Third International Electronic Conference on Synthetic Organic Chemistry (ECSOC-3), www.mdpi.org/ecsoc-3.htm, September 1-30, 1999

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Isomeric Isoxazolopyridinones: Synthesis, Tautomerism and Molecular Orbital Calculations

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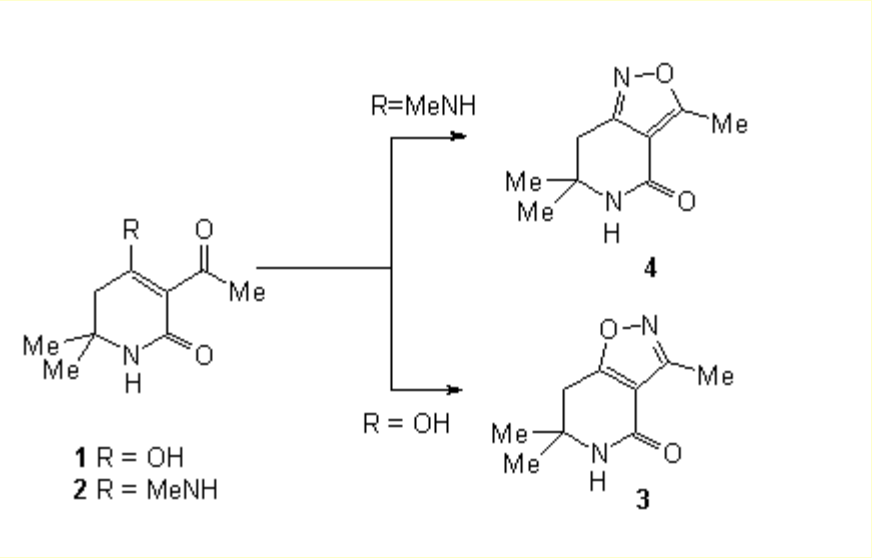
Received: 24 July 1999 / Uploaded: 6 August 1999

Abstract

Depending on the substituent at C-4 (OH or MeNH) 3-acyl-5,6-dihydropyridinones **1** and **2** react with hydroxylamine to give either isoxazolo[5,4-c]pyridinone **3** and isoxazolo[4,3-c]pyridinone **4**, respectively. The tautomeric equilibria of **1** and **2** are investigated by means of NMR spectroscopy and density functional calculations. The mechanisms of formation of **3** and **4** are interpreted with the aid of semiempirical molecular orbital calculations.

Introduction

Isoxazolo[4,5-c]pyridinones, e.g. **3**, show a wide variety of biological activity. They can act as hypolipidemic agents and are important precursors for hypnotics, muscle relaxants as well as tranquillizers[1]. The isomeric isoxazolo[4,3-c]pyridinones, e.g. **4**, are relevant synthons for analogues of herbicides[2]. In the following, the synthesis of the two isomeric compounds **3** and **4**, the feasibility to influence the isomer ratio as well as their tautomeric equilibria as evidenced by NMR spectroscopy and densitiy functional calculations, will be described.



Synthesis[3]

Acylation of 4-methylamino-5,6-dihydropyridin-2(1H)-one under *Friedel-Crafts* conditions selectively yields the 3-acetyl derivative **2.** Alkaline hydrolysis of **2** is used to synthesize the 4-hydroxy derivative **1**. In contrast to 3-acetyl-4-hydroxy-2(1H)-quinolinones, which on reaction with hydroxylamine, yield the oximes [4], both **1** as well as **2** cyclize to isoxazolopyridinones. Interestingly, there is a strong dependence of the outcome of these cyclizations on the substituent at C-4: In case of the 4-hydroxy derivative **1** exclusively the isoxazolo[4,5-c]pyridinone **3** is formed. In contrast, reaction of the 4-methylamino derivative **2** with hydroxylamine results in a mixture of **3** and the isomeric isoxazolo-[4,3-c]pyridione **4**. The composition of this mixture can be regulated by the reaction conditions, namely the acidity of the solution:

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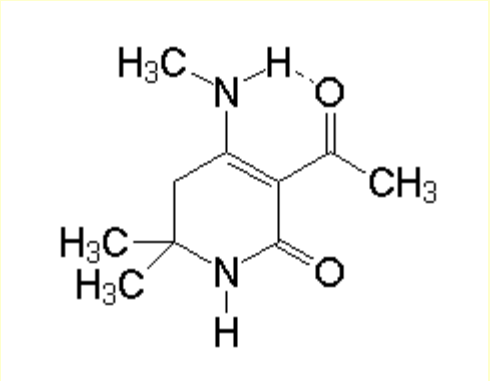
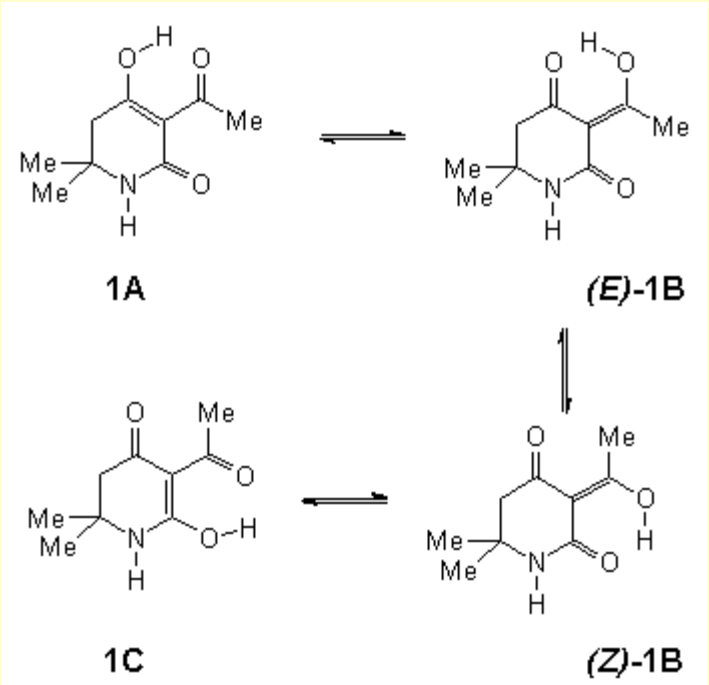
starting material	basic	neutral	weakly acidic	acidic
1	*decomposition*	**3** (52%)	**3** (63%)	*decomposition*
2	**4** (15%)	**4**(17%)	**3**(27%) + **4**(24%)	**3** (32%)

Tautomeric Equilibria of 1 and 2

4-Methylaminopyridin-2(1H)-one **2** exists according to NMR spectroscopy in one single tautomeric form with an intramolecular hydrogen bond between the 4-MeN-H and the 3-acetyl group:



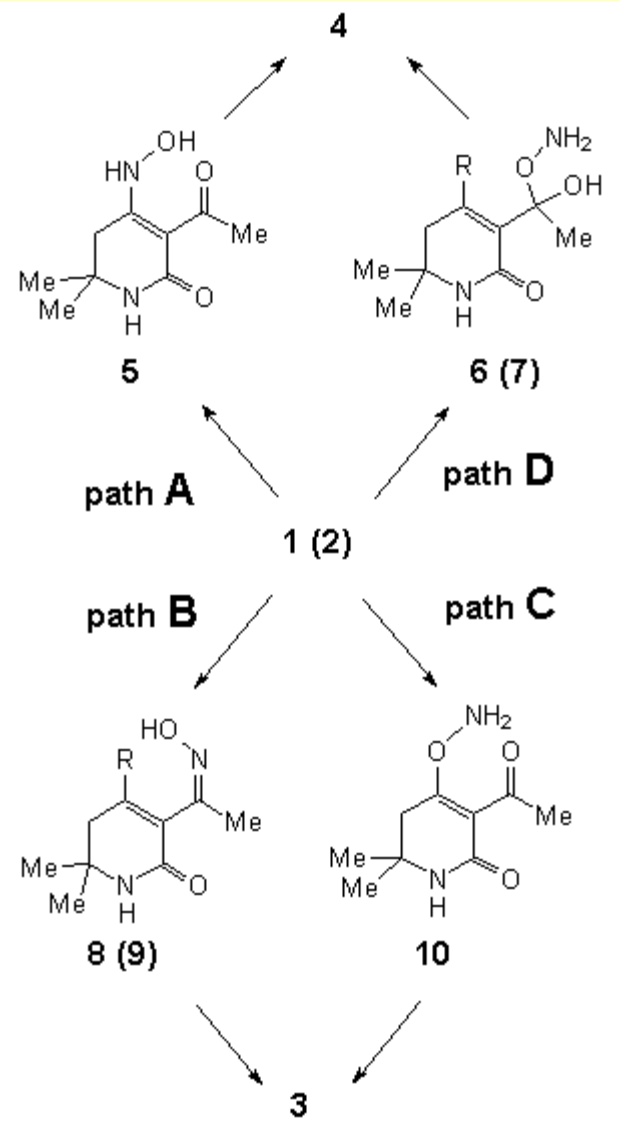
In contrast, for **1** both a tautomeric as well as configurational equilibrium was established by NMR spectroscopy:



Structure **1C** appears to be negligible, **1A** and *(E)*-**1B** are in a rapid equilibrium (approx. 20%) and *(Z)*-**1B** is the dominant species.
Hybrid Hartree-Fock/densitiy functional calculations (Table 1) corroborate these experimental results.

Molecular Orbital Calculations[5]

In order to rationalize this unexpected behavior and to establish the mechanisms of these reactions, semiempirical molecular orbital calculations (PM3) including solvent effects (SCRF approximation) were performed. For **1**, both tautomeric forms - **1A** and *(Z)*-**1B** - were taken into account; for **2** only the amino tautomer was treated. For each structure four different pathways were considered:



The detailed mechanisms for these four pathways turned out to be quite complicated [5]; thus, in Table 2 only the relative energies of the rate determining transition states are collected.
The main conclusions from these calculations are:

- The highest activation energies are found for reaction of the nucleophile with the vinylic (C-4 or exocyclic) carbon atom of compounds **1** and **2**. Thus, depending on the respective mechanism either addition of the nucleophile to form the intermediates (Scheme 3) or their cyclization, will be rate determining.
- Proton transfer steps are characterized by the highest activation energies; solvent assistance should lower these barriers.
- Reaction of hydroxylamine via its oxygen atom as nucleophile is far less feasible than reaction via the nitrogen atom.
- Tautomer *(Z)*-**1B** is not only more stable than **1A** but also more reactive.
- For the hydroxy derivative **1** the preferred reaction is calculated to be formation of **3** via path B.
- The preferred reaction of the 4-methylamino derivative **2** is formation of **4** via path A.

References

[1] J. Nadelson (Sandoz), US 4 049 813 (1977); (1978); CA 88, 68 62w; J. Nadelson(Sandoz), Ger Offen

2 609 127 (1976); (1976); CA 85, 192582r; J. Nadelson (Sandoz), US 4 131 679 (1978); (1979); CA 90, 186802z.
[2] P. Roschger and W. Stadlbauer, Liebigs Ann. Chem. 821 (1990); W. Steinschifter, W. Fiala and W. Stadlbauer, J. Heterocycl. Chem. 31, 1647 (1994); T. Kappe and B. Schnell, J. Heterocycl. Chem. 33, 663 (1996).
[3] R. Weis, K. Schweiger and W. M. F. Fabian, Monatsh. Chem. 129, 1285 (1998).
[4] T. Kappe, R. Aigner, M. Jobstl, P. Hohengassner and W. Stadlbauer, Heterocycl. Commun. 1, 341 (1995).
[5] W. M. F. Fabian, K. Schweiger and R. Weis, J. Phys. Org. Chem., in the press.

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