Thesis of Ph.D. dissertation

New Cyclizations to Fused Azoles

László Filák

Supervisor: Dr. Zsuzsanna Riedl
D.Sc.

Eötvös Loránd University
Chemistry Doctoral School

Synthetic Chemistry, Materials Science and Biomolecular Chemistry

Head of Chemistry Doctoral School: Dr. György Inzelt

Head of Doctoral programmes: Dr. Tamás István Horváth

Chemical Research Center, Hungarian Academy of Sciences
Institute of Biomolecular Chemistry
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1. Introduction

Our research group has been dealing with the synthesis of azoles fused to heterocycles for a long time. In the course of this work several pyrazole and triazole compounds were synthetized. Three areas have been studied:

- On one hand, the aim of the present Ph.D. work was the synthesis of new, linearly fused [1,2,4]triazoles starting from various 2,3-diaminoisoquinolinium salts. An interesting rearrangement was observed, and clarification of its mechanism seemed of particular interest.
- Earlier a new thermal cyclization was observed to yield fused pyrazoles. As a continuation of these studies, extension of this methodology to other ring systems and rationalization of the mechanism of this reaction was planned.
- The third part of my Ph.D. dissertation deals with transformation of benzothiazoles. Also in this case, fused pyrazoles were synthetized, and an unexpected expansion of thiazole ring was observed under special reaction conditions.

2. Experimental Methods

Synthetic organic chemical methods were applied in the course of our work. The progress of the reactions and the purity of the products was monitored by TLC. The prepared compounds were purified by column chromatography and recrystallization. Identification of the structures was carried out by modern spectroscopic methods ($^1$H-, $^{13}$C- NMR, 2D- NMR, IR, and MS) and by elemental analysis. The new products were also characterized by their melting points.

3. Results

3.1 Synthesis of s-Triazoles Linearly Fused to Isoquinoline

3.1.1 3-Aminoisoquinolines (I) (R₁=H, Me, Et, benzyl, CN) were synthetized according to literature procedures. These compounds were N-aminated with TSH reagent to give 2,3-diaminoisoquinolinium salts (II). In the case of 4-Me, 4-Et, 4-benzyl substituted N-amino derivatives (II) reaction with aromatic and aliphatic aldehydes under basic conditions afforded new [1,2,4]triazolo[1,5-b]isoquinolines (III). An intermediate: the dihidrotriazolium
salt (IV) was isolated in several cases, which underwent oxidation in air in the presence of a base to give the product (III).

![Chemical structure](image)

3.1.2 No triazoles were formed in reactions of diamino salts containing hydrogen or electron withdrawing group in position 4 (II, \(R_1^1=\text{H or CN}\)) with aldehydes under basic conditions but, instead, unexpected products: isoquinolylhydrazones (V) were isolated. The structure of this compound was proved by X-ray diffraction in one case. The mechanism of the transformation was rationalized with the help of \(^{15}\text{N}\) labeling. The \(N\)-amino (*) and the exo amino groups (#) were separately labeled in two experiments. The positions of the \(^{15}\text{N}\) isotopes were identified by \(^{15}\text{N}\)-\(^1\text{H}\) HMQC and direct \(^{15}\text{N}\)-NMR measurements both in the starting compounds and in the products. The results revealed that in the cases of the hydrazone formation a Dimroth-rearrangement takes place: hydrazone derivatives (V) were formed by the ring opening and ring closure of the isoquinoline in the presence of a nucleophile. An intermediate of the cyclization (VI) was isolated, which could be transformed to the same hydrazone product (V) as obtained from the diamino salt with aldehydes. Linearly fused triazoles (III) were synthetized from the unsubstituted \(N\)-amino derivatives by exclusion of water by using molecular sieve, which hindered the formation of the nucleophile necessary to the Dimroth rearrangement.
3.2 Cyclization to Fused Pyrazoles

3.2.1 Fused pyrazoles (VIII) have been synthesized by the reactions of pyrazinylketones (VII) with arylhydrazines under acidic conditions. The experimental results revealed that the cyclization proceeds via hydrazone (IX) intermediate. The ring closure starting from isolated hydrazones took place both under acidic and basic conditions.
3.2.2 This method was also extended for pyridazine derivatives. The pyrazolopyridazines (XI) have been obtained either from ketones under acidic, or from hydrazone (XII) under both acidic and basic conditions.

No ring closed product was formed from methyl substituted ketones or hydrazones under any of the reaction conditions used.

3.2.3 Mechanistic considerations revealed, that the pyrazole-cyclization could also take place in a percyclic manner by participation of two double bonds and lone pair of the hydrazone nitrogen atom. This possibility was supported experimentally: pyrazinylketone hydrazone (IX) was heated under neutral conditions (in dichlorobenzene) to yield pyrazole (VIII). Several those derivatives could be synthetized by this method, that were not available by the acidic or basic method. Pyrazoles fused to pyridine (XIV), isoquinoline (XV) and R=Me substituted pyridazine (XIII, R=Me) could also be obtained by this method.
Theoretical calculations revealed that the mechanism of the cyclization significantly depends on the reaction conditions applied: under neutral and acidic conditions the reaction is pericyclic, whereas in the presence of base a pseudopericyclic route is preferred. Thus, the mechanism of the cyclization was tunable by the choice of the reaction conditions.

3.3 Synthesis and Transformation of N-aminobenzothiazoles

3.3.1 2-Benzylbenzothiazoles (XVI) were N-aminated by TSH reagent and the formed tosylate salts (XVII) were reacted with triethyl orthoformate under basic conditions (TEA). 1,5-Electrocyclization took place, and ring closed products: pyrazolobenzothiazoles (XVIII) were formed.

3.3.2 Further reactivity of the N-amino salts (XVII) was studied by transformation with aromatic and aliphatic aldehydes in the presence of triethylamine. An amident behaviour was experienced in our experiments: benzothiadiazine (XIX) was formed in reactions with butyraldehyde, whereas benzothiazines (XX) were obtained with aromatic aldehydes. Thus, ring expansion took place in both cases.
The transformation was interpreted by supposing a nucleophilic attack of a hydroxide ion on the five membered thiazole ring followed by ring opening. Accordingly, an intermediate is formed in which the sulphur atom can attack two different carbon atoms to yield the two products (XIX, XX).

4. Publications related to the Dissertation

Papers:


Lectures:


