

B 4123

Ph.D. Thesis

**Application of  $\gamma$ -oxocarboxylic acids and amino acid  
derivatives for the preparation of heterocycles;  
retro Diels-Alder reactions**

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## Introduction and aims

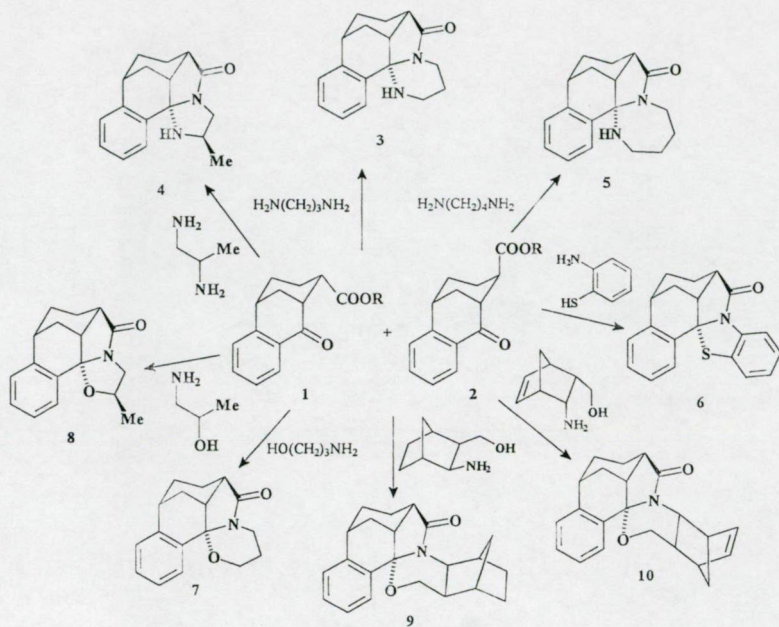
The condensation of aliphatic and cyclic  $\gamma$ - and  $\delta$ -oxocarboxylic acids with bi-functional reagents (aminoalcohols, diamines and aminothiols) is one of the main research topics at the Institute of Pharmaceutical Chemistry, University of Szeged. A successful, mild retro Diels-Alder (RDA) process has been developed for the preparation of heterocycles containing one or more fused rings from norbornene amino acids, when the parent heterocycles built on cyclopentadiene are heated to their melting points or boiled in solvents to yield compounds which have a heteroaromatic or quasi-heteroaromatic character.

The present work deals with the preparation of heterocycles from newly synthesized  $\gamma$ -oxocarboxylic acids. The reactions of *diendo*- and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-hydrazides or 2-aryl-1-cyclohexanecarboxylic acid with ethyl 2-(2-oxocyclopentyl)acetate, followed by an RDA process, have led to a number of derivatives. A new method has been developed for the synthesis of heterocycles in a double RDA reaction. The application of furan as a diene instead of cyclopentadiene allowed the formation of *non-conjugated* heterocycles.

The syntheses were carried out in the usual preparative way on a preparative scale. The compounds were separated and purified by crystallization and/or column chromatography. The new compounds were characterized by their melting point, IR and NMR data, elemental analysis and in some cases mass spectrometry. Occasionally, X-ray crystallography was used. The ratios of some isomeric mixtures were measured by HPLC analysis.

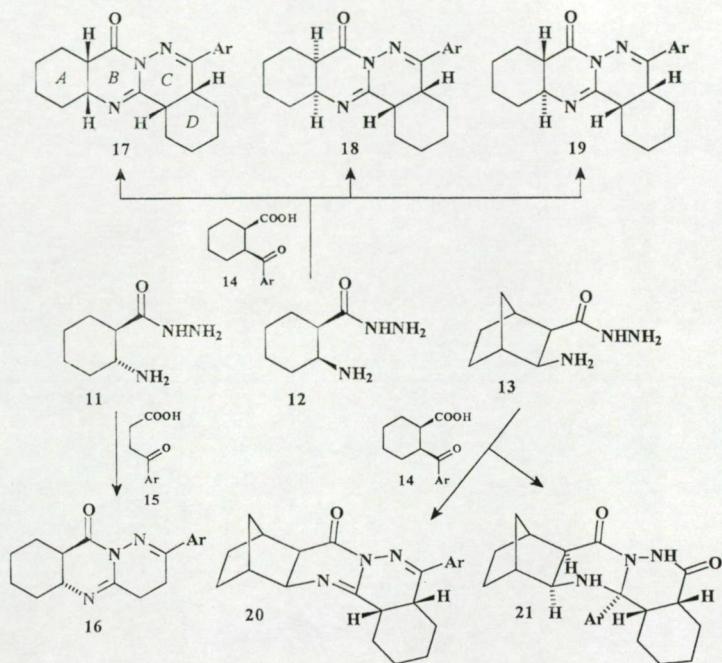
## Results and Discussion

1. Stereoisomeric mixtures of oxoesters **1** and **2**, synthesized from 4-phenylcyclohexane-1,2-dicarboxylate *via* Friedel-Crafts acylation and intramolecular cyclization, were hydrolysed and cyclized with bidentate nucleophiles to penta-, hexa- and heptacyclic indole derivatives **3-10** (Scheme 1). NMR measurements and X-ray analysis of the polycyclic compounds revealed that the cyclization requires an *equatorial* carboxylic group (**1**). Compound **2** containing an *axial* carboxyl was isomerized to **1** during the reactions in basic media. These fused systems consist of 16-22 carbons and 2 hetero atoms, but possess only limited conformational mobility.



Scheme 1

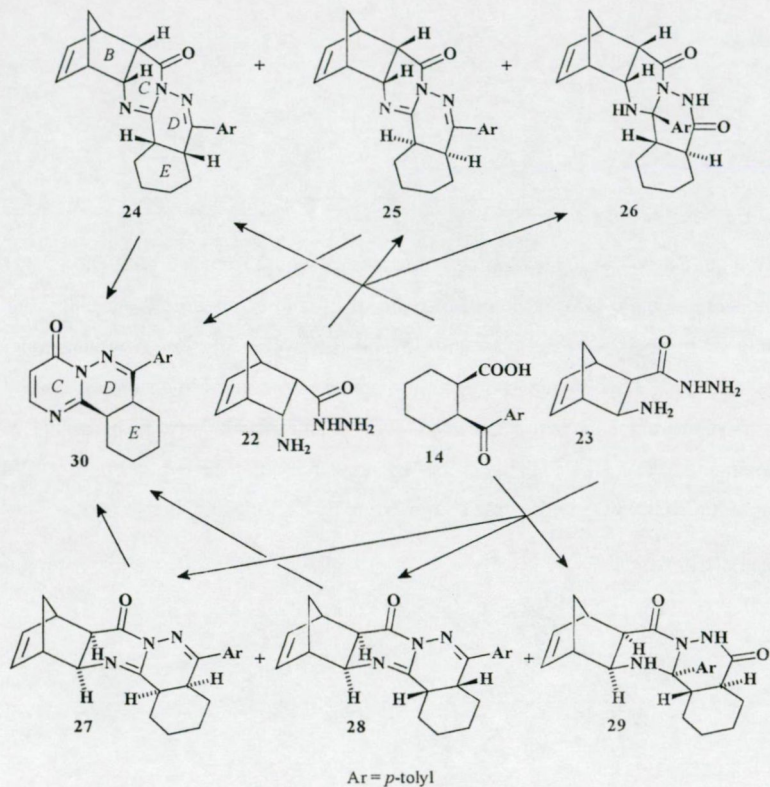
2. The cyclizations of the anthranilic hydrazides **11-13** with *cis*-2-toluoyl-1-cyclohexanecarboxylic acid (**14**) or 3-(*p*-chlorobenzoyl)propionic acid gave phthalazino[1,2-*b*]quinazolines **17-19**, pyridazo[6,1-*b*]quinazoline **16**, the *diexo* norbornane analogue **20** and bisacyl derivative **21** (Scheme 2). Compounds **17** and **18** contain 2 *cis*-fused cyclohexane rings *A* and *D*, with the difference that either the annelational hydrogens at the *A/B* and *C/D* fusions are all *cis*, **17**, or the 2 at the *A/B* fusion and the 2 at the *C/D* fusion are *trans*, **18**. In **19**, the *A/B* rings are *trans*, while the *C/D* rings are *cis*, *i.e.* the ring closure takes place with isomerization of the starting hydrazide **12**.



Ar = *p*-chlorophenyl (15 and 16) or *p*-tolyl (14 and 17-21)

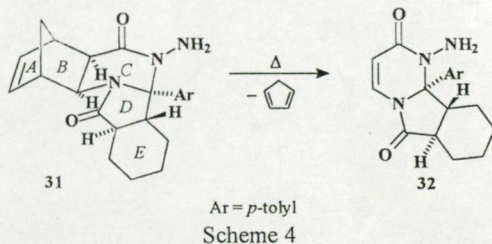
Scheme 2

3. The reactions of *dien*do- and *di*exo-3-aminobicyclo[2.2.1]hept-5-ene-2-hydrazides (22 and 23) with oxocarboxylic acid 14 yielded partly saturated methylene-bridged phthalazino[1,2-*b*]quinazolinones 24, 25 and 27, 28 and phthalazino[1,2-*b*]quinazolidinediones 26 and 29. On heating, the separated diastereoisomers 24, 25 and 27, 28 underwent retrodiene decomposition: cyclopentadiene split off to yield the oxypyrimido[2,1-*a*]phthalazine 30 (Scheme 3). The *B/C* and *D/E* annelational hydrogens of compounds 24 and 27 are on the same side of the condensed pentacyclic skeleton. The *D/E* ring annelation of the accompanying bisacyl compounds 26 and 29 is *trans*.

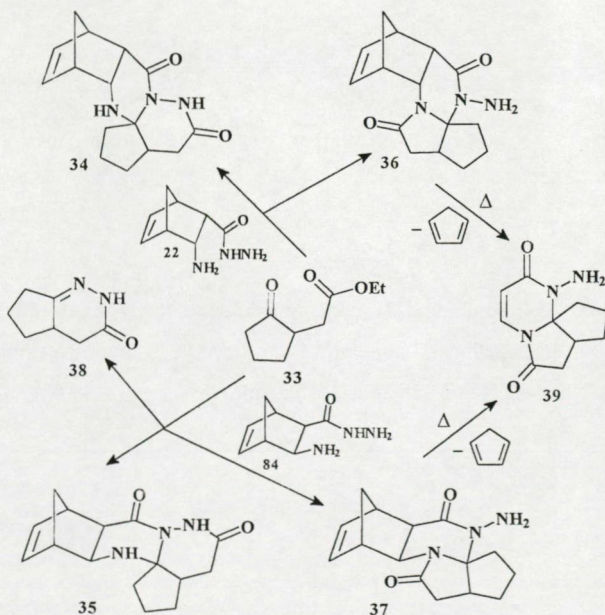


Scheme 3

As a by-product, compound 31 containing a saturated *trans*-isoindolone part was isolated from the reaction mixture of 14 and 23. On heating, 31 furnished 32, cyclopentadiene being cleaved off in an RDA reaction.

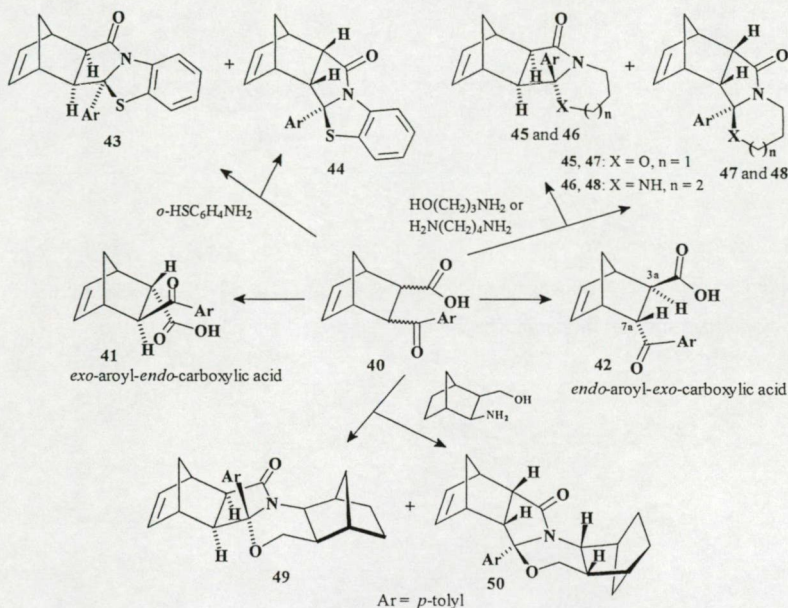


4. The *diendo*- and *diexo*-aminohydrazides **22** and **23** reacted with ethyl 2-(2-oxocyclopentyl)acetate (**33**) to yield a mixture of **34** and **36** or **35**, **37** and **38**. After separation of bisacyl hydrazides **34** and **35** and the cyclopenta-fused pyridazinone, compounds **36** and **37** containing a free amino group were heated to decomposition by the loss of cyclopentadiene to give the *N*-aminocyclopenta[2,3]pyrrolo[1,2-*a*]pyrimidine (**39**) (Scheme 5). This is the first example among RDA reactions of the preparation of a derivative with a free amino group by cycloreversion.



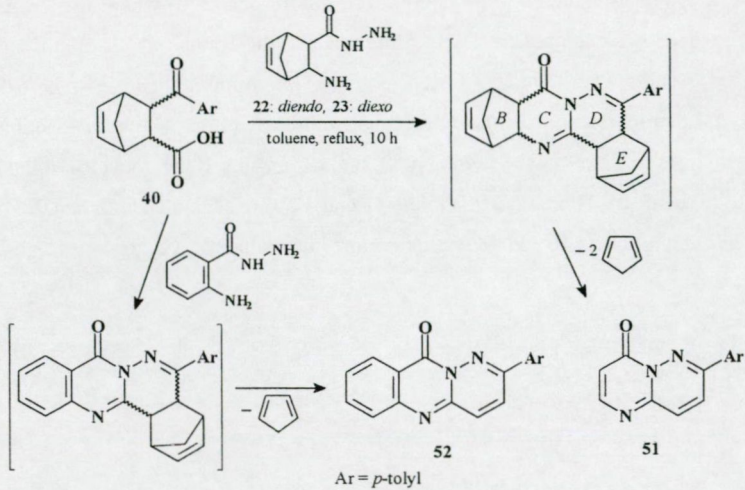
Scheme 5

5. A ready isomerization of the aroyl group occurred when the *trans*-aroylacrylic acid-cyclopentadiene Diels-Alder adduct **40** containing a mixture of oxocarboxylic acids **41** and **42**, was reacted with *o*-aminothiophenol, 3-amino-1-propanol, 1,4-diaminobutane or *diexo*-norbornane-aminoalcohol. All these reactions yielded a mixture of *diexo*- (**43**, **45**, **46** and **49**) and *diendo*-fused heterocycles (**44**, **47**, **48** and **50**) (Scheme 6). The diastereoisomers **41** and **42** were separated and the ratio of the oxoacids and products **46** and **48** was determined by using HPLC.



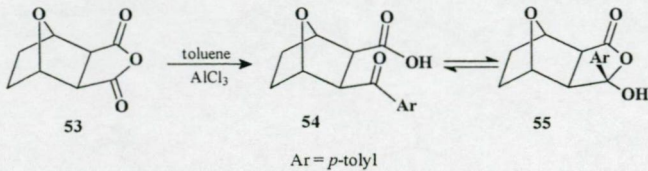
Scheme 6

6. When the *diendo*- **22** or *diexo*-aminohydrazone **23** was boiled in toluene with a mixture of oxocarboxylic acids **40**, the pyrimido[1,2-*b*]pyridazine **51** was obtained directly in a double RDA process, when 2 cyclopentadienes split off the parent molecule. The reaction of anthranilic hydrazide and **40** furnished the benzo-fused analogue **52** (Scheme 7).



Scheme 7

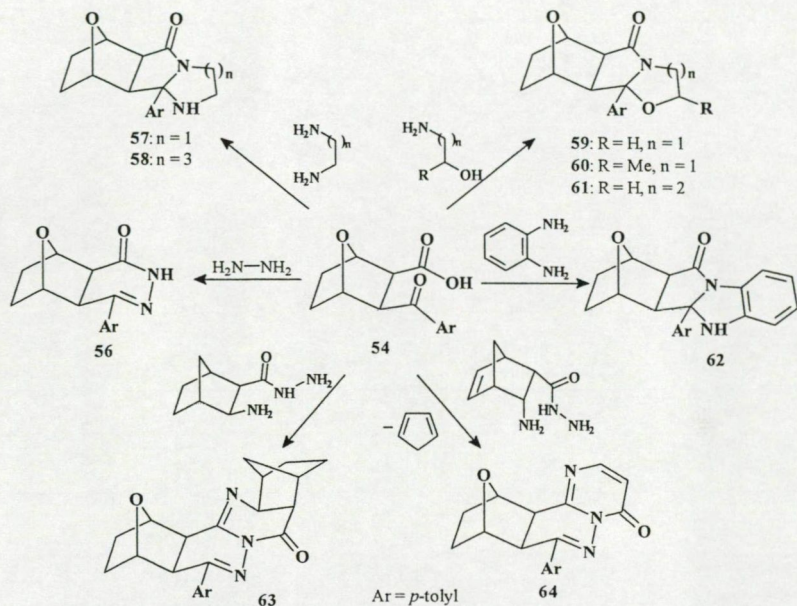
7. The *diexo*-7-oxanorborene-2,3-dicarboxylic anhydride **53** was transformed with toluene/ $\text{AlCl}_3$  to the oxocarboxylic acid **54**. Compound **54** exists as a mixture with its cyclo tautomer **55** (Scheme 8).



Scheme 8

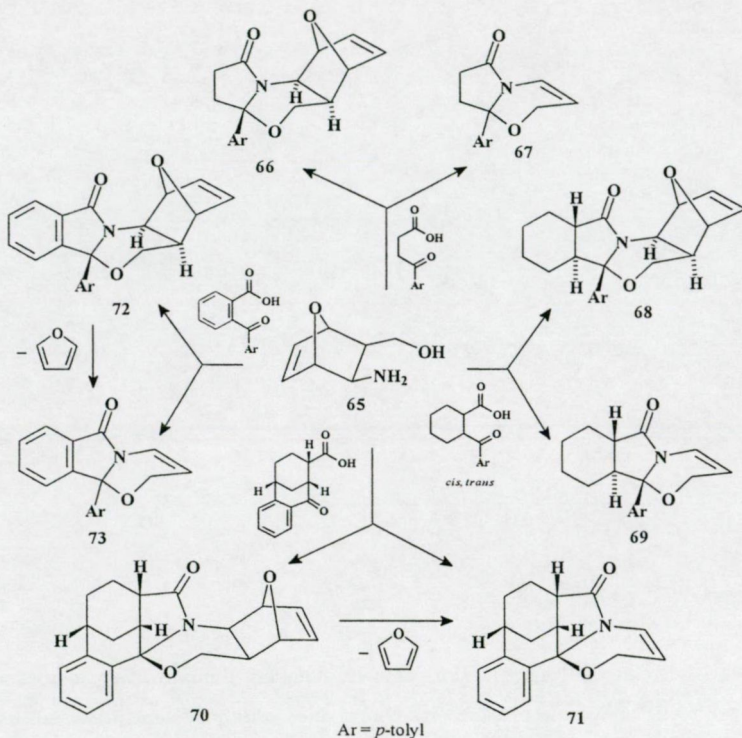
The 3-*exo-p*-toluoyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (**54**) was reacted with hydrazine, diamines and aminoalcohols and resulted in oxygen-bridged isoindoles and phthalazines **56-64** (Scheme 9).





Scheme 9

8. After ammonolysis and Hoffmann degradation, the *diexo*-7-oxanorborene-2,3-dicarboxylic anhydride prepared by Diels-Alder addition from furan and maleic anhydride was transformed to the aminoacid. On reduction with  $\text{LiAlH}_4$ , the aminoalcohol **65** was obtained. From this, with oxocarboxylic acids, *diexo*-oxanorborene-fused products (**66**, **68**, **70** and **72**) and their RDA derivatives, 1,3-oxazines (**67**, **69**, **71** and **73**), were formed (Scheme 10). When the isolated **70** and **72** were boiled in chlorobenzene, the [1,3]oxazinoisindoles **71** and **73** were obtained in good yields. The results show the advantage of the application of the furan instead of cyclopentadiene: 1,3-oxazines which have no oxo, dioxo or thioxo groups can be prepared in this way.



Scheme 10

### Publications related to the Ph.D. thesis

- I. Gábor Bernáth, **Ferenc Miklós**, Géza Stájer, Pál Sohár, Zsolt Böcskei and Dóra Menyhárd:  
 Synthesis and stereochemistry of saturated or partially saturated pyridazino[6,1-*b*]-, and phthalazino[1,2-*b*]quinazolinones  
*J. Heterocycl. Chem.* **35**, 201-205 (1998) IF 0.696
- II. **Ferenc Miklós**, Ferenc Csende, Géza Stájer, Pál Sohár, Reijo Sillanpää, Gábor Bernáth and József Szünyog:  
 Synthesis and structure of methanobenzocyclooctene derivatives  
*Acta Chem. Scand.* **52**, 322-327 (1998) IF 1.257

- III. Ferenc Miklós, Géza Stájer, Pál Sohár, Gábor Bernáth and Reijo Sillanpää:  
Transformation of oxomethanobenzocyclooctenecarboxylic acids to pyrrolidinone-fused penta-, hexa- and heptacyclic hetero compounds  
*Heterocycles* **48**, 1407-1414 (1998) IF 0.831
- IV. Ferenc Miklós, Géza Stájer, Pál Sohár and Zsolt Böcskei:  
Double retro Diels-Alder reaction applied for preparation of a pyrimido[1,2-*b*]pyridazine  
*Synlett* **2000**, 67-68 IF 2.763
- V. Pál Sohár, Ferenc Miklós, Antal Csámpai and Géza Stájer:  
Preparation of pyrimido[2,1-*a*]phthalazines and an aminopyrimido[2,1-*a*]isoindole by retro Diels-Alder reaction  
*J. Chem. Soc., Perkin Trans. 1* **2001**, 558-564 IF 2.208
- VI. Géza Stájer, Ferenc Miklós, Pál Sohár and Reijo Sillanpää:  
Preparation of 9-amino-1,9-diazatricyclo[6.4.0.0<sup>4,8</sup>]dodecane-2,10-dione by a retro Diels-Alder reaction  
*Eur. J. Org. Chem.* **2001**, 4153-4156 IF 2.193
- VII. Ferenc Miklós, Pál Sohár, Antal Csámpai, Reijo Sillanpää, Mária Péter and Géza Stájer:  
*endo*↔*exo* Isomerization and application of aroylnorborenecarboxylic acids for stereoselective preparation of heterocycles  
*Heterocycles* **57**, 2309-2320 (2002) IF1.045
- VIII. Ferenc Miklós, Iván Kanizsai, Steffen Thomas, Erich Kleinpeter, Reijo Sillanpää and Géza Stájer:  
Preparation and structure of *diexo*-oxanorbomane-fused 1,3-heterocycles  
*Heterocycles* **63**, 63-74 (2004) IF 1.045
- IX. Ferenc Miklós, Anasztázia Hetényi, Pál Sohár and Géza Stájer:  
Preparation and structure of *diexo*-condensed norbornane heterocycles  
*Monatsh. Chem.* **135**, 839-847 (2004) IF 0.813
- X. Géza Stájer, Ferenc Miklós, Iván Kanizsai, Ferenc Csende, Reijo Sillanpää and Pál Sohár:  
Application of furan as a diene. Preparation of condensed 1,3-oxazines by retro Diels-Alder reaction  
*Eur. J. Org. Chem.* **2004**, 3701-3706 IF 2.194

Total impact factor 15.05