SELECTED REACTIONS OF
4H-PYRIDO[1,2-a]PYRIMIDIN-4-ONES AND
AN AZOXYQUINOXALINE

Thesis

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1. Introduction

The pyrido[1,2-α]pyrimidine skeleton is a privileged scaffold for facile access to “drug-like” small molecules, which usually fulfil the requirements of the “rule of five”. In particular, 4H-pyrido[1,2-α]pyrimidin-4-ones have attracted the attention of the pharmaceutical community, as they display diverse biological activities (Figure 1).\(^1\)

![Risperidone 1 (R = H) Paliperidone 2 (R = OH)](image)

**Figure 1.** Some biologically active 4H-pyrido[1,2-α]pyrimidin-4-ones

The functionalization of 4H-pyrido[1,2-α]pyrimidin-4-ones has not been widely explored, and the syntheses from 2-aminopyridines sometimes give poor yields.\(^2\) We, therefore set out to study the functionalizability of this bicycle, for which cross-coupling reactions seemed to be an appropriate synthetic tool. As of now, systematic investigations have not been reported on the cross-couplings of 4H-pyrido[1,2-α]pyrimidin-4-ones; merely a few examples of the Suzuki–Miyaura,\(^3\) Söll\(^4\) and Buchwald–Harwig\(^5\) reactions have been published.

This thesis reports on the synthesis of halogen derivatives of 4H-pyrido[1,2-α]pyrimidin-4-one, and presents an account of investigations of their reactivity in Suzuki–Miyaura and Hiyama cross-coupling reactions.

The second part of the thesis deals with two unexpected transformations of azoxyquinoxaline \(96\) (\(N,N'\)-diquinoxalin-2-yldiazene \(N\)-oxide). As only a few heterocyclic azoxy compounds have been investigated in the Wallach rearrangement,\(^6\) we set out to extend the generic Wallach rearrangement to the heterobicyclic ring systems, starting our investigations with \(96\) (Figure 2). This revealed some surprising products, depending on the reaction media.

![96](image)

**Figure 2.** \(N,N'\)-Diquinoxalin-2-yldiazene \(N\)-oxide \(96\)

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2. Methods

The syntheses of the halo derivatives of 4H-pyrido[1,2-a]pyrimidin-4-one were carried out on a 20 g scale. Cross-coupling reactions were performed on a 100 mg scale in commercially available 4 mL screw-cap vials. Transformations of 51 were carried out on a 1-5 g scale. Reactions were monitored by TLC (Silica gel 60 F$_{254}$), HPLC (VWR AV Hitachi Elite LaChrom), LC-MS (Acquity UPLC, László Balázs) or GC (Shimadzu GC-2010) chromatography. Crude products were purified by crystallization, column chromatography (Silica gel 60) or flash chromatography (CombiFlash Retrieve).

New compounds were characterized by means of NMR (Bruker Avance 200 or Bruker Avance-II 400, Sándor Boros), MS (Shimadzu GCMS-QP2010S), HRMS (Waters LCT Premier XE, László Balázs) or GC (Shimadzu GC-2010) chromatography. Crude products were purified by crystallization, column chromatography (Silica gel 60) or flash chromatography (CombiFlash Retrieve).

MO theory employing the DFT method at the B3LYP6-311++G(2d,2p) level of theory was used to discuss the potential geometry of 6-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones in vacuum (Gábor Vlád, Zoltán Mucsi). The calculated data are in fair agreement with those obtained from single-crystal X-ray diffraction studies (for compounds 21l, q and 108; Ringaku R-AXIS Rapid IP, László Párkányi). Melting points were determined in open capillary tubes with a Büchi 535 apparatus and are uncorrected.

3. New derivatives of 4H-pyrido[1,2-a]pyrimidin-4-one

3.1. Literature

3.1.1. Synthesis of halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones

The synthetic method widely used for the preparation of 4H-pyrido[1,2-a]pyrimidin-4-ones involves the condensation of 2-aminopyridines with 1,3-bifunctional compounds (e.g. 13') to yield intermediates 14', which are cyclized in a one-pot procedure or after isolation to furnish 16 (Scheme 1). The cyclization can be carried out through the action of heat, acid or basic reagents. Typical 1,3-bifunctional compounds applied in these syntheses are β-oxo esters, malonic esters, (2-alkoxymethylene)malonic esters and their

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congeners. From a synthetic aspect, the most convenient 1,3-bifunctional compounds to deal with are 2-(alkoxymethylene)malonic acid esters.

The first pyridopyrimidone 16 (R^3 = COOEt) was prepared by Lappin, who reacted 2-aminopyridines 9 with (2-ethoxymethylene)malonic ester 13' (R^1 = Et) and cyclized the resulting condensed product 14' in boiling diphenyl ether (Scheme 1). The method was later extended by Hermecz and his co-workers, who cyclized acrylic, succinic and glutaric esters to furnish various 3-substituted pyridopyrimidones 16 in moderate to excellent yields.

When intermediate 14' was unsubstituted in position C(6), the product was pyridopyrimidone 16, whereas from 6-substituted malonates 14' 7-substituted 1,8-naphthyridin-4(1H)-one 17, or a mixture of 16 and 17 was isolated. Hermecz et al. established that electrocyclization of the primarily formed N-(2-pyridyl)iminoketene 15 takes place at position N(1). Depending on the natures of R and R^3, the first formed 16 may be transformed into 17 under the conditions of the ring closure. Other research groups have also paid attention to the effect of the C(6) substituent. The experimental data indicate that the presence of a C(6) substituent enhances the ring transformation ability. The driving force is the release of the strain accumulated in the ground-state between the C(4)=O group and the C(6) substituent.

Meldrum’s acid derivative 14' (R^1 = isopropylidene) was also subjected to the ring closure protocol. When the cyclization was performed under acidic conditions, pyrido-pyrimidone-3-carboxylic acid 16 (R^3 = COOH) was isolated. The thermal cyclization of 14' (R = isopropylidene) was accompanied by decarboxylation at position C(3) (Scheme 1).

Scheme 1. Syntheses of 4H-pyrido[1,2-a]pyrimidin-4-ones

3.1.2. Cross-coupling reactions of halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones

As of now, systematic investigations have not been reported on cross-couplings of (pseudo)halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones; merely a few examples of the Suzuki–Miyaura, Stille and Buchwald–Harwig reactions have been published.

The pyrido[1,2-a]pyrimidin-4-one skeleton was substituted in positions C(3), C(7) and C(9) in cross-coupling reactions, using the appropriate 3-iodo, 3-, 7- or 9-bromo or 9-triflate derivatives and, generally, Na_2CO_3 as base and 5 mol% Pd(PPh_3)_4 as catalyst. Palani et al. reduced the long reaction periods by the application of microwave technique and / or Pd^{0}-

catalysts with high donicity, e.g. Pd(dppf)Cl$_2$.$^{14}$ Yoshida and co-workers synthesized potential MexAB-OprM specific efflux pump inhibitors from a 2-chloro derivative. Mainly (het)aryl and alkenyl groups were introduced by means of the Suzuki–Miyaura and Stille techniques.$^{4}$ Buchwald–Hartwig aminations of a 9-bromo derivative led to benzylamine and aniline derivatives usually in poor yields.$^{5}$

3.2. Results and discussion

3.2.1. Syntheses of halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones

For the synthesis of pyridopyrimidones 21, Meldrum’s acid 55 was selected instead of dimethyl malonate, because 55 is a stronger CH acid,$^{15}$ and thermal cyclization of 19 gives 21 directly in a one-pot reaction. The detailed synthetic route for 21 is depicted in Scheme 2. The addition of 6-unsubstituted malonates 19a-k to preheated diphenyl ether afforded 21a-k in yields of 59-84%. Our work-up protocol provided 15-30% better yields for 21i-k (R = 7-Cl, 7-Br, 7-I) than those in the earlier methods.$^{13,16}$ 3-Halopyridopyrimidones 57 were obtained from 4H-pyrido[1,2-a]pyrimidin-4-one 21a in yields of 76-86% by reaction with the respective N-halosuccinimide.$^{17}$ 13 halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones (nine new compounds) were synthesized.

6-Substituted malonates 19m-p were also subjected to the ring-closure protocol, and the results are shown in Table 1. The thermal cyclization of the 6-fluoro, 6-chloro and 6-bromo derivatives 19m-o afforded not pyridopyrimidones 21m-o, but mixtures of 7-halo-naphthyridones 58m-o and 1-(6-halo-2-pyridyl)-3-[(6-halo-2-pyridylamino)methylene]-1,2,3,4-tetrahydropyridine-2,4-diones 59m-o. Products 58 and 59 were separated by fractional crystallization from EtOH, as 59 exhibited lower solubility.

By-product 59 might be formed in a [4+2]-cycloaddition from iminoketene 60. The cyclodimerization may occur in a head-to-head (leading to 62) or a head-to-tail manner.

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**Scheme 2.** Syntheses of halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones

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Table 1. Thermal cyclization of malonates 19m-p

<table>
<thead>
<tr>
<th>Compd.</th>
<th>6-R</th>
<th>21 [%]</th>
<th>58 [%]</th>
<th>59 [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>19m</td>
<td>F</td>
<td>71</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>19n</td>
<td>Cl</td>
<td>–</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>19o</td>
<td>Br</td>
<td>–</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>19p</td>
<td>I</td>
<td>81</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

[a] HPLC purity at 220 nm: 80-95%; [b] + / – : detected / not detected by LC-MS

Table 2. Calculated ground-state geometry of 6-substituted pyridopyrimidones 21a,l-p

<table>
<thead>
<tr>
<th>Compd.</th>
<th>6-R</th>
<th>ν</th>
<th>Bond length N(5)–C(4) [pm]</th>
<th>Bond length C(6)–R [pm]</th>
<th>Distance O–R [a] [pm]</th>
<th>Torsion angle O=C(4)–C(6)–R [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>21a</td>
<td>H</td>
<td>0</td>
<td>146.5</td>
<td>107.8</td>
<td>222.4</td>
<td>0.01</td>
</tr>
<tr>
<td>21l</td>
<td>Me</td>
<td>0.52</td>
<td>147.2</td>
<td>150.5</td>
<td>263.6</td>
<td>15.2</td>
</tr>
<tr>
<td>21m</td>
<td>F</td>
<td>0.27</td>
<td>149.4</td>
<td>132.1</td>
<td>251.8</td>
<td>12.6</td>
</tr>
<tr>
<td>21n</td>
<td>Cl</td>
<td>0.55</td>
<td>148.2</td>
<td>173.4</td>
<td>278.6</td>
<td>30.0</td>
</tr>
<tr>
<td>21o</td>
<td>Br</td>
<td>0.65</td>
<td>148.2</td>
<td>190.2</td>
<td>287.1</td>
<td>30.8</td>
</tr>
<tr>
<td>21p</td>
<td>I</td>
<td>0.78</td>
<td>147.7–150.1</td>
<td>212.2–215.1</td>
<td>296.9–308.6</td>
<td>27.5–33.8</td>
</tr>
</tbody>
</table>

[a] distance between the geometric centres

(furnishing by-product 59). The DFT calculations indicate that the latter is ~ 30 kJ/mol more preferable. The structure of 59 was elucidated by means of detailed NMR studies. 18

6-Iodo derivative 19p surprisingly yielded 6-iodo-4H-pyrido[1,2-a]pyrimidin-4-one 21p as the only isolated product. To prove the structure, 21p was also synthesized by an independent route – via lithiation from non-halogenated heterocycle 21a (Scheme 3). 19 As far as we aware, this is the first example of the functionalization of the 4H-pyrido[1,2-a]-pyrimidin-4-one skeleton at position C(6).

Theoretical considerations were devoted to the explanation of these surprising results. We carried out calculations on the potential ground-state geometry of selected 6-substituted pyridopyrimidones. The calculated geometry of 21a,l-p was analysed with respect to possible (de)stabilizing forces and the interactions caused by the C(6) substituent. Some selected characteristic data are shown in Table 2.

In summary, the thermal ring transformation ability of 4H-pyrido[1,2-a]pyrimidin-4-ones is governed by both the steric and the electrostatic interactions between the oxygen of the carbonyl group and the substituent in the peri position. We demonstrated that for 6-substituted pyridopyrimidones 21, when the C(6) substituent X has a lone pair(s) on the atom (e.g. X = F) connected to the ring, the lone pair electrons’ repulsion of substituent X and the oxygen of the C(4)=O group could play a particular role in the ring transformation. 20 The electrostatic interaction gradually decreases in the sequence F > Cl > Br > I derivatives (Figure 3). The ready polarizability of the electron cloud of the iodine atom also decreases the repulsive

Table 2. Calculated ground-state geometry of 6-substituted pyridopyrimidones 21a,l-p


19 This method could not be extended to the preparation of the other 6-halo-4H-pyrido[1,2-a]pyrimidin-4-ones 21. Experiments using electrophiles such as Br2, 1,2-dibromoethane, NBS, NCS, CO2, DMF, Me–S–S–Me or benzaldehyde were not successful. Only a D atom could be introduced onto position C(6) by using D2O.

interaction. Furthermore, 6-iodo derivative 21p may be stabilized by weak intramolecular halogen bonding.\textsuperscript{21} The 6-iodo derivative 21p is therefore more stable than the other 6-halo derivatives, even at high temperature (~260 °C).\textsuperscript{11}

![Figure 3. Calculated electrostatic potential surfaces of 6-halo-4H-pyrido[1,2-a]pyrimidin-4-ones 21a-l-p](image)

### 3.2.2. Cross-coupling reactions of halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones

The functionalization of the 4H-pyrido[1,2-a]pyrimidin-4-one ring system is not a completely settled topic. Accordingly, we set out to study the functionalizability of this bicycle, for which cross-coupling reactions seemed to be the appropriate synthetic tool. Accordingly to the promising literature data, the commercial availability and the ease of handling of various boronic acids, we started our investigations with the Suzuki–Miyaura reaction.

To prove the reactivity of the 4H-pyrido[1,2-a]pyrimidin-4-one skeleton, we carried out coupling reactions with phenylboronic acid (Ar = Ph) and 2-, 3-, 7-, 8- and 9-chloro derivatives (63, 57, 21c, f, i).\textsuperscript{22} The reactions were monitored by HPLC. Relative reactivity was characterized by HPLC yields after a 4 h reaction period. We found that the reactivity sequence for the conditions depicted in \textbf{Scheme 4} was reasonably well predicted by the “rule of Handy and Zhang”,\textsuperscript{23} as only the sequence for positions C(2) and C(8) seems to be reversed, as follows:

\begin{align*}
\text{Posn. C(8) (7.97 ppm)} & \geq \text{C(2) (8.31 ppm)} > \text{C(9) (7.70 ppm)} > \text{C(7) (7.30 ppm)} > \text{C(3) (6.34 ppm)}. \\
\end{align*}

A plausible explanation might be that, in the case of 8-chloro derivative 21f, the reaction (oxidative addition) might have an $S_1$1 rather than an $S_2$2 nature relative to the other chloro derivatives.

To demonstrate the functionalizability of the 4H-pyrido[1,2-a]pyrimidin-4-one skeleton, a wide range of substituents were introduced onto the bicycle. Some selected examples prepared from chloro derivatives are depicted in \textbf{Scheme 4}. The reaction conditions applied and the work-up protocol were not optimized. The crude products were purified by column or


\textsuperscript{22} 2-Chloro-4H-pyrido[1,2-a]pyrimidin-4-one 63 is commercially available. It was used after recrystallization from diisopropyl ether.

\textsuperscript{23} Handy and Zhang proposed a simple guide for predicting the order of cross-coupling reactions in polyhalogenated heteroaromatics, based upon the $^1$H NMR chemical shifts of the parent non-halogenated heteroaromatics: Handy, S. T.; Zhang, Y. \textit{Chem. Commun}. \textbf{2006}, \textit{299}.

\textsuperscript{24} The chemical shift of 6-H (8.96 ppm) could not be considered as it is influenced by the anisotropic effect of the neighbouring C(4)=O carbonyl group.
flash chromatography. The isolated yields varied from poor to excellent (38-99%). 28 pyridopyrimidones (17 new derivatives) were synthesized.

To reduce the long reaction periods (24-96 h), iodo and bromo derivatives were also tested in the reaction. A preference was observed for the hydrodehalogenation side-reaction in the slow-reacting positions C(3) and C(7) (~10%), especially for 3- and 7-iodo derivatives (57c and 21k), leading to better isolated yields for chloro and bromo compounds.

In summary, various het(aryl), alkenyl and benzyl substituents were introduced onto the 4H-pyrido[1,2-α]pyrimidin-4-one skeleton, making use of comparatively cheaper chloro derivatives under simple conditions.

The Hiyama cross-coupling of an organosilicon reagent is known as alternative methodology to the Suzuki–Miyaura reaction for the synthesis of biaryl compounds. Preliminary investigations of the coupling of 7-bromo derivative 21j with trimethoxyphenylsilane 85 were also performed, and a comparison was made with the Suzuki–Miyaura reaction. A series of palladium catalysts, fluoride sources and solvents were tested; the most reasonable combination is shown in Scheme 5. We found that 4H-pyrido[1,2-α]pyrimidin-4-one substrates are more sensitive to the Hiyama reaction conditions, yielding the expected 7-phenyl derivative 66 in only a medium isolated yield, as the N(5)–C(4) intramolecular amide bond undergoes hydrolysis under the harsh reaction conditions. Other halo derivatives furnished the expected phenyl derivatives 64-68,21q in poor to good HPLC yields (~15-85%).
4. Unexpected transformations of an azoxyquinoxaline

4.1. Literature

4.1.1. Wallach rearrangement

Treatment of azoxybenzene 87 and its derivatives with strong acids is known to result in the corresponding hydroxyazobenzene 88 (Scheme 6). This transformation is called the Wallach rearrangement. At low acidities, the hydroxy group generally appears in the para position and product 88 is obtained. Though blocking of both para positions may give rise to the ortho-hydroxy derivative, ipso substitution at one of the para positions is also possible. At higher concentrations, other products may also be formed, e.g. azobenzene, or some polymeric materials of aniline and arylsulfonic acids.

Despite the experimental evidence, the mechanism has not yet been completely identified. In support of the experimental observations, MO theory employing the semi-empirical AM1 method has been used to locate and discuss the energetics of the intermediates and transition-states for the rearrangement in vacuum.

The experimental data seem to provide a firmer basis for the dicationic intermediate mechanism (Scheme 6), though other mechanisms, involving an unsymmetrical quinonoid or an N,N'-oxide intermediate with only one positive charge, have also been proposed. The main feature of the dicationic intermediate mechanism is the postulated involvement of the symmetrical intermediate 93. It has proved possible to obtain 89 and 93 as stable species in super acid solutions: dication 93 has been detected by ¹H NMR in a system of fluorantimonic acid and azoxybenzene 93 at -50 °C.

![Scheme 6. Wallach rearrangement](image)

4.2. Results and discussion

4.2.1. Acid-catalysed transformation of azoxyquinoxaline 96

We first applied the original Wallach rearrangement conditions, treating azoxy compound 96 with conc. sulfuric acid at 140 °C for 10 min. A red product was isolated, and characterized by HRMS. Surprisingly, the assay did not indicate any oxygen atom: instead of the Wallach rearrangement, formally HNO was eliminated from 96. On the basis of 2D NMR measurements, a new pentacyclic system, imidazo[1,2-a:4,5-b']diquinoxaline 98, is proposed.

Table 3. Influence of the nature of the medium and temperature on the transformation of 96

<table>
<thead>
<tr>
<th>Medium</th>
<th>pKₐ</th>
<th>Temp. [°C]</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>conc. H₂SO₄</td>
<td>-3.0</td>
<td>140</td>
<td>98</td>
<td>63</td>
</tr>
<tr>
<td>CH₃SO₃H</td>
<td>-2.6</td>
<td>140</td>
<td>98</td>
<td>56</td>
</tr>
<tr>
<td>CF₃COOH</td>
<td>-0.25</td>
<td>72</td>
<td>98</td>
<td>56</td>
</tr>
<tr>
<td>HCOOH</td>
<td>3.77</td>
<td>101</td>
<td>98</td>
<td>67</td>
</tr>
<tr>
<td>AcOH</td>
<td>4.76</td>
<td>118</td>
<td>108</td>
<td>85</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>4.76</td>
<td>140</td>
<td>108</td>
<td>87</td>
</tr>
<tr>
<td>glycol</td>
<td>4.76</td>
<td>140</td>
<td>108</td>
<td>80</td>
</tr>
</tbody>
</table>

Scheme 7. Possible mechanism of formation of imidazodiquinoxaline 98

4.2.2. Thermal transformation of azoxyquinoxaline 96

When pKₐ of the medium was systematically increased, dramatic changes were observed. Reaction in boiling acetic acid for 10 min provided a homogeneous yellow reaction mixture. The isolated product was characterized by HRMS: the assay indicated the elimination of N₂ from 96. 2D NMR measurements suggested the structure 1-(quinoxalin-2-yl)quinoxalin-2(1H)-one 108, which was proved by single-crystal X-ray crystallography (Table 3).34

The question arose of the possibility of a thermal reaction; the same product was obtained from neutral organic solvents, e.g. acetic anhydride and glycol, and even from neat 96. Yields and reaction conditions are listed in Table 3. In solvents, the N₂ elimination proceeded at much lower temperatures, indicating a strong solvent effect. Accordingly, we carried out thermoanalytical studies (DSC, TG and DTG analyses).

This type of thermal transformation does not appear to have been widely described in the literature: only one example of the thermolytic loss of N₂ from azoxy compounds is known.35 On the evidence of these studies and the literature data, we proposed a mechanistic pathway involving a [2+2]-cycloreversion step, which should lead to the cleavage of both C–N bonds (Scheme 8).

5. **Summary of the new findings**

1. A productive one-pot synthesis was developed for the preparation of halogenated 4H-pyrido[1,2-α]pyrimidin-4-ones by the thermal cyclization and decarboxylation of isopropylidene (2-pyridylamino)methylenemalonates, prepared from 2-aminopyridines and isopropylidene methoxymethylenemalonate formed in situ from Meldrum’s acid and trimethyl orthoformate. Seven new derivatives were synthesized.\(^1\)

2. The thermal cyclization of isopropylidene (6-fluoro-, 6-chloro- and 6-bromo-2-pyridylamino)methylenemalonates was found to afford a mixture of 7-halo-1,8-naphthyridin-4(1H)-ones and 1-(6-halo-2-pyridyl)-3-[(6-halo-2-pyridylamino)methylene]-1,2,3,4-tetrahydropyridine-2,4-diones as by-products. An explanation of the formation of the by-products was proposed: the pyridin-2,4-dione structure results from a head-to-tail \([4+2]\)-cyclo-dimerization from an \(N\)-(2-pyridyl)iminoketene intermediate. Possible intermediates and transition-states were determined by calculation, employing the DFT method at the B3LYP6-311++G(2d,2p) level of theory.\(^1\)\(^2\)

3. We reported the first example of the functionalization of the 4H-pyrido[1,2-α]pyrimidin-4-one skeleton at position C(6): 6-iodo-4H-pyrido[1,2-α]pyrimidin-4-one was synthesized from 4H-pyrido[1,2-α]pyrimidin-4-one via lithiation. The method could not be extended to other 6-halo derivatives.\(^2\)

4. DFT calculations were carried out on the potential ground-state geometry of 6-substituted-4H-pyrido[1,2-α]pyrimidin-4-ones at the B3LYP6-311++G(2d,2p) level of theory to investigate possible (de)stabilizing forces and interactions caused by the C(6) substituent. We demonstrated that the thermal ring transformation ability is governed by both the steric and the electrostatic interactions between the oxygen of the carbonyl group and the substituent in the \textit{peri} position. When the C(6) substituent has a lone pair(s) on the atom connected to the ring, the lone pair electrons’ repulsion of the substituent and the oxygen of the C(4)=O group could play a particular role in the ring transformation.\(^2\)

5. The reactivity sequence in the Suzuki–Miyaura cross-coupling reactions of the different positions of the 4H-pyrido[1,2-α]pyrimidin-4-one skeleton was investigated, and was found to be: posn. C(8) \(\geq\) C(2) \(>\) C(9) \(>\) C(7) \(>\) C(3). With the use of comparatively cheaper chloro derivatives under simple conditions, 17 new derivatives of 4H-pyrido[1,2-α]pyrimidin-4-one were synthesized in good to excellent yields.\(^3\)
6. Preliminary investigations of the Hiyama cross-coupling of halogenated 4H-pyrido[1,2-a]pyrimidin-4-ones with trimethoxyphenylsilane were performed and in addition, a comparison with the Suzuki–Miyaura reaction was also made. We found that 4H-pyrido[1,2-a]pyrimidin-4-one substrates are more sensitive under the Hiyama reaction conditions, yielding the expected phenyl derivatives only in poor to good HPLC yields, as the N(5)–C(4) intramolecular amide bond undergoes hydrolysis under the harsh reaction conditions.\(^{[4]}\)

7. I recognized that the treatment of \(N,N'\)-diquinoxalin-2-yldiazene \(N\)-oxide with strong acids or thermally led to two different reaction pathways, furnishing imidazo[1,2-a:4,5-b']diquinoxaline and 1-(quinoxalin-2-yl)quinoxalin-2(1H)-one, respectively. Possible interpretations of the formation of the two different products are proposed\(^{[5],[6]}\).

6. Publications

6.1. Publications relating to the Thesis


6.2. Oral presentations


6.3. Poster presentations

módosítása Átmenetifémek Katalizált Reakciókban – Sanofi-aventis Thesis Day,


iminometilen]keténk Gyűrűzárási Reakcióiról – Elméleti Szerves Kémiai
Munkabizottsági Ülés, Budapest, 1 December, 2008.


amino)metilen]malonátok Gyűrűzárási Reakcióiról – Heterociklusos Munkabizottsági