Synthesis and skeleton rearrangement of condensed pyridazinones and conformational analysis of the medium ringmembered products

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1. History and objectives

1.1. Literary history of the medium-membered systems

The following narrow range of the executed research of Kormendy in 1980s, my supervisor, Antal Csámpai and András Szabó in the middle of 1990s, forms the direct history of my investigitions performed in range of the fused pyridazinones[1,2,3]. The tricyclic zwitterions (**3a,b**) were prepared with ring closing of the aminoalcohol derivatives (**2a,b**) of 4-chlorophthalazin-1(2*H*)-one (**1**) under acidic condition. The treatment of the two ring homologs, with acetic anhydride at reflux temperature, led two different products. The transformation of **3a** to 2,3-dihydrophthalazine-1,4-dione derivative **4** can be defined with acylation of N1 atom of imidazole ring and nucleophilic attack of the acetate ion at the amidium centre followed by ring opening linked with N→O acylmigration. In contrast, **3b** undergoes with boiling acetic anhydride and propionic anhydride such ringtransfromations while the reagent incorporated in the sceleton of the tetracyclic products (**5a,b**)[2]. This interesting transformation was interpreted by the primary addition of the enol/enolate form of the anhydrides on the amidium centre, followed by acylation of the lactam part of the pyridazinone ring linked with fission, and intramolecular acylation of N1 atom of the tetrahydropyrimidine ring. The reaction carried out with propionic anhydride, proved to be diastereospeciphic. The methyl group in *exo*-position containing **5b** was isolated as single product.

Körmendy and co-workers observed firstly the base catalized ring expansion of the **5** type tetracycles (Figure 1). The path of the 10% watery $NaHCO_3$ solution induced reaction was defined by the fission of the imid involving the N3 atom in the pyrazole ring[1]. The *trans*-annular ring opening, following the cleavage of the acyl group, led to the pyrazolobenzodiazoninones (**6a,b**), while according to the idea of the authors, the fission of the C2-N3 bond provided the tricyclic carboxylic acids (**7a,b**). The constitution and the space structure of the recent compounds and **6a,b** weren't examined. During my work, I carried on these researches.

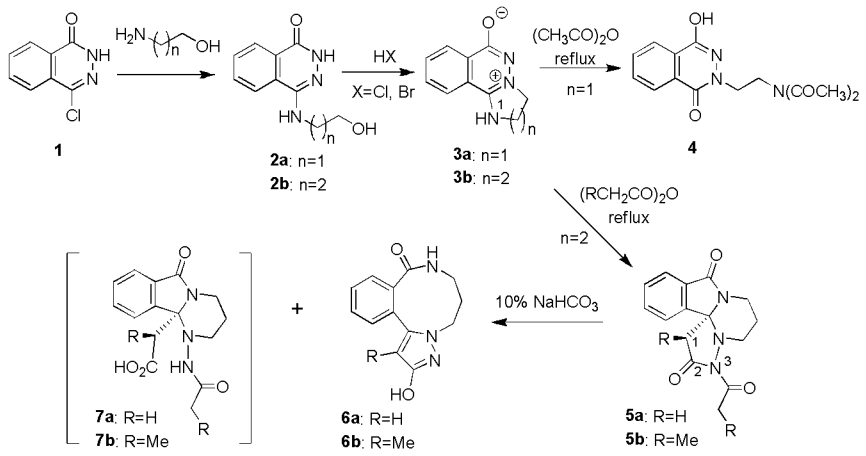

Figure 1

[1] Körmendy, K.; Ruff, F.; Kövesdi, I. *Acta Chim. Hung.* **1986,** *125*, 415–426.

[2] Körmendy, K.; Kálmán, A.; Koritsánszky, T.; Kövesdi, I.; Sohár, P.; Ruff, F. *Acta Chim. Hung.* **1986,** *123*, 15-29.

[3] Szabó, A.; Csámpai, A.; Körmendy, K.; Böcskey, Zs. *Tetrahedron* **1997**, *53*, 7021-7034.

1.2. Synthesis of (S_p)-2-formylferrocene-1-carboxylic acid precursor

Kagan and his co-workers proceed from ferrocenecarboxaldehyde (**8**). It can't be lithiated, because the alkylanion is added to the formyl group and the corresponding carbinol is formed, therefore the formyl group must be masked in two steps. Firstly **8** was converted to dimetoxymethylferrocene (**9**) with trimethyl orthoformate, applying acid catalysis, then in the second step it was converted to (2*S*,4*S*)-4-(hydroxymethyl)-2-ferrocenyl-1,3-dioxane [**(*S*,*S*)-10,** Figure 3] with (S)-(-)-1,2,4-butanetriol, applying acid catalysis. **(*S*,*S*)-10** can't be lithiated, because it has free OH group. It was deprotonated with NaH in dry THF, then the alcoholate salt was treated with iodomethane (Williamson-ether synthesis). The formed ferrocenecarboxaldehyde is masked by a chiral protecting group. (2*S*,4*S*)-4-(methoxymethyl)-2-ferrocenyl-1,3-dioxane **(*S*,*S*)-11** was lithiated with *tert*-buthyllithium[4].

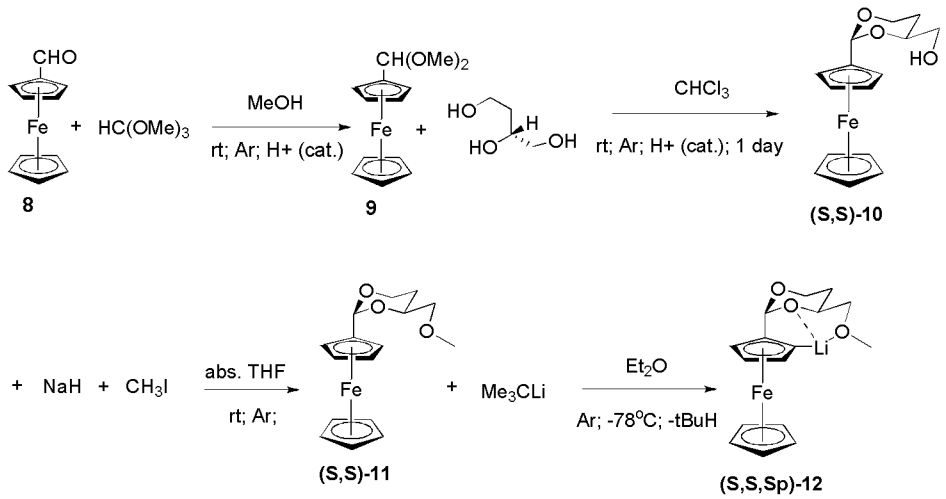

Figure 2

[4] Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan*, H., B. *J. Org. Chem.* **1997**, *62*, 6733-6745.

2. Publicated own results

2.1. Benzene-, pyridine- and naphtocondensed middle-sized systems

At the beginning of my synthetic work I carried out the triazapentalenodindanone→pyrazolobenzodiazocinones transformations, so a series of new pyrazolobenzodiazocinones were prepared. In addition the range of pyrazolobenzodiazocinones was enlarged with the 1-phenyl derivative (Figure 4), which was prepared directly from the zwitterion, using boiling phenylacetic anhydride. The intermedier triazaindenoinden underwent in spontaneous ring enlargement under the employed conditions. The spatial structure and the conformational stability of the differently substituted ring systems were studied in details with DNMR measurements and solvent model (IPCM) also containing quantum chemical method [B3LYP/6-31G(d,p)]. In two and three steps taking place reactions measured and theoretical calculated activating free energy values are excellent

consistent with each other. I experienced that, in position 1 methyl- and phenylsubstituated pyrazolobenzodiazoninoes were rigid even at high temperature, but in contrast the R=H substituent didn't prevent the flipping of the pyrazol ring, the conformational chirality possessing ring system racemized at a temperature not to much higher than room temperature. The conformational flexibility of the varieties of the 1-Me and 1-H substituted less ringmembered pyrazolobenzodiazocins (R^2=R^3=Me) didn't show big differences, but the ring system is rigider, so these models can be forced to racemize just between 80°C and 90°C.

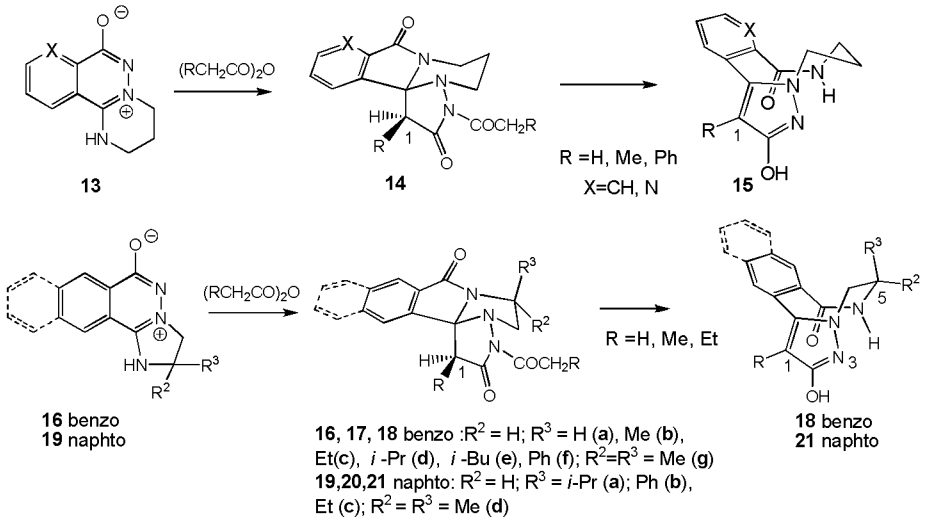

Figure 3

I tried to bridge the diallyl derivative of a pratically completely rigid benzodiazonine **22** with RCM reaction using Grubbs II catalyst (Figure 4), but instead of the bridging, according to the theoretical calculations for the strained ring system leading transformation, deallylation and olefin isomerization took place. The bridging was carried out with dialkylation using 1,3-*bis*-bromomethylbenzene as reagent and NaH as base, the formed ring system (**26**) showed just a little strain according to the DFT calculations too. According to the X-ray diffraction and NMR measurements the

pyrazolobenzodiazocins, diazonines and the bridged derivative (**26**) have boat conformation.

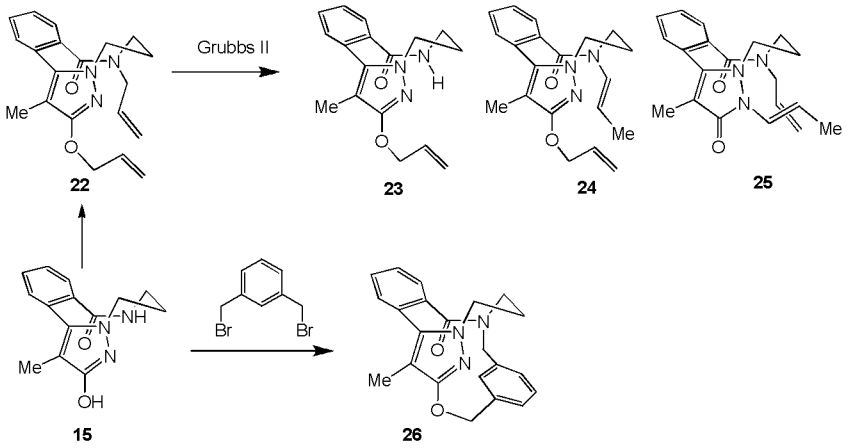

Figure 4

1-ethyl substituted triaza- and benztriazapentalenoinden (**17**, R=Et, R^2=R^3=Me) were prepared with boiling butiric anyhidride and with transannular ring opening of these pentalenoindens 1-ethylpyrazolobenzo- and naphtodiazocine (**18**, R=Et, R^2=R^3=Me, Figure 3), were prepared, and these diazocins showed complete rigidity. In contrast 1-H and 1-Me substituted models, the 1-ethyl derivative doesn't racemize even at high temperature according to DNMR measurements, however in the case of the first two models the naphthalene ring compared to the benzene ring increases slightly the conformational flexibility and this result is consistent with the DFT calculations.

From 8,9,10,11-tetrahydropyrido[1,2-*b*]pyrido[3',2'-*d*]pyridazine-5-ium-7-olate (**13**, X=N, Figure 4) a tetraazaindenoindene (**14**, X=N, Figure 3) was prepared using acetic anhydride, with the ring enlargement of **14** the 1-H substituted pyrazolopyridodiazonine (**15**, X=N, Figure 3) and according to the DNMR measurement and in correspondence with the DFT calculations, this pyrido condensed diazonin has rigider skeletal structure than the benzene analog.

Some chiral benzphtalazinium-olate derivatives (**19a-c**, Figure 5) were prepared from α,α,α',α'-tetrabromo *o*-xylene across 2,3-naphtalic anhydride using chiral amino alcohols. Different diastereomers (**20a-31a***, **20b-31b***, **20c-31c***, R^1 = H) were formed from these zwitterions with refluxing acetic anhydride depended on the reaction time employed (1.5 hours or 5 hours). These experimental facts were confirmed with theoretical calculations too.

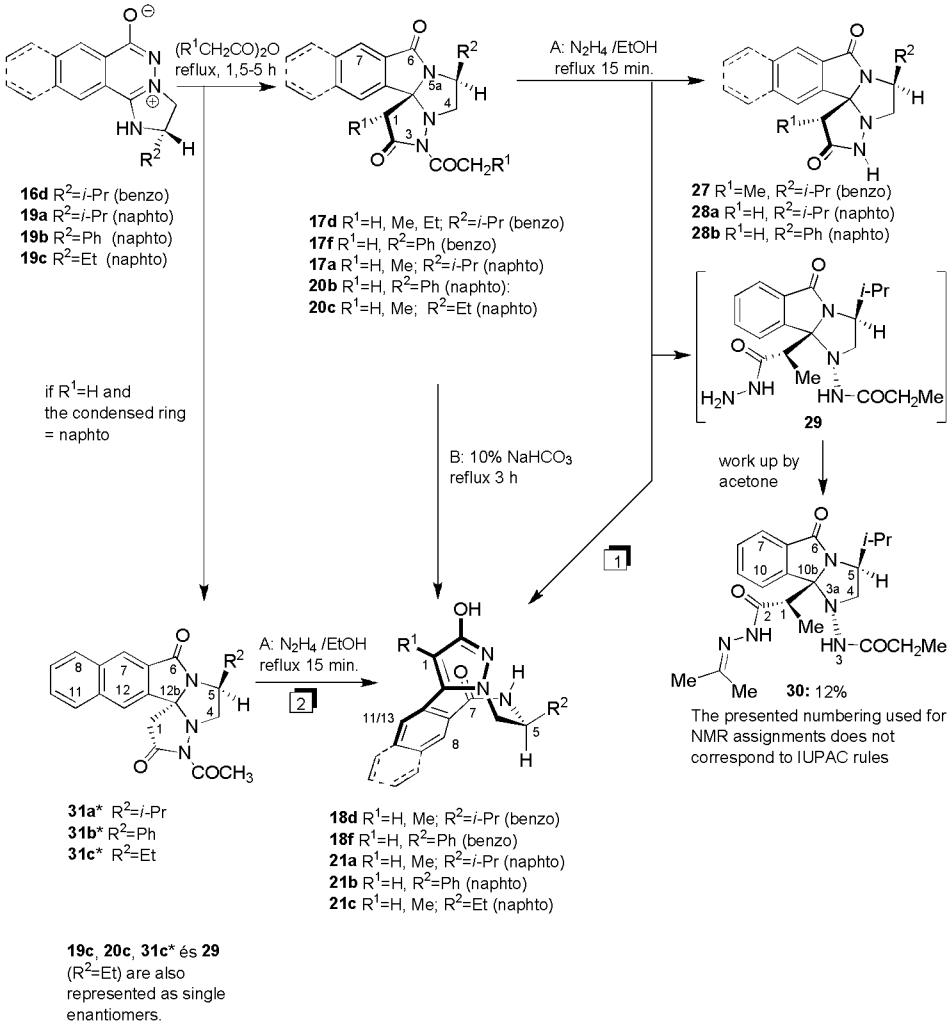

Figure 5

2.2. New heterocyclic ring system: synthesis of (S_p)-ferroceno[*d*]pyridazin-4(3*H*)-one and some derivatives of it

2.2.1. Synthesis of S_p-2-formylferrocene carboxylic acid

The (2*S*,4*S*,S_p)-4-(methoxymethyl)-2-(lithioferrocenyl)-1,3-dioxane [**(*S*,*S*,S_p)-32,** Figure 6] was quenched with a lot of electrophile, however with CO_2 it wasn't, so S_p-2-formylferrocene carboxylic acid **(S_p)-34** was prepared firstly in our research group in a three-step one-pot reaction. **(*S*,*S*,S_p)-32** was quenched with from dry ice with dry argon stream driven CO_2 gas, then the precipitated carboxylate salt was treated with tin(II)-chloride containing HCl solution, so the carboxylic acid freed up and the acetal hydrolyzed back to formyl group.

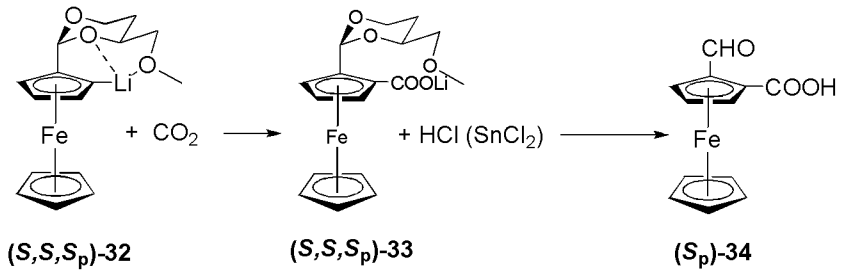

Figure 6

2.2.2. Synthesis of ferroeno[d]pyridazinones

I envisaged the hydrazine-mediated cyclisation of [**(S_p)-34**] to obtain ferroceno[*d*]pyridazinone [**(S_p)-38a**], which can be considered as the precursor of a variety of *N*-alkylated derivatives. Contrary to our expectations the reaction conducted in refluxing ethanol afforded dimer [**(S_p,S_p')-35**] in good yield without being contaminated by pyridazinone product. When a five-fold excess of hydrazine-hydrate was used as reagent [**(S_p,S_p')-35**] could again be isolated from the reaction mixture. This observation is in accord with the facile hydrazine-mediated conversion of formylferrocene yielding dimmer azine. Since the carboxyl group seemed to be deactivated by the

highly electron-releasing ferrocene moiety, [**(*S*$_p$)-34**] was converted into acid fluoride [**(*S*$_p$)-36**] by treatment with cyanuricfluoride and pyridine in DCM. To our pleasure [**(*S*$_p$)-36**] could be isolated in unexpectedly high yield which was converted into the first targeted ferroceno[*d*]pyridazinone [**(*S*$_p$)-38a**] in good yield on short treatment with hydrazine hydrate in dry THF at room temperature. The reactions employing alkylhydrazine-type reagents gave the corresponding N3-alkylated pyridazinones [**(*S*$_p$)-38b-e**] in substantially lower yields which could not be increased by employing prolonged reaction time and elevated temperature. On the other hand, the N-alkylation reactions of the easily accessible [**(*S*$_p$)-38a**] with bezylbromide, 2-bromomethylpyridine and ethyl bromoacetate [**(*S*$_p$)-38a→(*S*$_p$)-38e-g**] carried out under basic conditions (NaH/THF) at room temperature demonstrated an alternative synthetic route to versatile products containing the novel metallocene scaffold. Attempted cyclisations of [**(*S*$_p$)-36**] with phenylhydrazine and 4-nitrophenylhydrazine, respectively, carried out in THF at room temperature led also to the formation of complex mixtures. Employing the same reagents in refluxing ethanol [**(*S*$_p$)-34**] afforded hydrazones [**(*E*)-(*S*$_p$)-37a,b**] which – on prolonged heating in the different mixtures of EtOH and AcOH – underwent decomposition reactions.

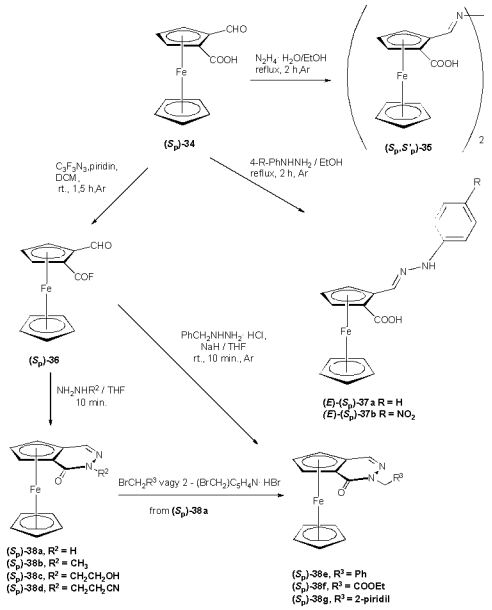

Figure 7

Scientifical publications

DNMR, DFT and preparative study on the conformation of (Z)-4,5,6,7-tetrahydropyrazolo[1,5-e]benzo[g][1,5]diazonin- 8-ones and (Z)-4,5-dihydropyrazolo[1,5-d]benzo[f][1,4]diazocin-7(6H)-ones
Gyömöre, Á.; Kovács, Z.; Nagy, T.; Kudar, V.; Szabó, A.; Csámpai, A., *Tetrahedron* **2008**, *64*, 10837-10848.

Study on medium ring heterocycles: synthesis and structure of novel condensed pyrazolo[1,4]diazocinones including single enantiomers
Gyömöre, Á.; Holczbauer, T.; Czugler, M.; Csámpai A., *Tetrahedron* **2011,** 67, 2979-2990.

Synthesis and structure of planar chiral ferroceno[d]pyridazinones, the first representatives of a novel class of fused metallocenes
Gyömöre Á.; Csámpai*, A. *J. Organomet. Chem.* **2011**, *696*, 1626-1631.

Presentations

Gyömöre, Á.; Csámpai, A. „*Experiments on preparation of optically active (Z)-4,5,6,7-tetrahydro-pyrazolo[1,5-e]benzo[g][1,5]diazocin-8-ones and (Z)-4,5-dyhidropyrazolo[1,5-d] benzo[f][1,4]diazocin-7(6H)-ones*"

20th-22nd May, 2009. MTA Heterocyclic chemistry working committee meeting

Gyömöre, Á.; Csámpai, A. „*New results in synthesis and moleculadinamical examination of condensed diazocins és diazonins*"

19th-21st May, 2010. MTA Heterocyclic chemistry working committee meeting

Gyömöre, Á.; Csámpai, A.; Czugler, M. „*Synthesis and moleculadinamical examination of condensed diazocins és diazonins, over and above syntheis and X-ray diffraction examaniation of ferrocene containing quaterner salts and their reineckats*"

20th October, 2010. MTA-KKI SZKI self-introducing presentation

Gyömöre, Á.; Csámpai, A.; Czugler, M.; Holczbauer, T. „ *Preparation of chiral and non-chiral condensed pyridazinones and new ferrocene containing Reinecke-salts, their reactions and moleculadinamical and X-ray diffraction examination of the products"*

24th-26th March, 2011. MTA Inorganic and organometallic chemistry working committee and MTA material –and molecular structure working committee meeting