the crude reaction mixture of coupling reaction leading to adducts **144** after removal of the solvent and without isolation of the product resulted in the formation of vinyl azides **154** in good overall yields (35-51%).



91

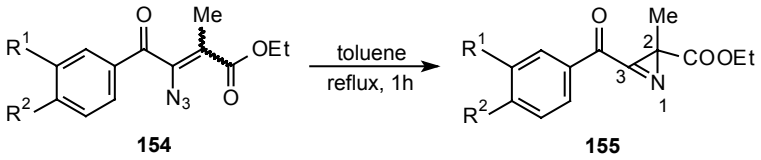
143

***syn,anti*-144**

154

91, 144, 154	a	b	c	d	f	g
R^1	H	H	H	H	H	MeO
R^2	H	MeO	F	Cl	Ph	H

With the vinyl azides **154** in our hands, we examined their thermolysis. Heating of azides **154** resulted in the formation of 3-acyl-2-alkoxycarbonyl-2*H*-azirines **155** in moderate to good yields (33-70%). Such 2*H*-azirines were almost unknown in the literature.



154

155

154, 155	a	b	c	d	f	g
R^1	H	H	H	H	H	MeO
R^2	H	MeO	F	Cl	Ph	H

In summary, we have improved the synthesis of α-azido ketones and demonstrated that various electrophiles can be used to trap the corresponding carbanion intermediate generated from α-azido ketones. Tri- and tetrafunctionalized products of these C–C bond forming reactions could be transformed to 2-acylaziridines, 2-acylspiroaziridines, 5-substituted 3-acylisoxazoles and trisubstituted 2*H*-azirines.

4. Lists of Publications, Lectures and Posters in the Field of the Dissertation

Publications

1. Tamás Patonay, Éva Juhász-Tóth, Attila Bényei

Base-Induced Coupling of α-Azido Ketones with Aldehydes - An Easy and Efficient Route to Trifunctionalized Synthons 2-Azido-3-hydroxy Ketones, 2-Acylaziridines, and 2-Acylspiroaziridines

Eur. J. Org. Chem. **2002**, 285-295.

2. Éva Juhász-Tóth, Tamás Patonay

Synthesis of Tetrafunctionalized 2-Azido-3-hydroxy-1,4-diones and Their Transformation into 5-Substituted 3-Acylisoxazoles

Eur. J. Org. Chem. **2002**, 3055-3064.

3. Tamás Patonay, József Jekő, Éva Juhász-Tóth

Synthesis of Ethyl 3-Aroyl-2-methyl-2H-azirine-2-carboxylates via Ethyl 4-Aryl-3-azido-2-methyl-4-oxobut-2-enoates

Heterocycles, közlésre beküldve

4. Tamás Patonay, Zoltán Dinya, József Jekő, Éva Juhász-Tóth, Attila Kiss-Szikszai

E I Fragmentation of α-Azido Ketones

J. Mass Spectrom., összeállítás alatt

Lectures

1. Juhász-Tóth Éva, Patonay Tamás

α-Azido-ketonok előállítása és felhasználásuk heterociklusok szintézisében

MTA Heterociklusos Kémiai Munkabizottság Előadóülése, 1999. 05. 27-28, Balatonszemes

2. Juhászné Tóth Éva

α-Azido-ketonok előállítása és felhasználásuk heterociklusok szintézisében

XXII. Kémiai Előadói Napok, 1999. 11. 1-3, Szeged

3. Juhász-Tóth Éva, Patonay Tamás

Újabb eredmények az α-azido-ketonok transzformációi területén

MTA Heterociklusos Kémiai Munkabizottság Előadóülése, 2000. 05. 25-26, Balatonszemes

4. Juhász-Tóth Éva, Patonay Tamás

3-Azido-kromanonok és egyéb α-azido-ketonok kapcsolása 1,2-diketonokkal és 2-oxo-karbonsavészterekkel

MTA Flavonoidkémiai Munkabizottság Előadóülése, 2000. 12. 11., Budakalász

5. Kiss Attila, Juhász-Tóth Éva, Patonay Tamás, Dinya Zoltán

α-Azido-ketonok, 3-azido-kromanonok és flavanonok tömegspektroszkópiás vizsgálata

MTA Flavonoidkémiai Munkabizottság Előadóülése, 2000. 12. 11., Budakalász

6. Juhász-Tóth Éva, Patonay Tamás

3-Acil-5-szubsztituált izoxazolok előállítása α-azido-ketonokból

MTA Heterociklusos Kémiai Munkabizottság Előadóülése, 2002. 05. 23-24, Balatonszemes

Posters

1. Éva Juhász–Tóth, Tamás Patonay,

New Synthesis of 2-Acylaziridines from 2-Azido-3-hydroxyketones

17th International Congress of Heterocyclic Chemistry, August 1-6, 1999, Vienna, Austria

2. Tamás Patonay, Éva Juhász-Tóth

α-Azido-ketones as Precursors of Versatile Tetrafunctionalized Building Blocks

8th Belgian Organic Synthesis Symposium, July 10-14, 2000, Ghent, Belgium

3. Éva Juhász-Tóth, Tamás Patonay

α-Azido-ketones as Precursors of Versatile Tetrafunctionalized Building Blocks

8th Blue Danube Symposium on Heterocyclic Chemistry, September 24-27, 2000, Bled, Slovenia

4. Attila Kiss-Szikszai, Éva Juhász-Tóth, Zoltán Dinya, Tamás Patonay

Mass Spectrometric Studies of α-Azido-ketones

19th Informal Meeting on Mass Spectrometry, 29 April-3 May, 2001, Noszvaj

5. Éva Juhász-Tóth, Tamás Patonay

Simple Synthesis of Isoxazole Derivatives and Vinyl Azides from α-Azido Ketones

9th Blue Danube Symposium on Heterocyclic Chemistry, June 16-20, 2002, Tatranská Lomnica, Slovak Republic