Synthesis of Hetero-ring Fused Diazines

PhD Theses

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Summary

[*d*]-Annelated pyridazines have primarily been of interest as structurally related analogues of 4,5-disubstituted pyridazines possessing remarkable biological activities. These achievements have prompted us to elaborate further new methodologies for the syntheses of novel polyfused diazines, utilizing Suzuki cross coupling and subsequent ring closure reactions.

Substrate-, reagent- and temperature-dependent halogen-displacement reactions of halopyridazinones with iodide were studied. The monohalogen compounds thus obtained were used as starting materials for cycloaddition and electrocyclization reactions.

1,3-Dipolar cycloaddition reactions of 5-ethylsulfonyl- as well as 5-chloro-2-methyl-3(2*H*)-pyridazinones led to simple and convenient preparations of pyrazolo[3,4-*d*]pyridazinones. The results of these experiments were also analyzed by FMO theory.

Suzuki reactions of halopyridazinones and the subsequent ring closure reactions of their products *via* nitrene insertion or nucleophilic substitution, were elaborated as efficient synthetic routes for pyridazino[4,5-*b*] and -[3,4-*b*]indoles. This methodology was extended to reactions of chloropyrimidine and chloropyrazine, and pyrimido[5,4-*c*]cinnoline, pyrazino[1,2-*b*]indazole, and pyrazino[2,3-*b*]indole ring systems were synthesized. By this procedure various substituents could be easily introduced into the products using appropriately substituted precursors.

Tandem Suzuki – aza-Wittig, and tandem Suzuki – condensation reactions were developed as further methods for the syntheses of pyridazino[4,5-*c*]isoquinolines.

Pyridazino[4,5-*c*]quinoline system was obtained *via* carbodiimide intermediate by tandem aza-Wittig – electrocyclization reaction, whereas pyrimido[5,4-*c*]quinoline was also available *via* ring closure reaction utilizing a carbodiimide. The different reactivities of pyridazines, pyrimidines, and pyrazines could be well explained taking their different electronic properties into consideration.

The constitution of each product was proven by spectroscopic investigations.

INTRODUCTION AND AIMS

In the last decades, [*d*]-annelated pyridazines have received much attention as structurally related analogues of 4,5 disubstituted pyridazines possessing remarkable biological activities. Among these bicyclic derivatives, too, Mátyus et al. at the Institute for Drug Research Budapest, later at the Department of Organic Chemistry at the Semmelweis University, have identified some interesting lead compounds for further synthetic and structure-activity studies. These achievements prompted us to elaborate other synthetic pathways toward novel di- and polyfused diazines, based on various carbon-carbon and/or carbon-nitrogen bond forming reactions which may also be useful for the preparation of new series of fused ring systems with pharmacological interest. As another important aspect of these studies the new fused pyridazines are themselves interesting compounds for pharmacological studies.

Synthetic strategies of my work were as follow:

1) Application of *1,3-dipolar cycloaddition* reactions for syntheses of pyrazolo[3,4-*d*]pyridazinones using different 5-substituted pyridazinones as strating materials.
2) Application of *Suzuki cross coupling* reaction between halodiazines and arylboronic acids and subsequent ring closures towards polyfused heterocyclic compounds.
3) Application of *Suzuki cross coupling* reaction between haloaminodiazines, as well as haloiminophosphoranes and arylboronic acid and following ring closure reactions.

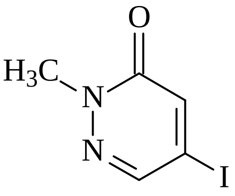
Results of these investigations are reported in this PhD work.

RESULTS

PhD work can be summarised in the following main chapters.

i) At first, substrate-, reagent- and temperature-dependency of halogen-displacement reactions of halogenopyridazinones with iodide were studied. Reactions of 5-chloro-, and 4,5-dichloropyridazin-3(2*H*)-ones with 57% hydrogen iodide or sodium iodide in dimethyl formamide (DMF) afforded iodopyridazin-3(2*H*)-ones (**48**, **188** and **183-186**, respectively) *via* nucleophilic substitution followed by hydrodehalogenation. These experiments indicated that the an iodo atom at 4-postion is more sensitive toward hydrodehalogenation.

The monohalogen compounds thus obtained were also used as starting materials for cycloaddition and electrocyclization reactions.



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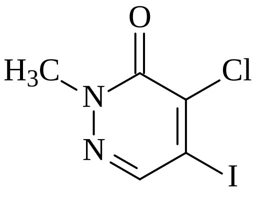

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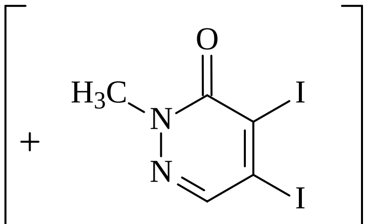

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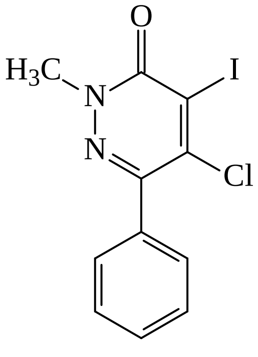

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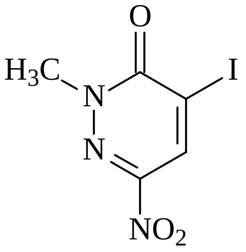

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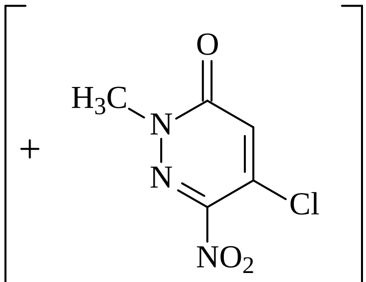

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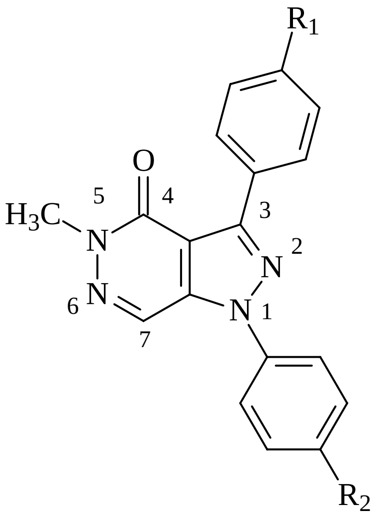
ii) The second part of our program focused on 1,3-dipolar cycloaddition reaction of 5-substituted 3(2*H*)-pyridazinones with diarylnitrile imines generated *in situ* from benzaldehyde-phenylhydrazones or α-chlorobenzylidene-phenylhydrazines to obtain diarylpyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones.



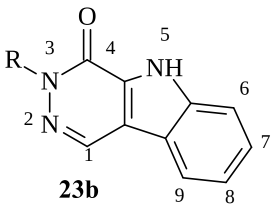
	R1	R2
200	H	H
201	CH_3O	H
202	CH_3	H
203	H	CH_3O
204	CH_3	CH_3O

As dipolarophile, 5-ethylsulfonyl-2-methyl-3(2*H*)-pyridazinone was used in the first experiments. This compound was earlier shown to exhibit high reactivity in Diels-Alder reaction with normal electron demand as well as in a dipolar cycloaddition reaction with diazomethane. When it was allowed to react with nitrile imines in refluxing ethanol, 1,3-diaryl-1*H*-pyrazolopyridazin-4(5*H*)-ones (**200**-**204**) were obtained as the sole isolable products. Using 5-iodo- or chloro-pyridazinones as dipolarophiles with the same dipoles, the preparative yields of pyrazolopyridazines were form to be strongly dependent on the reaction conditions.

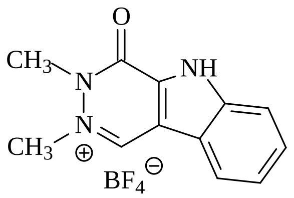
Both procedures may offer a simple and efficient way for preparation of 1,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4(5*H*)-ones.

iii) Next the Suzuki cross coupling reaction was investigated. 5-Iodo-2-methylpyridazin-3(2*H*)-one (**48**) readily underwent coupling with *N*-protected anilinoboronic acids to yield the corresponding arylpyridazinones which proved to be suitable starting compounds for the preparation of pyridazino[4,5-*b*]indoles (**23**, **210**):

a) deprotection to the amine;
b) diazotation to a diazonium salt and its, *in situ*, transformation to an arylazide;
c) ring closure *via* a nitrene.



23b
23d



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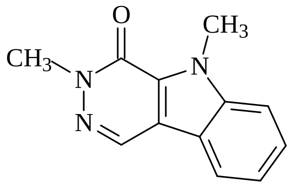
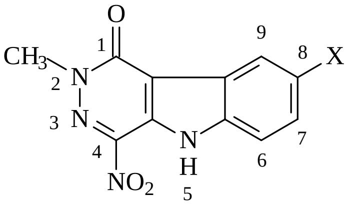


23c

R: Me, Ph



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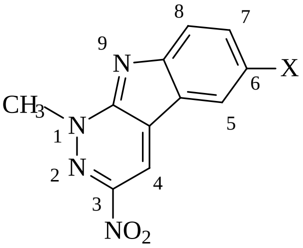

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X: H, Cl

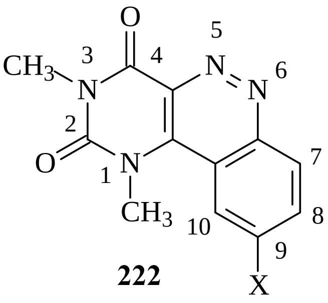
We also used 4-iodo-2-methyl-6-nitropyridazin-3(2*H*)-one (**185**) which can be prepared from dichloronitropyridazinone by sodium iodide in DMF in the next experiments.

From **185**, the 3-step procedures, gave 2-methyl-4-nitro-5*H*-pyridazino[4,5-*b*]indol-1(2*H*)-on (**216a**) and 8-chloro-2-methyl-4-nitro-5*H*-pyridazino[4,5-*b*]indol-1(2*H*)-on (**216b**), when 2-pivaloylamino-phenylboronic acid and its 5-chloro analogue were used, respectively, in the first step.

The aminophenyl compounds, which were synthetised in the above procedures – due to the proximity of the amino and oxo functions – could be taken into a condensation reaction in boiling phosphoryl trichloride to give 1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (**217a**) and 6-chloro-1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (**217b**), respectively.

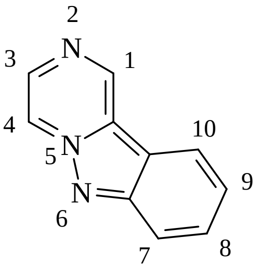
We aimed to adopt the synthetic methodology leading to the pyridazino[4,5-*b*]indole ring system (**23**, **216**) for the preparation of analogous pyrimido[5,4-*b*]indole derivatives. With this purpose we chose 6-chloro-1,3-dimethyluracil as the starting material. The Suzuki reaction of 6-chloro-1,3-dimethyluracil with 2-pivaloylaminophenyl boronic acid and its chloro-substituted derivative yielded the appropriate anilides. After deprotection, the amines were diazotated, but surprisingly, treatment of the diazonium salts with natrium azide did not afford the expected azido compounds. Instead, an intramolecular azo-coupling occured, resulting in pyrimido[5,4-*c*]cinnoline derivatives (**222a, 222b**).

The third diazine, the pyrazine was also investigated. Suzuki coupling reactions of 2-chloropyrazine with aryl boronic acids are known, but the obtained products are not transformed to policyclic diazines in the literature. Thus, 2-chloropyrazine was reacted with 2-pivaloylaminophenyl boronic acid. The obtained amide was then hydrolysed to the amine, diazotation and subsequent azidation led to the expected azido compound, which was then refluxed in 1,2-dichlorobenzene. The pyrazino[2,3-*b*]indol (**155**) was obtained only in trace amount, the main product was the pyrazino[1,2-*b*]indazole (**232**).



222

X: H, Cl



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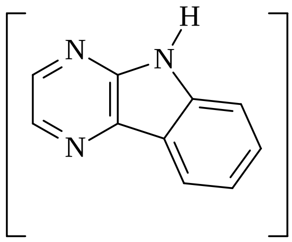

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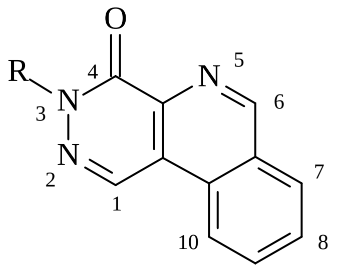
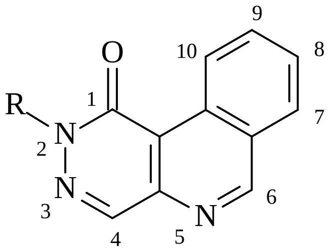
iv) Synthesis of fused diazines was also achieved *via* iminophosphoranes. 4-Bromo-5-pyridazinyliminophosphoranes, which were produced from the corresponding azide by triphenylphosphine were reacted with 2-formylphenylboronic acid to pyridazino[4,5-*c*]isoquinolin-1(2*H*)-ones (**136**) by a Suzuki cross coupling – aza-Wittig tandem.

In another route, precursors of ring closures, *N*^{2}-substituted 4-bromo-5-amino-, as well as 5-bromo-4-amino-pyridazinones were prepared from the appropriate 4,5-dibromo compounds by aqueous ammonia, and they were transformed to pyridazino[4,5-*c*]isoquinolines (**135**, **136**).

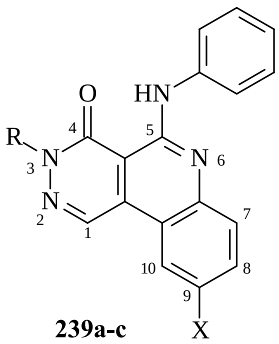




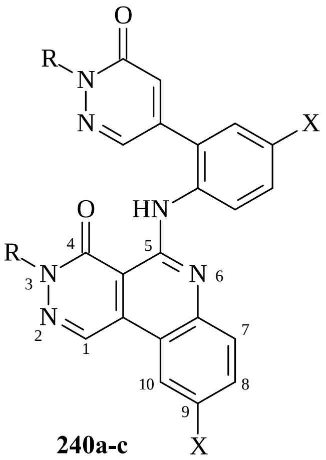
R: Me **135a** **136a**

Bn **135b** **136b**

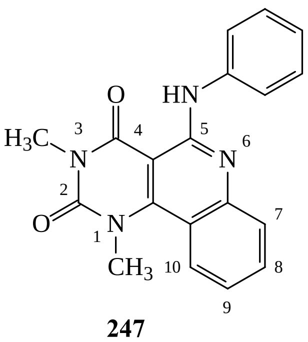
Reaction of aryliminophosphoranes with phenylisocyanate gave diarylcarbodiimides. These compounds *via* aza-Wittig – electrocyclic ring closure tandem reaction, led to 5-substituted pyridazino[4,5-*c*]quinolines (**239**, **240**, **247**).



239a-c



240a-c



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R: Me, Ph

X: H, Cl

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Abstract

Gy. Beke, L. Károlyházy, G. Krajsovszky, R.D. Enriz, S.A. Zacchino, F. Hernádi, P. Kovács, P. Mátyus: **Pyridazine Derivatives with Potential Antifungal Activity.** *European Journal of Pharmaceutical Sciences* **11** Suppl. 1 (2000) S106 (**IF**: 1,212)

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(L): lecture
(P): poster presentation

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