Synthesis of Hetero-ring Fused Diazenes

PhD Theses

Dr. Gábor Krajsovszky

Semmelweis University

Under the supervision Péter Mátyus DSc

Budapest
2007
Synthesis of Hetero-ring Fused Diazines

Dr. Gábor Krajsovszky

Under the supervision of Professor Péter Mátyus, DSc
Semmelweis University, Department of Organic Chemistry

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(2H)-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(2H)-ones with 57% hydrogen iodide or sodium iodide in dimethyl formamide (DMF) afforded iodopyridazin-3(2H)-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.

![Chemical structures](image1.png)

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

iii) Next the Suzuki cross coupling reaction was investigated. 5-Iodo-2-methylpyridazin-3(2H)-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.
We also used 4-iodo-2-methyl-6-nitropyridazin-3(2H)-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-5H-pyridazino[4,5-b]indol-1(2H)-one (216a) and 8-chloro-2-methyl-4-nitro-5H-pyridazino[4,5-b]indol-1(2H)-one (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-1H-pyridazino[3,4-b]indole (217a) and 6-chloro-1-methyl-3-nitro-1H-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-pivaloylamino phenylboronic 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 occurred, 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 polycyclic 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).
iv) Synthesis of fused diazines was also achieved via iminophosphoranes. 4-Bromo-5-
pyrdazinyliminophosphoranes, which were produced from the corresponding azide by triphenylphosphine were reacted with 2-formylphenylboronic acid to pyridazino[4,5-
In another route, precursors of ring closures, N2-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).

![Chemical Structures](image)

Reaction of aryliminophosphoranes with phenylisocyanate gave diarylcarbodiimides. These 
compounds via aza-Wittig – electrocyclic ring closure tandem reaction, led to 5-substituted 

![Chemical Structures](image)

R: Me, Ph  
X: H, Cl
PUBLICATIONS

Papers


Abstract

Lectures and poster presentations


(L): lecture

(P): poster presentation
ACKNOWLEDGEMENTS

Hereby in particular, I express my sincere gratitude to Professor Péter Mátyus, the supervisor of my PhD study, for his continuous support and valuable advice as well as discussions during of my work.

I am indebted to G. Hajós, Zs. Riedl and N. Haider for the supervision of our cooperation work.

The following scientists are also acknowledged for their important contributions to my work: B. Podányi, S. Boros and A. Csámpai (NMR spectroscopy); A. Csámpai, B. Balogh and K. Keserű (computational chemistry calculations); Gy. Horváth, K. Ludányi and C. Meyers (mass spectrometry); Á. Puhr-Forgó (elementary analyses); P. Tétényi Jr. (IR spectroscopy).

I would like to thank co-authors of my publications, such as papers, abstract, lectures and poster presentations published in the field of my work.

Special thanks Andrea Gaál, Petra Dunkel and co-workers of Department of Organic Chemistry for their help in some part of my experimental work.

I am grateful to the Austrian Academic Exchange Service, OTKA, and ETT for the financial support.

I express my tanks to all who contributed in any way to my dissertation.