HUNGARIAN UNIVERSITY OF AGRICULTURE AND LIFE SCIENCES

ENVIRONMENTAL SCIENCES DOCTORAL SCHOOL

Environmentally sound syntheses for the preparation of new *N*-containing heterocyclic frames and their derivatives

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PhD DISSERTATION THESIS BOOK

ALEKSZI-KASZÁS ANNA EDIT

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Doctoral school's:

Name: Hungarian University of Agricultural and Life Sciences

Environmental Sciences Doctoral School

Discipline: Environmental Sciences

Head of the school: Csákiné Prof. Dr. Michéli Erika

DSc, MTA member, Professor, Director of Institute,

Head of Department,

Hungarian University of Agriculture and Life Sciences

Szent István Campus

Institute of Environmental Sciences

Supervisor: Prof. Dr. Nemes Péter

Professor Emeritus,

University of Veterinary Medicine Budapest

Chemistry Department

……. …….

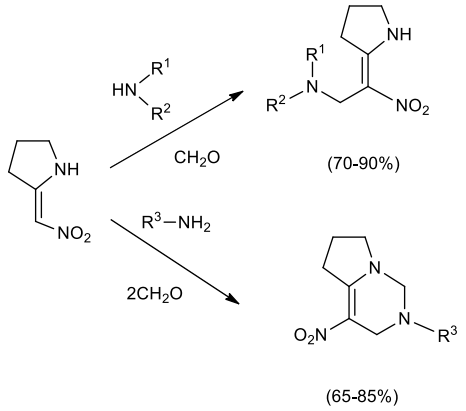
Signature of the Head of Doctoral School Signature of the Supervisor

1 Background and objectives of the work

The research work has been carried out at the Department of Chemistry of the University of Veterinary Medicine, under the direction of Dr. Péter Nemes.

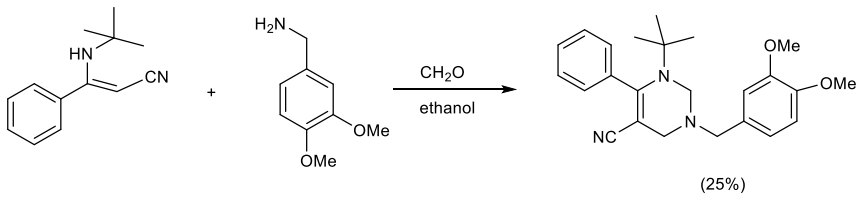
Previous research projects of the Department aimed at the synthesis of new nitrogen-containing polycyclic scaffolds and their derivatives. Several publications have been published on *Mannich*-reactions of push-pull alkenes, electron-withdrawing group activated enamines, are summarized as follows.

The *Mannich*-reaction of nitromethylene pyrrolidine with formaldehyde and secondary amines leads to an aminomethyl derivative. The enamine, with primary amines and 2 equivalent formaldehydes, yielded tetrahydropyrimidine derivatives (**Scheme 1**).



Scheme 1.: *Reaction of nitromethylene pyrrolidine with formaldehyde and secondary/primary amines*

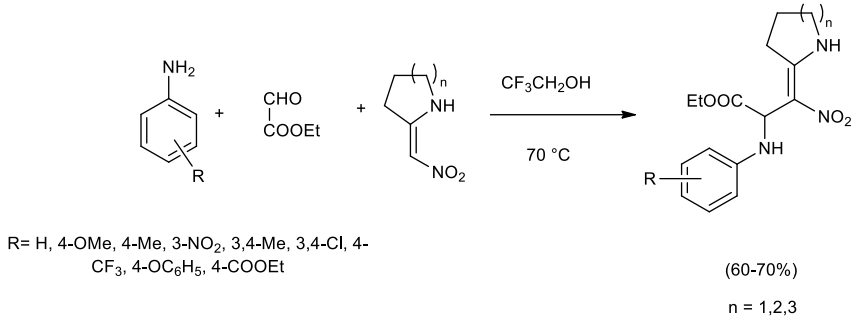
The reaction can also be carried out with other enamines. Open-chain enaminonitrile, gave tetrahydropyrimidines (**Scheme 2**).



Scheme 2.: *Preparation of tetrahydropyrimidine*

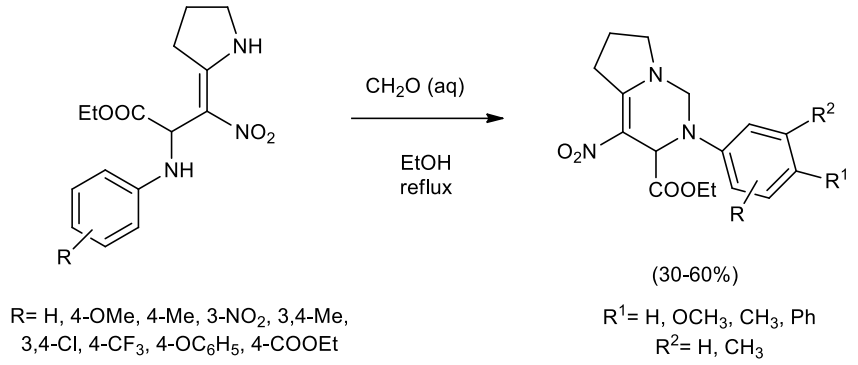
The one-pot procedure of 5-,6- and 7-membered cyclic nitroenamines with various aromatic amines and ethyl glyoxylate resulted in also the desired *Mannich*-type products. Trifluoroethanol as a solvent had a significant effect on the conversion and

thus on the yield due to its special properties: weak nucleophilic character, high polarity and strong hydrogen bond formation potential (**Scheme 3**).



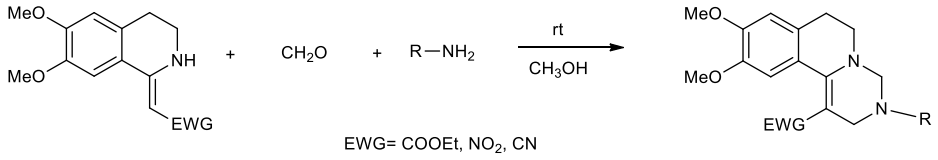
Scheme 3.: *Preparation of Mannich-products by one-pot method*

The *Mannich*-products were then transformed with formalin to produce pyrrolo-pyrimidines (**Scheme 4**.).



Scheme 4.: *Preparation of pyrrolopyrimidines*

Mannich-reaction of tetrahydroisoquinoline skeletal enamines led to tetrahydro-pyrimido-isoquinoline derivatives (**Scheme 5**).



Scheme 5.: *Preparation of tetrahydropyrimido-isoquinoline derivatives*

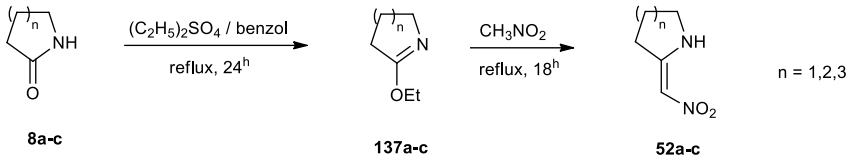
In the present work, I investigated the transformation possibilities of various enamines substituted by electron withdrawing groups in the β-position. My objectives can be summarized as follows:

- Investigation of the reactions of enamines with electrophiles and double electrophiles, with environmental aspects in mind.
- By synthesizing new compounds, we wanted to expand the scope of available derivatives. Furthermore, the targeted compounds can be valuable in preparative chemistry, and they also have potential biological activity based on literature examples, so these new derivatives are of special importance.
- Separation, structural elucidation of stereoisomers, and development of a stereoselective synthesis.
- Selective hydrogen addition of the heterocyclic compounds produced, comparison of different methods, and stereochemical analysis of the products.

2 Materials and methods

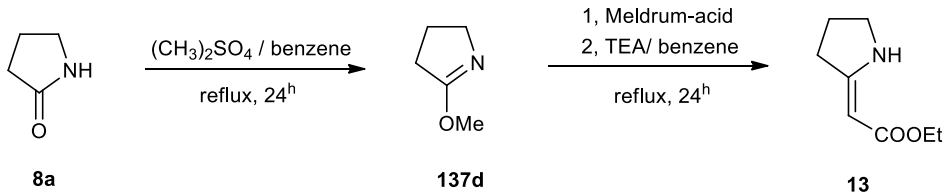
The starting materials were 5-, 6- and 7-membered nitroenamines (**52a-c**) prepared according to literature procedures.

The synthesis consisted of two main steps. The lactams were heated with diethyl sulphate to form the iminoether intermediate, which is then refluxed in nitromethane to obtain the desired nitroenamines (hereinafter referred to as 5-, 6-, 7-NEA) (**Scheme 6**).



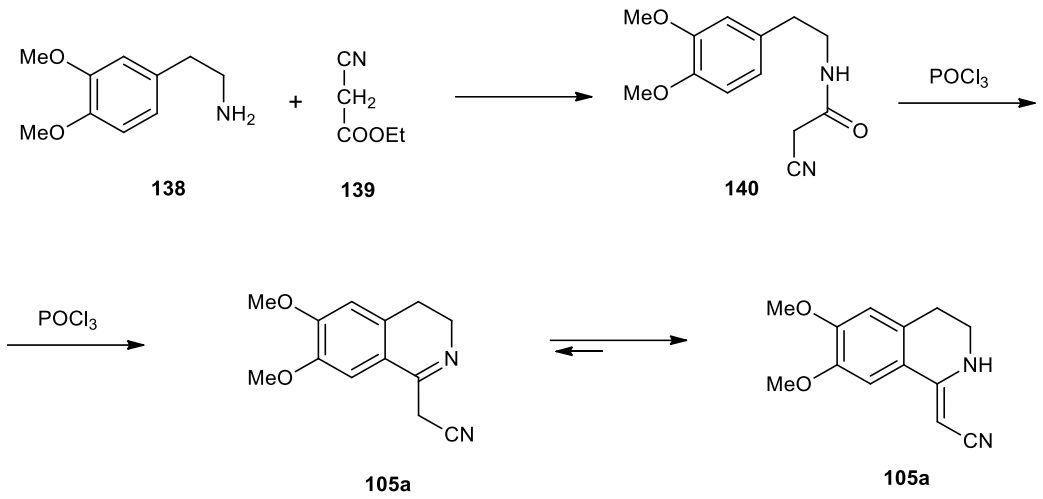
Scheme 6.: *Preparation of push-pull alkenes*

Ethyl 2-(pyrrolidin-2-ilidin) acetate **13** (hereinafter referred *enaminoester* or ENAE), obtained through the iminoether (**137d**) with Meldrum acid (**Scheme 7**).



Scheme 7.: *Preparation of ethyl 2-(pyrrolidin-2-ilidine) acetate (13)*

2-(3,4-dimethoxyphenyl)ethylamine (**138**) and ethyl cyanoacetate (**139**) reaction is the first step of the preparation of 2-(6,7-dimethoxy-3,4-dihydroisoquinoline-1-yl)acetonitrile (**105a**). The formed 2-cyano-N-[2-(3,4-dietoxyphenyl)ethyl]acetamide's (**140**) ring-closing happened with *Bischler-Napieralski* reaction by heating in chloroform with $POCl_3$ (yield 80%) (**Scheme 8**).



Scheme 8.: *Preparation of 2-(6,7-Dimethoxy-3,4-dihydroisoquinoline-1-yl)acetonitrile*

For the room temperature and heated reactions, we used thick-walled flask reactors resistant to pressure up to 10 bar, which were closed by a Teflon plug.

The hydrogenation reactions were carried out in a stainless-steel pressure reactor.

For the single crystal X-ray diffraction measurements different cleaning methods were necessary. The first cleaning step for getting the proper size and quality was column chromatography, followed by several recrystallizations.

The single-crystal X-ray, ECD and VCD measurements were carried out in collaboration with the University of Debrecen.

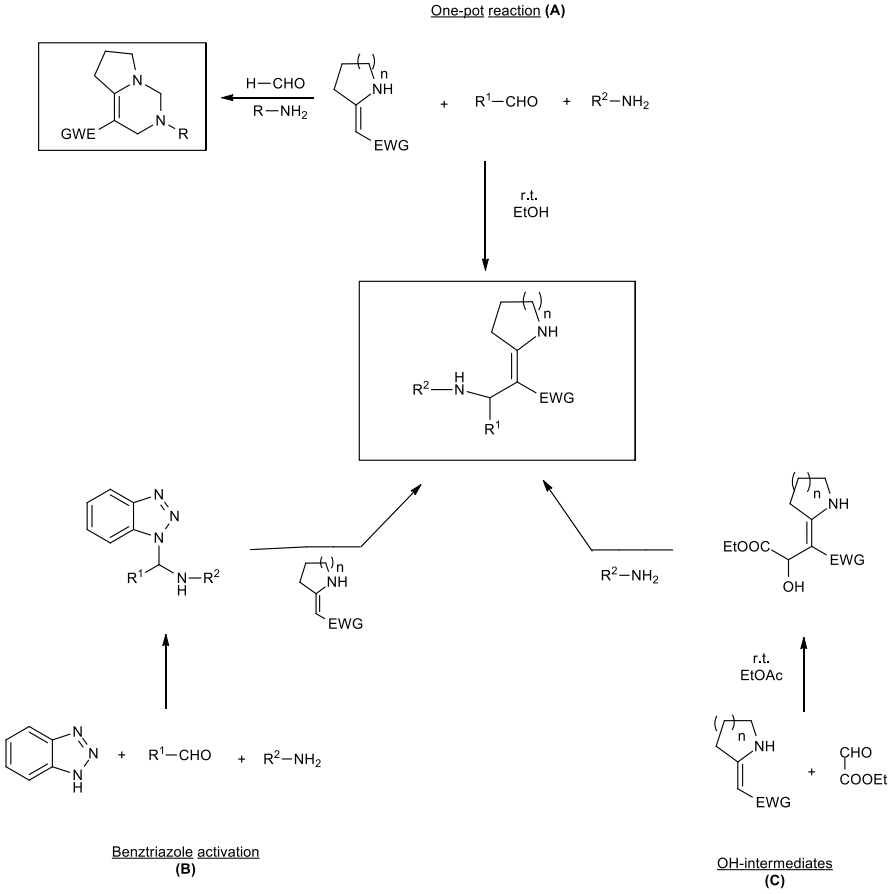
3 Results and discussion

3.1 Mannich-type condensation reactions of push-pull alkenes

In the first phase of the research, we investigate the *Mannich*-reactions of the push-pull alkenes, primary amines and aldehydes and prepared new compounds. These diversely substituted products can form valuable heterocyclic compounds.

Extending the previous research of the Department we planned to prepare new pyrrolo-pyrimidine derivatives in the reaction of enamines, formaldehyde and various amines. We investigated three different reaction paths (**Scheme 9**):

- The *"one-pot"* reactions, **(A)**
- Carried out with benzotriazole activation, **(B)**
- Two-step synthesis via OH-intermediates **(C)**

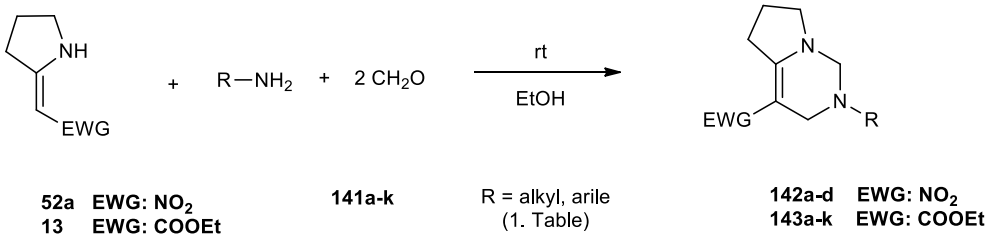


Scheme 9.: *Mannich reactions of push-pull alkenes*

3.1.1 „One-pot" reactions

3.1.1.1 Mannich-reactions of enamines, formaldehyde and primary amines

Double *Mannich*-reactions of 2-nitromethylenepyrrolidine with aliphatic amines and formaldehyde have been described in previous publications. We have set ourselves the production of new *pyrrolo-pyrimidine* derivatives with enaminoester and aromatic amines (**Scheme 10**).



Scheme 10.: *Reaction of nitroenamine and enaminoester with formaldehyde and primary amines*

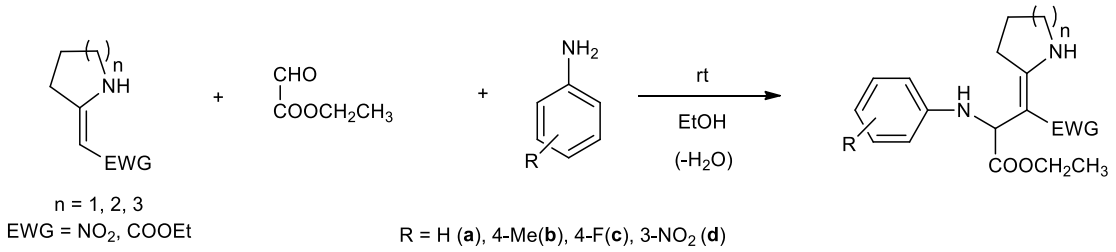
The **13** enaminoester reacted with primary aliphatic amines and formaldehyde formed analogous of pyrimidine derivatives with good yield (**143a-k**). The synthesis of *N*-aryl derivatives was less successful, and 4-methyl-, and 4-methoxyaniline gave the expected compounds (**Table 1**).

	Product	EWG	R	Yield (%)
1.	**142a**	NO_2	Ph	77
2.	**142b**	NO_2	4-MePh	63
3.	**142c**	NO_2	4-MeOPh	72
4.	**142d**	NO_2	2-MeOPh	49
5.	**143a**	COOEt	$CH(CH_3)_2$	82
6.	**143b**	COOEt	$C(CH_3)_3$	61
7.	**143c**	COOEt	CH_2Ph	42
8.	**143d**	COOEt	2-MeOPhCH_2CH_2	64
9.	**143e**	COOEt	3,4-MeOPhCH_2CH_2	77
10.	**143f**	COOEt	cPentyl	68
11.	**143g**	COOEt	cHexyl	70
12.	**143h**	COOEt	N-Bn-piperidin-4-yl	58
13.	**143i**	COOEt	N-Et-piperidin-3-yl	60
14.	**143j**	COOEt	4-MePh	18
15.	**143k**	COOEt	4-MeOPh	29

Table 1.: *Reactions of nitroenamine and enaminoester with formaldehyde and primary amines*

3.1.1.2 *Mannich* -reactions of enamines with ethyl glyoxylate and primary amines

Different nitroenamines/ethyl glyoxylate and anilines give *Mannich*-product in ethanol at room temperature. We could prepare aromatic-, and aliphatic amines as new compounds (**Scheme 11**).



52a-c
13

143a

145-148 a-d

	145	146	147	148
n	1	2	3	1
EWG	NO_2	NO_2	NO_2	COOEt
	a-b	a-c		a-d

Scheme 11.: *Reaction of nitroenamine/enamino ester, ethyl glyoxylate and anilines*

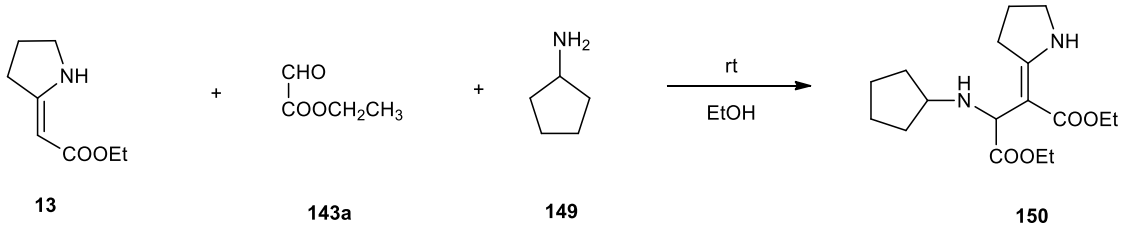
The reactions were carried out in ethanol at room temperature according to the green chemistry aspects.

It was found that the conversion was 100% in ~12 hours with 5-, 6-, 7-nitroenamines as well and the products were isolated with medium production. In properly diluted (0,5 mol/L) system, the clean products were separated from the reaction mixture without further processing or purification (**Table 2**).

	Product	EWG	n	R	Solvent	Yield (%)
1.	**145a**	NO_2	1	H	EtOH	34
2.	**145b**	NO_2	1	4-F	EtOH	40
3.	**146a**	NO_2	2	H	EtOH	74
4.	**146b**	NO_2	2	4-F	EtOH	63
5.	**146c**	NO_2	2	4-Me	EtOH	75
6.	**147a**	NO_2	3	H	EtOH	60
7.	**147b**	NO_2	3	4-F	EtOH	50
8.	**147c**	NO_2	3	4-Me	EtOH	38
9.	**148a**	COOEt	1	H	EtOH	30
10.	**148b**	COOEt	1	4-F	EtOH	57
11.	**148c**	COOEt	1	4-Me	EtOH	61
12.	**148d**	COOEt	1	3-NO_2	EtOH	-
13.	**148d**	COOEt	1	3-NO_2	EtOAc	31

Table 2.: *Production values of Mannich-products (one-pot reaction, room temperature)*

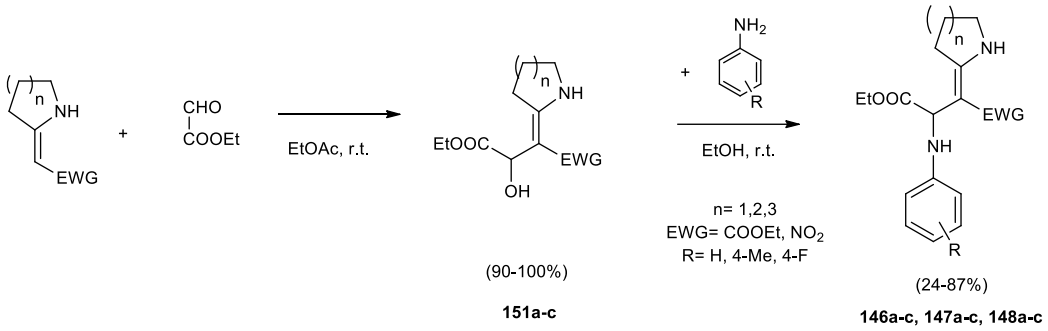
We would have liked to make the reaction with aliphatic amines at the optimal parameters, but it wasn't successful. We tried to carry out the reaction under different reaction conditions using different catalysts. Finally, we got product **150** with 56% yield. (**Scheme 12**).



Scheme 12.: *Preparation of diethyl 2-(cyclopentylamin)-3-(pyrrolidin-2-ilidin)succinate*

3.1.2 Production of *Mannich*-products via addition of intermediate of enamine to ethyl glyoxylate

After the *"one-pot"* method, were hoping the better yield, we produced *OH intermediates* (**151a-c**) and its reaction with anilines furnished the *Mannich*-compounds (**Scheme 13**).



Scheme 13.: 151a-c *Preparation and reactions of the OH intermediate with anilines*

Isolated pyrrolidine-2-ylidenemethanol derivative (**151a**), piperidine-, (**151b**) and azepane (**151c**) intermediates were reacted with anilines, such as 4-Me- and 4-F-aniline. The *Mannich*- products prepared in ethanol at room temperature with medium or less yield (**Table 3**).

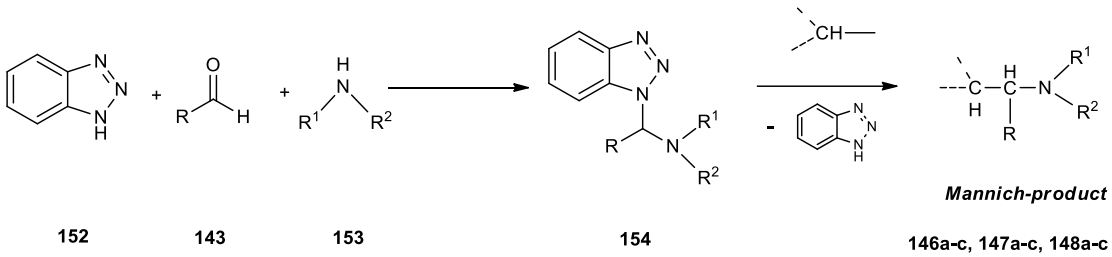
	Product	n	EWG	R	Yield (%)
1.	**146a**	2	NO_2	H	24
2.	**146b**	2	NO_2	4-F	30
3.	**146c**	2	NO_2	4-Me	59
4.	**147a**	3	NO_2	H	87
5.	**147b**	3	NO_2	4-F	25
6.	**147c**	3	NO_2	4-Me	36
7.	**148a**	1	COOEt	H	44
8.	**148b**	1	COOEt	4-F	68
9.	**148c**	1	COOEt	4-Me	52

Table 3.: *Results of production of Mannich-products via OH intermediate*

3.1.3 Syntheses with benzotriazole activation

3.1.3.1 *Mannich*-reactions of enamines with formaldehyde and secondary amines

The moderate yield and synthesizing of new compounds from other amines/aldehydes were the reason for trying Katritzky's benzotriazole *methodology.* We synthetized the necessary adduct from the reaction of benzotriazole, aldehyde and amine, then that was reacted with a CH-active compound to obtain *Mannich*-products (**Scheme 14**).

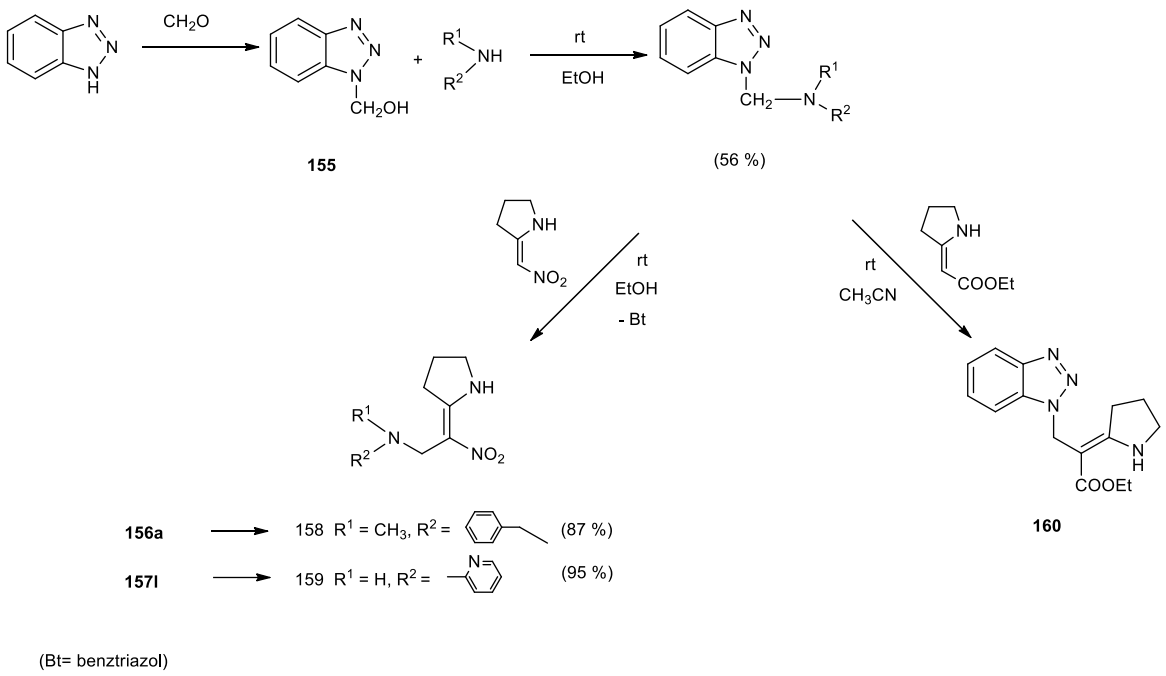


Scheme 14.: *Katritzky's benzotriazole methodology to the production of Mannich products*

The benzotriazole (Bt) easily reacts with starting substances and it has an activating effect.

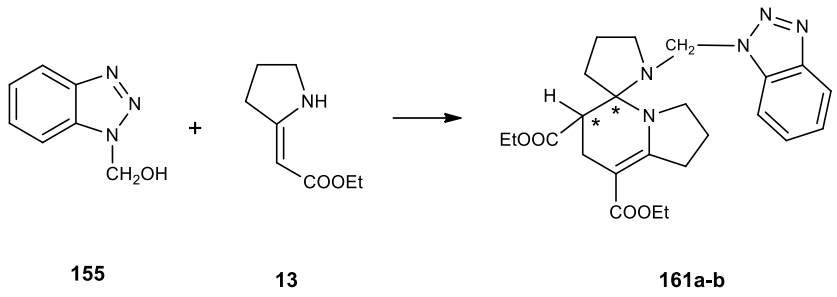
The synthesis was carried out in two steps. Firstly, the benzotriazole was hydroxymethylated with formaldehyde and then it reacted with aromatic amines to give the benzotriazole adduct with good yield. The Bt-adduct produced aminomethylated enamine with nitromethylene-pyrrolidine (95% yield). With *N*-benzyl methylamine the yield was 87%.

The another nucleophilic reagent was the enaminoester. In this reaction an unexpected product, benzotriazolomethyl derivative of the enaminoester **160** was formed (**Scheme 15**).



Scheme 15.: *Reaction of aminomethylbenztriazole with 5-NEA and the formation of benztriazolylmethyl-enaminoester*

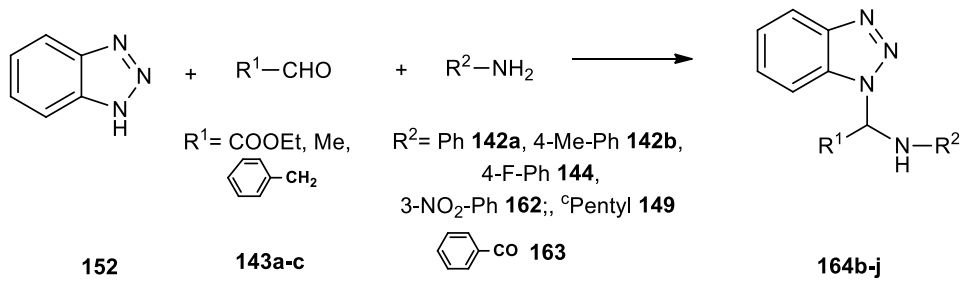
The reaction steps were also performed in reverse order: the 1-hydroxymethylbenzotriazole **155** was reacted with an enaminoester. However, the reaction resulted in an unexpected pair of diastereomer/spiro compounds (**Scheme 16.**).



Scheme 16.: *Preparation of diastereomeric spiro compounds*

3.1.3.2 Preparation of benzotriazole adducts with aldehydes and primary amines

The benzotriazole adducts were prepared with different aldehydes and amines. (**Scheme 17**). The reaction was successful in ethanol at room temperature.



Scheme 17.: *Synthesis of benzotriazole adducts*

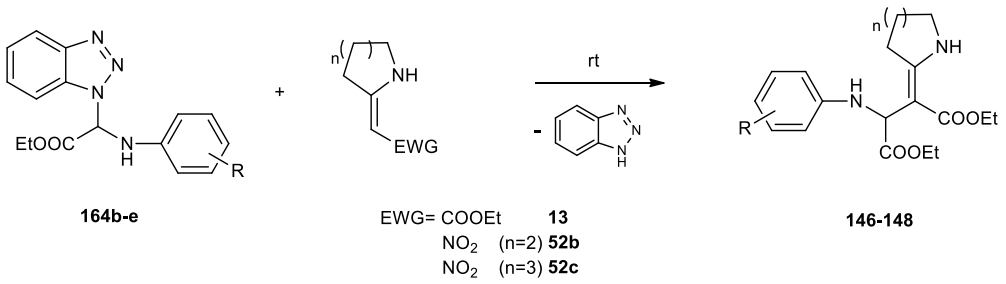
The substituted aromatic amines with ethyl glyoxylate formed the corresponding benzotriazole adducts, with medium yield (41-72%) (**Table 4**).

	Product	**R^1**	**R^2**	**Solvent**	**Temperature**	**Yield (%)**
1.	**164a**	COOEt	Ph	EtOH	RT	41
2.	**164b**	COOEt	4-F-Ph	EtOH	RT	53
3.	**164c**	COOEt	4-Me-Ph	EtOH	RT	72
4.	**164d**	COOEt	3-NO_2-Ph	toluene	reflux	53
5.	**164e**	COOEt	cPentyl	EtOH	RT	69
6.	**164f**	COOEt	Benzamide	toluene	reflux	74
7.	**164g**	CH_3	Benzamide	toluene	reflux	71
8.	**164h**	Bn	4-F-Ph	EtOH	RT	92
9.	**164i**	Bn	4-Me-Ph	EtOH	RT	58
10.	**164j**	Bn	3-NO_2-Ph	EtOH	RT	82

Table 4.: *Production of benzotriazole adducts with various aldehydes and amines*

3.1.4 Production of *Mannich*-compounds via benzotriazole adducts with enamines

In the next phase of my work, we investigated the reactivity of our adducts with enamines, enaminoesters (**Scheme 18**).



Scheme 18.: 164b-e *Reaction of benzotriazole adducts with enaminonitriles* ***52b-c*** *and enaminoester****13***

The experiments were carried out in different green solvents, such as ethanol, polyethylene glycol (PEG) and water. Furthermore, we prepared the reactions on solid heterogeneous phase (Al_2O_3/SiO_2) (**Table 5**).

	Product	R	EWG	n	Solvent	Solid phase (eq)	Yield (%)
1.	**146c**	4-Me-Ph	NO_2	2	PEG-400	-	43
2.	**147c**	4-Me-Ph	NO_2	3	PEG-400	-	81
3.	**148a**	Ph	COOEt	1	H_2O	-	30
4.	**148a**	Ph	COOEt	1	PEG-400	-	15
5.	**148a**	Ph	COOEt	1	EtOH	-	59
	148b	4-F-Ph	COOEt	1	PEG-400	-	37
	148b	4-F-Ph	COOEt	1	EtOH	-	57
6.	**148c**	4-Me-Ph	COOEt	1	PEG-400	-	60
7.	**148c**	4-Me-Ph	COOEt	1	-	Al_2O_3/acidic(1)	35
8.	**148c**	4-Me-Ph	COOEt	1	-	SiO_2 (1)	36
9.	**148c**	4-Me-Ph	COOE	1	EtOH	-	51
12.	**148d**	3-NO_2-Ph	COOEt	1	PEG-400	-	22
13.	**148d**	3-NO_2-Ph	COOEt	1	EtOH	-	31

Table 5.: *Reaction of benzotriazole adducts with enaminonitriles* ***52b-c*** *and with enamino ester* ***13***

3.1.5 Comparison of production methods of *Mannich*-products

Comparing the yields of the same products it can be said that the optimal method for *Mannich*-reactions of push-pull alkenes is the one-pot method. (**Table 6**).

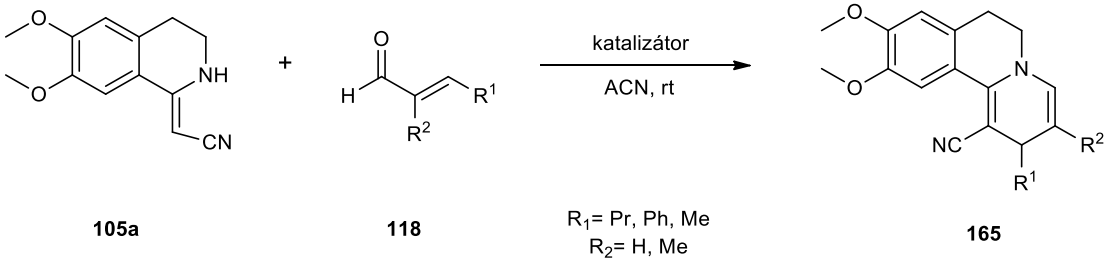
	Product	**n**	**EWG**	**R**	***Benzotriazole adduct (%)***	***One-pot (%)***	***OH intermediate (%)***
1.	**146a**	2	NO_2	Ph	-	74	24
2.	**146b**	2	NO_2	4-F-Ph	-	63	30
3.	**146c**	2	NO_2	4-Me-Ph	43	75	59
4.	**147a**	3	NO_2	Ph	-	60	87
5.	**147b**	3	NO_2	4-F-Ph	-	50	25
6.	**147c**	3	NO_2	4-Me-Ph	81	38	36
7.	**148a**	1	COOEt	Ph	41	44	44
8.	**148b**	1	COOEt	4-F-Ph	37	57	68
9.	**148c**	1	COOEt	4-Me-Ph	60	61	52

Table 6.: *Comparison of the production for each method*

2. Regio- and stereoselective synthesis of benzoquinolizidine derivatives

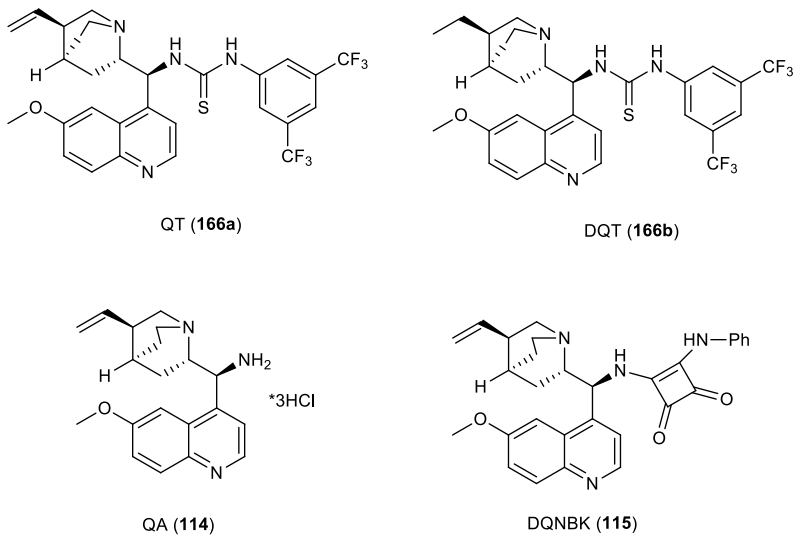
3.2.1 Organocatalytic synthesis

The cinchona bifunctional organocatalysis focused on the enantioselective *Michael*-additions in last few years. Based on this, we tested them at different against in enaminonitrile (**105a**) and α,β-unsaturated aldehydes reactions (**118)** (**Scheme 19.**).



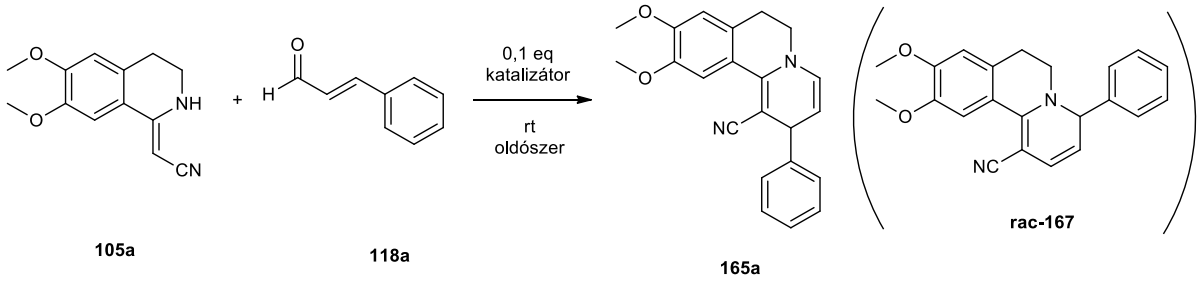
Scheme 19.: *Reaction of enaminonitrile with aldehydes*

The reaction of enaminonitrile and cinnamon aldehyde was investigated with the following organocatalysts (**Scheme 20**).



Scheme 20.: *Structure of investigated bifunctional organocatalysts*

Syntheses were carried out at room temperature with 1.1 mol equivalent cinnamon aldehyde and 0.1 equivalent catalysts (**Scheme 21**).



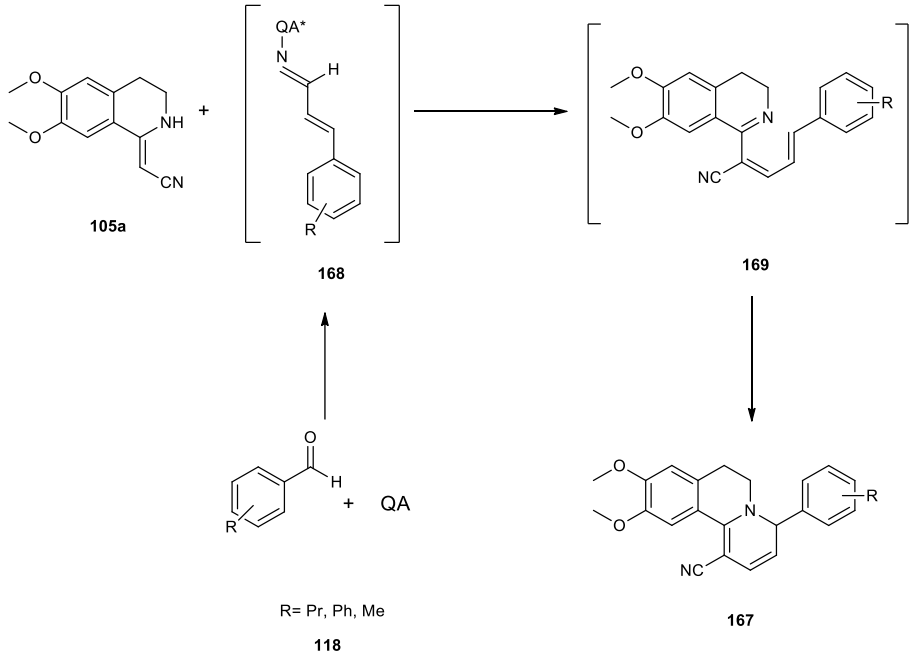
Scheme 21.: *Reaction of enaminonitrile with cinnamaldehyde in the presence of an organocatalyst*

Enantioselective reactions with the hydrochloric acid salt of QA and DQNBK were successful (**Table 7**). In 1.5 hours, 53% yield with 13% *ee* could be achieved. By increasing the reaction time, improvements were also seen in yield and *ee*. In dioxane, the *ee* increased to 29%, but in THF and ethyl acetate it dropped to zero.

	Product	Catalyst	Solvent	Reaction time (h)	Yield (%)	ee (%)
1.	**165a**	QA*3HCl (**114**)	ACN	1,5	53	13
2.	**165a**	QA*3HCl (**114**)	ACN	2	58	18
3.	**165a**	QA*3HCl (**114**)	dioxane	0,5	55	29
4.	**165a**	QA*3HCl (**114**)	THF	1,5	<10	0
5.	**165a**	QA*3HCl (**114**)	EtOAc	1,5	<10	0
6.	**165a**	DQNBK + TFA (**115**)	ACN	8	45	48
7.	**167**	QA + TEA (**114**)	ACN	24	55	0
8.	**167**	QA + TEA (**114**)	CH_2Cl_2	36	61	0

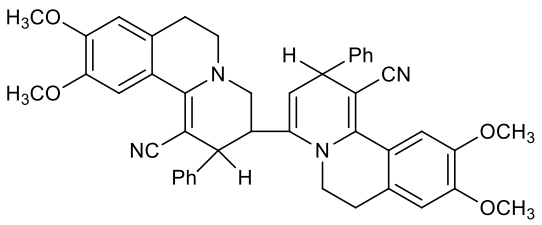
Table 7.: *Syntheses with cinchona bifunctional organocatalys*

It was found that using triethylamine in equivalent amounts to a QA catalyst, the regioselectivity of the reaction was different, and racemic 1,2-benzoquinolyzine derivative was formed by head-head annellation (**Scheme 22**).



Scheme 22.: *Formation of 6,7-dihydro-4H-benzo[a]quinolizine (rac-**167**)*

A heterodimer derivative formed due to trifluoroacetic acid (30% yield) (**Scheme 23**).



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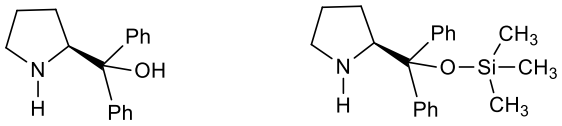
Scheme 23.: *The formed heterodimer*

In the next step we investigated diphenylprolinol-type catalysts (D2PM **113a** and D2PM-TMS **113b**) were expecting a higher *ee* (**Scheme 24**).



(S)-D2PM
113a

(S)-D2PM-TMS
113b

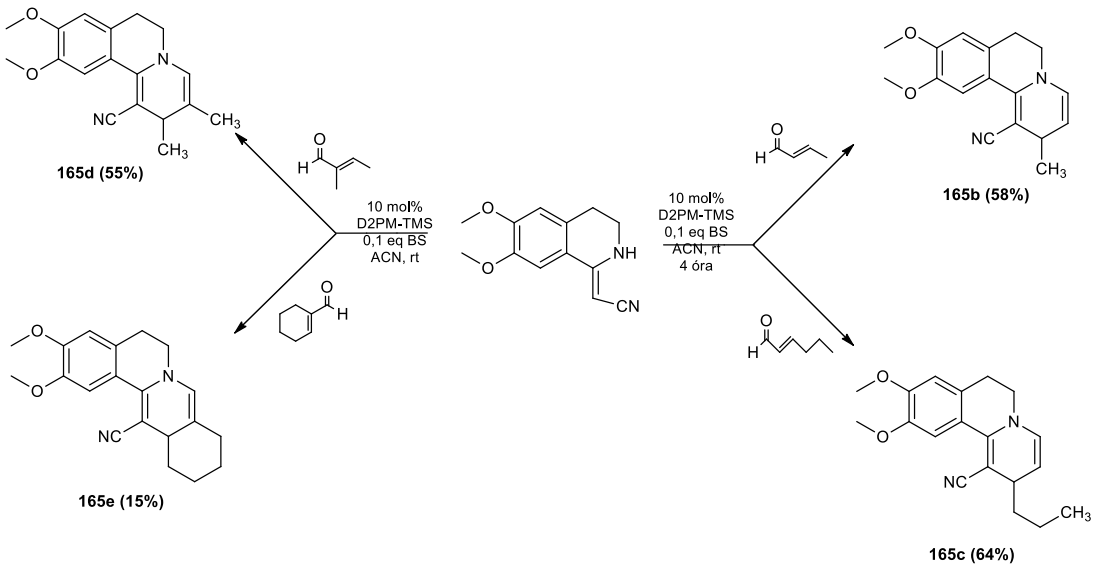
Scheme 24.: *Diphenyl(2-pyrrolidinyl) methanol (**113a**), and diphenyl-(2-pyrrolidinyl)-methanol-TMS (**113b**)*

The reactions were repeated several times under different conditions in different solvents, the main product was 6,7-dihydrobenzoquinolysin. In acetonitrile, the reaction rate at reflux temperature could be significantly increased, but *ee* was decreased. In dioxane at room temperature the *ee* was 82%. The presence of trifluoroacetic acid led to the formation of a contamination, but 0,1 equivalent benzoic acid always increased the reaction rate without decreasing the *ee* (**Table 8**).

	Product	113b (mol %)	Temp. (°C)	Solution	Reaction time (h)	Yield (%)	ee%
1.	**165a**	10	25	ACN	24	48	85
2.	**165a**	10	80	ACN	2	64	68
3.	**165a**	10*	25	ACN	4	58	81
4.	**165a**	30*	25	ACN	24	62	86
5.	**165a**	10*	80	ACN	2	58	76
6.	**165a**	20*	25	dioxane	72	53	88
7.	**165a**	10*	25	dioxane	72	68	92
8.	**165a**	10*	25	dioxane	4	69	82
9.	**165a**	10*	25	EtOAc	72	58	95
10.	**165a**	10*	25	EtOAc	5	56	91

Table 8.: *Reaction of cinnamaldehyde with enaminonitrile in the presence of a D2PM-TMS (**113b**) catalyst. (*: 10mol% benzoic acid)*

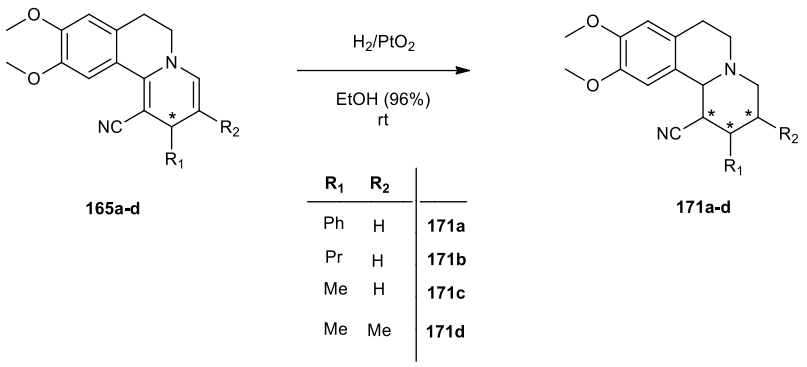
We tried to repeat the reaction with aliphatic aldehydes, α-position substituted aliphatic and alicyclic unsaturated aldehydes with the optimal parameters (**Scheme 25**). With crotonaldehyde and 2-hexenal the expected products formed at 58% and 64% yield. The HPLC separation of the enantiomers was successful with the hydrogenated derivatives. With tiglic aldehyde the yield was good, but with cyclohexane carbaldehyde it was less, in both cases formed racemic product.



Scheme 25.: *Enaminonitrile reaction with aliphatic, unsaturated and alicyclic aldehydes*

3. Hydrogenation of optically active benzoquinolyzines

In the next part of the research the optically active benzenequinolyzidine compounds were hydrogenated in the presence of PtO_2 catalyst (**Scheme 26**). In all cases, the reactions took place with 100% conversion.

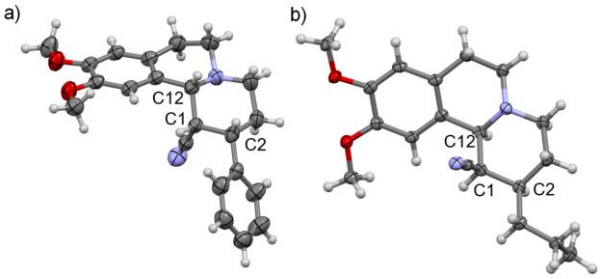


R_1	R_2	
Ph	H	**171a**
Pr	H	**171b**
Me	H	**171c**
Me	Me	**171d**

Scheme 26.: *Hydrogenation of benzoquinolizidine derivatives*

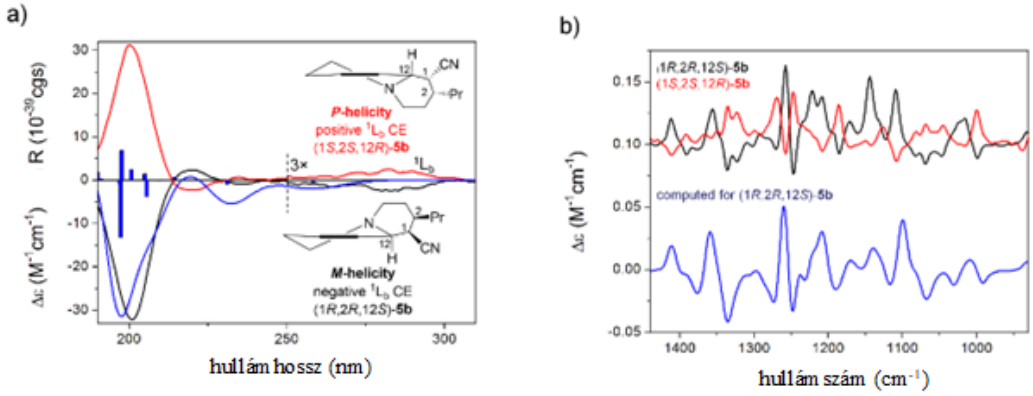
The stereochemistry of the resulting hexahydro analogues was studied. The absolute configuration of the three asymmetry centers was determined by single-crystal X-ray diffraction. We hypothesized that hydrogenation takes place diastereoselectively and the two newly formed asymmetry centers

determined by the configuration of the C-2 carbon atom. Both enantiomers were hydrogenated, and the X-ray diffraction measurements proved our hypothesis.



Scheme 27.: *a, The (R)-**165a** catalytic hydrogenation (1S,2S,12R)-**171a** ORTEP structure (50% probability).*
*b, ORTEP structure of **(1R,2R,12S)-171b** obtained from catalytic hydrogenation of **(R)**-165b (50% probability)*

The electronic circular dichroism (ECD) and vibrational circular dichroism (VCD) measurements were supported by DFT calculations. The measurements and calculated spectra proved the conclusions (**Scheme 28**).



Scheme 28.: *The (1R,2R,12S)-**171b** (black) and (1S,2S,12R)-**171b** (red) experimental, mirror image ECD (a) and VCD (b) spectra of (1R,2R,12S)- **171b** (blue) compared to the spectrum of calculated ECD and VCD.*

4 Conclusions and recommendations

In this dissertation, I describe the synthesis of some new *Mannich*-compounds. In the reactions nitroenamines and enaminoesters were used as CH-active reactants. The reactivity of nitroenamines and enaminoesters were different. The nitroenamines with anilines gave products in good yield, the enaminoesters gave analogue products in low yield. On the other hand, reactions of nitroenamines with primary aliphatic amines produced pyrrolo-pyrimidines in acceptable yields. The synthesis of **145-148 a-c** from enaminoester/enaminonitrile using anilines and ethyl glyoxylate was carried out by one-pot and sequential procedures. The benzotriazole activated method was investigated in two-step sequences. An environmentally friendly version of *Mannich*-reactions was also achieved.

In the domino *Michael* addition-cyclization-dehydration reaction of the 3,4-dihydroisoquinoline-1(2*H*)-ylidene-ethanitrile derivative, cinchona and diphenylprolinol-type organocatalysts were used to make the reaction enantioselective in which 6,7-dihydro-2*H*pyrido[2,1-a]isoquinoline derivatives were formed.

An enantiomeric excess of 95% and a yield of 69% were accessed in the domino reaction with the D2PM-TMS organocatalyst. The products of the domino reactions were hydrogenated with PtO_2 catalyst to produce optically active benzo[c]quinolizidine derivatives with three chirality centers in a diastereoselective method. Their stereochemistry was investigated by single-crystal X-ray diffraction. The ECD and VCD measurements were supported by DFT calculations

In conclusion, alternative green methods were developed and optimized in our research. New compounds were produced enantioselectively using potent organocatalysts. Enantioselective syntheses were reduced the amount of waste generated, increased atomic efficiencies and used green, environmentally benign solvents (mainly ethanol).

5 New scientific results

1. *Mannich*-type condensation reactions of push-pull alkenes were investigated according to three different methods:

- One-pot reactions
- By benzotriazole-adduct
- By production via OH-intermediate

The optimal method of preparing Mannich-products based on the experiments is the one-pot reaction. We prepared new compounds.

2. The regio- and stereoselectivity of organocatalytic reactions of 1-cyanomethylenetetrahydroisoquinoline and α,β-unsaturated aldehydes was investigated. Several catalysts were tested under different reaction conditions. The highest enantiomeric excess was obtained in acetonitrile with 10 mol% of a proline-type catalyst ((S)-D2PM-TMS) in combination with 10 mol% of benzoic acid (BA).

The developed enantioselective synthesis was successfully extended to aliphatic aldehydes, and the cascade reaction was successfully performed with 2-hexenal and crotonaldehyde.

3. The optically active benzoquinolyzidine derivatives were hydrogenated diastereoselectively in the presence of PtO_2 catalyst.

In collaboration with the University of Debrecen, the absolute configurations of the three asymmetry centers of the hexahydro analogues were determined by single-crystal X-ray diffraction and DFT-VCD and TDDFT-ECD calculations.

6 Publications

1. Full-text, peer-reviewed scientific publications in scientific journals (accepted for publication)

1.1 In a foreign language journal with impact factor (according to WEB OF SCIENCE):

Alekszi-Kaszás, Anna; Käfer-Beke, Klára; Varga, Tamás R.; Bényei, Attila; Kovács, Tibor; Mándi, Attila; Kurtán, Tibor; Simon, András; Nemes, Péter

Regio- and Stereoselective Synthesis of Benzoquinolizidines

CHEMISTRYSELECT 7: 9 Paper: e20210428, 6 p. (2022),

DOI: https://doi.org/10.1002/slct.202104286, **IF: 2.23** (2022)

Nagy, Daniel; Pilipecz, Mihaly V.; Kiss, Laszlo A.; Alekszi-Kaszas, Anna; Simon, Andras; Schlosser, Gitta Z.; Nemes, Peter; Varga, Tamas

Synthesis of 2-aryl-1,2,4-triazol-3-one derivatives from beta-nitroenamines

SYNTHETIC COMMUNICATIONS 51: 13 pp. 1956-1962, 7 p. (2021)

DOI: https://doi.org/10.1080/00397911.2021.1913504 **IF: 2.007** (2021)

Alekszi-Kaszás, Anna; Nemes, Péter; Tóth, Gábor; Halász, Judit; Scheiber, Pál

Mannich condensations of activated cyclic enamines

SYNTHETIC COMMUNICATIONS 48: 16 pp. 2099-2111, 13 p. (2018)

DOI: https://doi.org/10.1080/00397911.2018.1484488; **IF: 1.439** (2018)

4. Publications in Congress publications (in printed form or on electronic media - only for ISBN, ISSN or other certified publications)

4.3. One-page abstract in foreign or in Hungarian language, based on the lecture or poster presented, in an edited scientific journal or a special issue thereof

Nagy, Dániel; Alekszi-Kaszás, Anna; Kiss, László; Pilipecz, Mihály; Varga, Tamás
1,2,4-triazol-3-onok szintézise β-nitro-enaminból
In: Sótonyi, P.; Gálfi, P.; Vörös, K.; Magyar, T. (szerk.) Akadémiai beszámolók (2019) Paper: &Konferenciaközlemény

Alekszi-Kaszás, Anna ; Beke, Klára ; Nemes, Péter
Benzokinolizinek enantioszelektív szintézise
In: Sótonyi, P.; Gálfi, P.; Vörös, K.; Magyar, T. (szerk.) Akadémiai beszámolók
Budapest, Magyarország: Állatorvostudományi Egyetem (2019) p. 10, 1 p.
ISBN: 978-963-7149-29-0