Preparation of alkaloid derivatives and N-heterocyclic compound

Thesis

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1. Introduction, objectives

Pyrrolizidine, indolizidine, and quinolizidine are common skeletons in both natural and synthetic products that possess a wide range of biological activities. Most of them are toxic, but some compounds of this type are active agents of anti-inflammatory, analgesic or anti-leukemic drugs.

The structure elucidation and testing biological activity of the naturally occurring representatives were considerably hindered by the extremely low abundance of these materials which are usually attainable through isolation from the divers amphibians. For example, the 167B toxin was detected from the skin-extract of a frog of Panama in 1987, but its amount was enough only for a GC-MS analysis. The epiquinamide exhibiting a strong anticholinergic effect was isolated in 2003, however, its quantity from 183 frogs amounted to only 240 µg. In addition to their very strong physiological activity the significance of these natural products has been enhanced by the fact, that they can be applied as reference materials in study of neuromuscular transitions. It is understandable, that tremendous research work has been made worldwide to develop efficient methods for the synthesis of these alkaloids. These efforts are also stimulated by the aspects of environment protection, as well as by the goals of the drug research.

My work that I made in the Department of Chemistry, School of Veterinary Medicine, Szent István University can be attached to the area of synthetic organic chemistry outlined above. Exploiting the enhanced reactivity of push-pull alkenes, particularly that of the nitroenamines, our purpose was to develop new synthesis strategies, providing efficient and short routes to construct the basic ring skeletons of alkaloid molecules.

My research work has been directed onto three topics which includes the study of the reactions of nitroenamines with carbonyl compounds and unsaturated acid chlorides, furthermore, the investigation of the reductive transformations of the products obtained in the different cyclizations.
1. Reactions of the nitroenamines with different carbonyl compounds

The 2-nitromethylene-pyrrolidine (1a) reacts with 2a-d α-ketoaldehydes readily at room temperature without any catalyst furnishing crystalline products 3a-d in excellent yields. Using the nitroenamine 1b or 1c the analogous compounds 3e-h were formed, but with phenyl-glioxal (2c) the cyclic products 4a,b were produced (Scheme 1).

Scheme 1.

With ninhydrin (5) a similar cyclization took place resulted in the heterocyclic compounds 6a-c. Alloxan (7) gave an isolable product only with 2-nitromethylene-pyrrolidine (1a) (Scheme 2), and the formation of the adduct 8 was revealed.

Scheme 2.

The primary adducts 3c,d were cyclized in boiling alcohol, in the presence of hydrochloric acid to form bicyclic products 9a-e (Scheme 3). Interestingly, depending on the alcohol used as solvent, the corresponding alkoxy derivatives were obtained.

Scheme 3.

Under properly modified reaction conditions, i.e. 3c was stirred in MeOH/HCl at 0 °C, the intermediate 11 was isolated (Scheme 4). Upon refluxing 11 the expected ring-closure took place rapidly resulting in 9a. These experimental findings render likely our mechanistic
suggestion assuming the acid catalyzed formation of the cation 10 followed by the nucleophilic attack.

Scheme 4.

The chloride ion formed from hydrochloric acid and phenol also worked as a nucleophilic agents. These reactions gave compounds 12 and 13 (Scheme 5).

Scheme 5.

In the same way, also the adducts 6b,c could be alkylated under similar conditions, giving compounds 14a,b (Scheme 6).

Scheme 6.

2. [3+3] Cyclization reactions of nitroenamines with α,β-unsaturated carboxylic acid chlorides

Various indolizidine, quinolizidine and pyrido-azepin derivatives were prepared by the cyclization reaction of nitroenamines with α,β-unsaturated carboxylic acid chlorides. The nitroenamines 1a-c gave the products 16-19 with acryloyl chloride (15a) without any catalyst, at room temperature (Scheme 7). This observation can be explained with the high reactivity of acryloyl chloride, because use of other acid chlorides under the same conditions did not lead
to the products in the expected yields. Therefore finding an appropriate catalyst was necessary to increase the conversion.

Scheme 7.

In an attempt to find more efficient catalysts a number of compounds were tested in model reactions between nitromethylene-pyrrolidine (1a) and crotonoyl chloride (15a). The conversion of the reactants and the degree of side-reactions were semi-quantitatively monitored by TLC. Based on the conversion, the reaction time and the work-up procedure, La(OH)₃ and some carbonates MₙCO₃ (M = Li, Mg, Ca, Ba) were found to catalyze our reactions most efficiently, although LiF, LiOAc, Mg(OAc)₂·4H₂O also worked well. In majority of our experiments use of calcium-carbonate was favoured.

N-heterocyclic compounds 20-22 were prepared in the reaction of methacryloyl- (15b) or crotonoyl chloride (15c) with nitroenamines 1a-c (Scheme 8). The non-cyclized 21 was isolated as a by-product.
Scheme 8.

In some cases an unexpected double bond migration was found. It can be interpreted in terms of amidity values introduced by Mucsi and co-workers in 2007.

3. [3+3] Cyclization reactions of enaminonitriles with α,β-unsaturated carboxylic acid chlorides

β-Enaminonitriles were also tested with the acid chlorides used in the above transformations. The enaminonitriles 23 reacted with the acid chlorides 15a-c and gave the cyclized products 25a-c, but the open-chain compounds 26a,b were also isolated (Scheme 9).

Scheme 9.

The reaction of the enaminonitrile 27 with acryloyl- (15a) and crotonoyl chloride (15c) gave the 2-piperidone derivatives 28a,b (Scheme 10).
Scheme 10.

In the presence of BaCO$_3$ or La(OH)$_3$ catalyst, the reaction of β-enaminonitrile 28 with the non-aromatic α,β-unsaturated carboxylic acid chlorides 15a-c in acetonitrile led to 3,4-dihydro-2-pyridones 29a-c. On the other hand, in the reaction with cinnamoyl chloride (15d) the 2,3-dihydro-4-pyridone 30 was produced predominantly (Scheme 11). With $p$-methoxycinnamoyl chloride the compound 32 was synthesized through the intermediate ketone 31.

Scheme 11.
3.5. Reductions

The molecules of the unsaturated nitro-lactams prepared in the above syntheses have three reducable functional groups (double bond, lactam-, nitro-groups). Their reductions resulted in numerous compounds showing diverse structures.

Hydrogenations of the nitrolactam 17 using different catalysts gave the compounds 33-37 (Scheme 12).

Scheme 12.

The amino lactame 35 was reduced with lithium aluminum hydride to the amine 38 which can be transformed to C(1)-epiepiquinamide (39) by adapting the literature protocol. (Scheme 13).

Scheme 13.

On the other hand, the reduction with Red-Al led to a new ring system, which incorporates a fused azetidine ring. Its acylation resulted in the derivative 41.

Scheme 14.
Using other reductive methods (tin/hydrochloric acid, NaBH₄/Raney-nickel, NaBH₄/NiCl₂) the compounds 42-45 were prepared (Scheme 15).

![Chemical Structures](image)

**Scheme 15.**

### 3.6. Results

- A new and effective method was developed for the synthesis of various pyrrolizidine, indolizidine- and aza-azulene-derivatives. The reactions of nitroenamines with di- or tricarbonyl-compounds, as well as the reactions of different push-pull alkenes and α,β-unsaturated carboxylic acid chlorides were optimized and used them for the synthesis of N-heterocyclic compounds.

- Reduction of the primary products gave the opportunity for simple preparation of further bioactive molecules.

- The octahydro-quinolizin-1-ylamine was synthesized, and using a literature protocol it can be transformed to C(1)-epimer of epiquinamide.

- A new tricyclic ring system including a fused azetidine was prepared, isolated and acetylated.