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

Thesis

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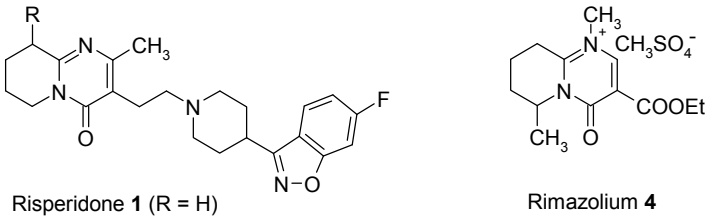
1. Introduction

The pyrido[1,2-*a*]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, 4*H*-pyrido[1,2-*a*]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)

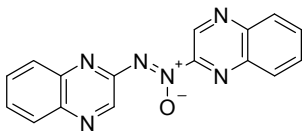
Rimazolium **4**

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

The functionalization of 4*H*-pyrido[1,2-*a*]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 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones; merely a few examples of the Suzuki–Miyaura,[3] Stille[4] and Buchwald–Harwig[5] reactions have been published.

This thesis reports on the synthesis of halogen derivatives of 4*H*-pyrido[1,2-*a*]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

Figure 2. *N,N*′-Diquinoxalin-2-yldiazene *N*-oxide **96**

[1] Hermecz, I.; Vasvári-Debreczy, L. *Compr. Heterocycl. Chem. III* **2007**, *12*, 77. Jones, K.; Vol. Ed.; Katritzky, A. R.; Execut. Ed.
[2] Lochead, A.; Saady, M.; Yaiche, P. *Eur. Pat. Appl.* 2,138,493 (**2009**).
[3] Liu, S.; Fu, J.; Kamboj, R.; Jia, Q.; Wood, M.; Chowdhury, S.; Sun, J. *PTO Int. Appl.* WO**2008**/097991.
[4] Yoshida, K.-i.; Nakayama, K.; Kuru, N.; Kobayashi, S.; Ohtsuka, M.; Takemura, M.; Hoshino, K.; Kanda, H.; Zhang, J. Z.; Lee, V. J.; Watkins, W. J. *Bioorg. Med. Chem.* **2006**, *14*, 1993.
[5] Knight, Z. A.; Chiang, G. G.; Alaimo, P. J.; Kenski, D. M.; Ho, C. B.; Coan, K.; Abraham, R. T.; Shokat, K. M. *Bioorg. Med. Chem.* **2004**, *12*, 4749.
[6] Buncel, E.; Keum, S.-R.; Rajagopal, S.; Cox, R. A. *Can. J. Chem.* **2009**, *87*, 1127.

2. Methods

The syntheses of the halo derivatives of 4*H*-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*), UV (Agilent 8453 UV-Visible spectrometer, *Mária Kiss*), IR (VERTEX 70, *Lászlóné Faragó*) and 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.

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 4*H*-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**). Calculations on 6-iodo derivative **21p** were carried out at the B3LYP/LANL2DZ, B3LYP/DGDZVP, B3LYP/CEP31G, B3LYP/CEP121G, MP2/LANL2DZ and MP2/DGDZVP levels, and the ranges are given. For characterization of the steric demand of C(6) substituents, we selected Charton's *v* values derived from the van der Waals radii.[7] Electrostatic potential surfaces are depicted at the 0.02 electron/au^3 density isocontour level (**Figure 3**). The energetic profile of the thermal cyclization leading to the formation of **21,58,59** was established, and possible intermediates and transition-states were also located.

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

3.1. Literature

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

The synthetic method widely used for the preparation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **16** involves the condensation of 2-aminopyridines **9** 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,[8] acid[9] or basic reagents.[10] Typical 1,3-bifunctional compounds applied in these syntheses are β-oxo esters, malonic esters, (2-alkoxymethylene)malonic esters and their

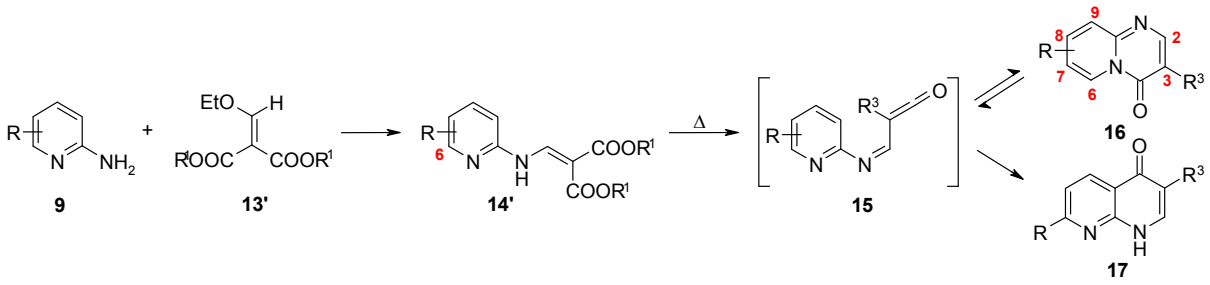
[7] Charton, M. *J. Am. Chem. Soc*. **1975**, *97*, 1552.
[8] a) Lappin, G. R. *J. Am. Chem. Soc.* **1948**, *70*, 3348. b) Sterling Drug Inc. *Brit. Pat.* 1,147,760 (**1969**).
[9] a) Hermecz, I.; Mészáros, Z.; Vasvári-Debreczy, L.; Horváth, A.; Horváth, G.; Pongor-Csákvári, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 789. b) Vasvári-Debreczy, L.; Hermecz, I.; Mészáros, Z.; Horváth, Á.; Simon-Párkányi, P. *J. Chem. Soc., Perkin Trans. 1* **1978**, 795.
[10] Vasvári-Debreczy, L.; Hermecz, I.; Mészáros, Z. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1799.

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**).[8a] The method was later extended by Hermecz and his co-workers, who cyclized acrylic,[9a] succinic and glutaric esters[9b] 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(1*H*)-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.[9] 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.[11] 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.[12]

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.[13] The thermal cyclization of **14'** (R = isopropylidene) was accompanied by decarboxylation at position C(3) (**Scheme 1**).[8b]



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

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

As of now, systematic investigations have not been reported on cross-couplings of (pseudo)halogenated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones; merely a few examples of the Suzuki–Miyaura,[3] Stille[4] and Buchwald–Harwig[5] 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.[3] Palani *et al.* reduced the long reaction periods by the application of microwave technique and / or $Pd^{(0)}$-

[11] Ferrarini, P. L.; Mori, C.; Manera, C.; Martinelli, A.; Mori, F.; Saccomanni, G.; Barili, P. L.; Betti, L.; Giannaccini, G.; Trincavelli, L.; Lucacchini, A. *J. Med. Chem*. **2000**, *43*, 2814.
[12] Hermecz, I.; Vasvári-Debreczy, L.; Simon, K. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1287.
[13] Ravina, I.; Zicane, D.; Petrova, M.; Gudriniece, E.; Kalejs, U. *Chem. Heterocycl. Compd.* **2002**, *38*, 836.

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]

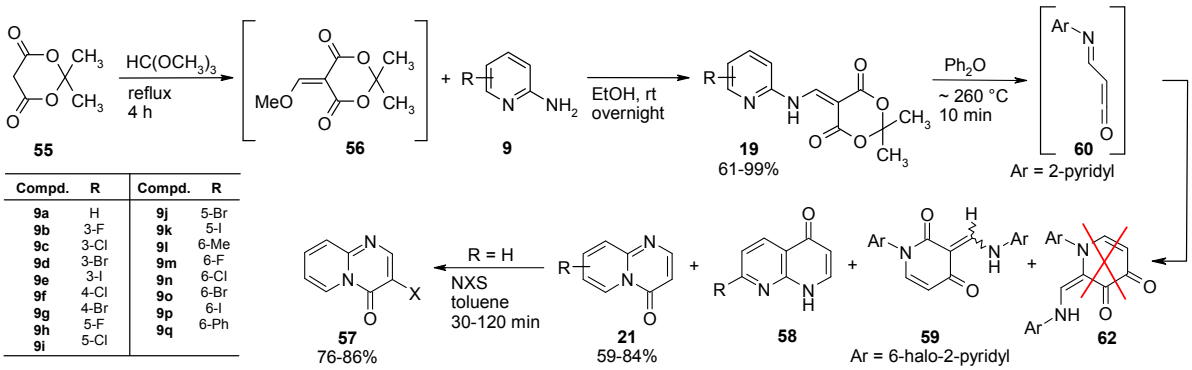
3.2. Results and discussion

3.2.1. Syntheses of halogenated 4*H*-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 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **21a** in yields of 76-86% by reaction with the respective *N*-halosuccinimide.[17] 13 halogenated 4*H*-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



Compd.	R	Compd.	R
9a	H	9j	5-Br
9b	3-F	9k	5-I
9c	3-Cl	9l	6-Me
9d	3-Br	9m	6-F
9e	3-I	9n	6-Cl
9f	4-Cl	9o	6-Br
9g	4-Br	9p	6-I
9h	5-F	9q	6-Ph
9i	5-Cl		

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

[14] a) Palani, A.; Rao, A. U.; Chen, X.; Shao, N.; Huang, Y. R.; Aslanian, R. G. *PTO Int. Appl.* WO**2010**/071819. b) Palani, A.; Berlin, M. Y.; Aslanian, R. G.; Vaccaro, H. M.; Chan, T.-Y.; Xiao, D.; Degrado, S.; Rao, A. U.; Chen, X.; Lee, Y. J.; Sofolarides, M. J.; Shao, N.; Huang, Y. R. *PTO Int. Appl.* WO**2010**/045303.

[15] a) Arnett, E. M.; Harrelson Jr., J. A. *J. Am. Chem Soc*. **1987**, *109*, 809. b) Wang, X.; Houk, K. N. *J. Am. Chem. Soc*. **1988**, *110*, 1870.

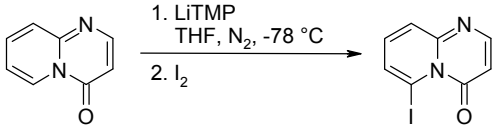
[16] Lee, W.-C.; Sun, L.; Shan, F.; Chuaqui, C.; Cornebise, M.; Pontz, T. W.; Carter, M.; Singh, J.; Boriaci-Sjodin, P. A.; Ling, L.; Setter, R. C. *PTO Int. Appl.* WO**2004**/072033.

[17] Adams, R.; Pachter, I. J. *J. Am. Chem. Soc.* **1954**, *76*, 1845.

Table 1. Thermal cyclization of malonates **19m-p**

Compd.	6-R	**21** [%]	**58** [%]	**59** [%][a]
19m	F	– [b]	71	6
19n	Cl	–	75	8
19o	Br	–	69	6
19p	I	81	+	+

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



21a **21p**
HPLC yield: ~ 80%
isolated yield: 27%

Scheme 3. Synthesis of 6-iodo-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one **21p**

(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-4*H*-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 4*H*-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 4*H*-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-subsituted 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**

Compd.	6-R	*ν*	Bond length N(5)–C(4) [pm]	Bond length C(6)–R [pm]	Distance O···R[a] [pm]	Torsion angle O=C(4)···C(6)-R [°]
21a	H	0	146.5	107.8	222.4	0.01
21l	Me	0.52	147.2	150.5	263.6	15.2
21m	F	0.27	149.4	132.1	251.8	12.6
21n	Cl	0.55	148.4	173.4	278.6	30.0
21o	Br	0.65	148.2	190.2	287.1	30.8
21p	I	0.78	147.7-150.1	212.2-215.1	296.9-308.6	27.5-33.8

[a] distance between the geometric centres

[18] A similar dimer formation was earlier described in the case of 2-pyridylketene: Khun, A.; Plüg, C.; Wentrup, C. *J. Am. Chem. Soc*. **2000**, *122*, 1945.

[19] This method could not be extended to the preparation of the other 6-halo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **21**. Experiments using electrophiles such as Br_2, 1,2-dibromoethane, NBS, NCS, CO_2, DMF, Me–S–S–Me or benzaldehyde were not successful. Only a D atom could be introduced onto position C(6) by using D_2O.

[20] The influence of the electron-pair repulsion of heteroatoms on a strong conformation preference was recently reported: a) Ballesteros-Garrido, R.; Blanco, F.; Ballesteros, R.; Leroux, F. R.; Abarca, B.; Colobert, F.; Alkorta, I.; Elguero, J. *Eur. J. Org. Chem*. **2009**, 5765. b) Chein, R. J.; Corey, E. J. *Org. Lett*. **2010**, *12*, 132.

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

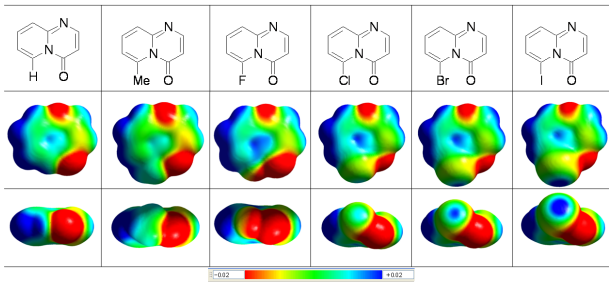


Figure 3. Calculated electrostatic potential surfaces of 6-halo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **21a,l-p**

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

The functionalization of the 4*H*-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 4*H*-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**).[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 **Scheme 4** was reasonably well predicted by the "rule of Handy and Zhang",[23] as only the sequence for positions C(2) and C(8) seems to be reversed, as follows:

Posn. C(8) (7.97 ppm) ≥ C(2) (8.31 ppm) > C(9) (7.70 ppm) > C(7) (7.30 ppm) > C(3) (6.34 ppm).[24]

A plausible explanation might be that, in the case of 8-chloro derivative **21f**, the reaction (oxidative addition) might have an S_N1 rather than an S_N2 nature relative to the other chloro derivatives.

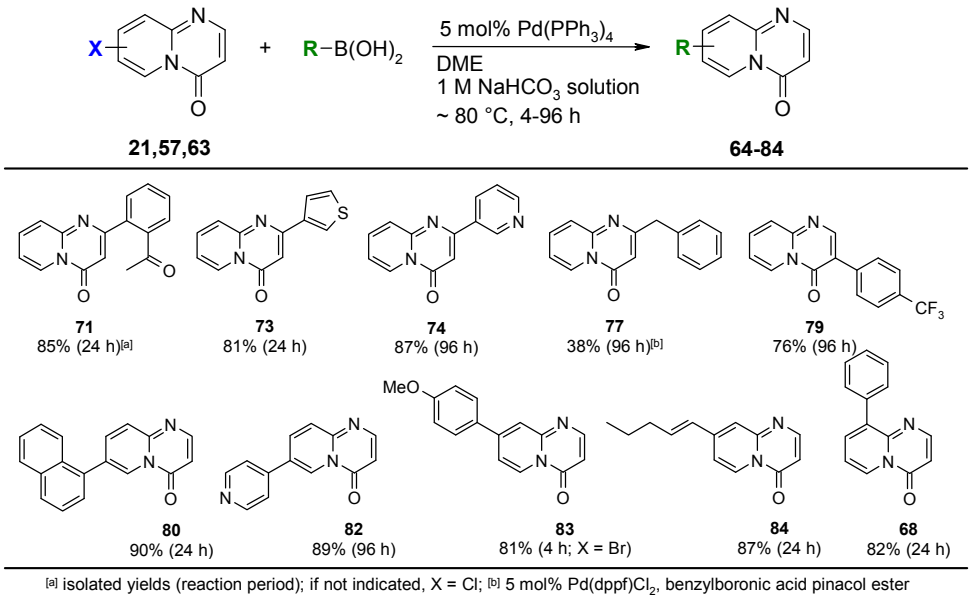
To demonstrate the functionalizability of the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton, a wide range of substituents were introduced onto the bicycle. Some selected examples prepared from chloro derivatives are depicted in **Scheme 4**. The reaction conditions applied and the work-up protocol were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

[21] Intramolecular halogen bonding: Palusiak M.; Grabowski S. *J. Struct. Chem*. **2008**, *19*, 5.

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

[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. *Chem. Commun*. **2006**, 299.

[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.



[a] isolated yields (reaction period); if not indicated, X = Cl; [b] 5 mol% $Pd(dppf)Cl_2$, benzylboronic acid pinacol ester

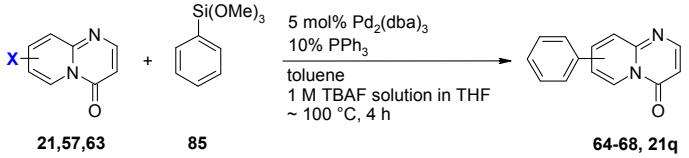
Scheme 4. Suzuki–Miyaura reactions of halogenated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

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 4*H*-pyrido[1,2-*a*]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.[25] 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 4*H*-pyrido[1,2-*a*]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%).



Comp.	X	HPLC yield [%]	Comp.	X	HPLC yield [%]
63	2-Cl	20	**21k**	7-I	75
57a	3-Cl	55	**21f**	8-Cl	15
57b	3-Br	75	**21g**	8-Br	25
57c	3-I	80	**21c**	9-Cl	40
21p	6-I	50	**21d**	9-Br	80
21i	7-Cl	55	**21e**	9-I	85
21j	7-Br	82			

Scheme 5. Hiyama reactions of halogenated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

[25] Hiyama, T. *J. Org. Chem.* **2002**, *653*, 58.

4. Unexpected transformations of an azoxyquinoxaline

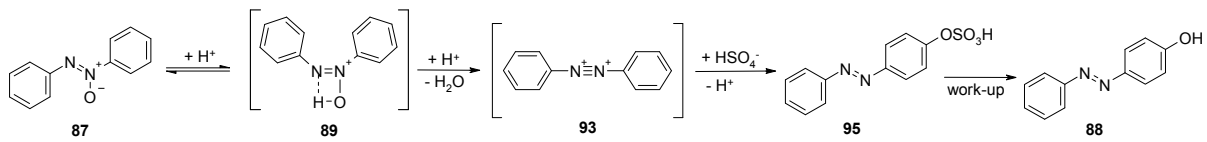
4.1. Literature

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,[26] *ipso* substitution at one of the *para* positions is also possible.[27] At higher concentrations, other products may also be formed, e.g. azobenzene,[28] or some polymeric materials of aniline and arylsulfonic acids.[26]

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.[29]

The experimental data seem to provide a firmer basis for the *dicationic intermediate* mechanism (**Scheme 6**), though other mechanisms, involving an unsymmetrical quinonoid[30] or an *N*,*N'*-oxide intermediate[31] 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 ^{1}H NMR in a system of fluoro-antimonic acid and azoxybenzene **93** at -50 °C.[32]



Scheme 6. Wallach rearrangement

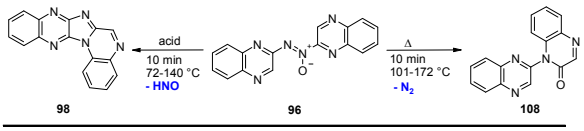
4.2. Results and discussion

4.2.1. Acid-catalysed transformation of azoxyquinoxaline 96

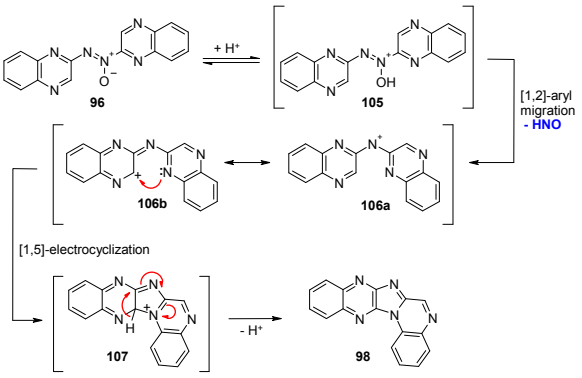
We first applied the original Wallach rearrangement conditions, treating azoxy compound **96** with conc. sulfuric acid at 140 °C for 10 min. A red product was isolated, and characterized by HRMS. Surprisingly, the assay did not indicate any oxygen atom: instead of the Wallach rearrangement, formally **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

[26] Dolenko, A.; Buncel, E. *Can. J. Chem.* **1974**, *52*, 623.
[27] Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 643.
[28] Shimao, I.; Fujimori, K.; Oae, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 546.
[29] a) Özen, A. S.; Erdem, S. S.; Aviyente, V. *Struct. Chem.* **1998**, *9*, 15. b) Cox, R. A.; Fung, D. Y. K.; Csizmadia, I. G.; Buncel, E. *Can. J. Chem.* **2003**, *81*, 535.
[30] Cox, R. A.; Buncel, E. *J. Am. Chem. Soc.* **1975**, *97*, 1871.
[31] Yamamoto, J.; Aimi, H.; Masuda, Y.; Sumida, T.; Umezu, M. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1565.
[32] Olah, G. A.; Dunne, K.; Kelly, D. P.; Mo, Y. K. *J. Am. Chem. Soc.* **1972**, *94*, 7438.

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



Medium	pK_a	Temp. [°C]	Product	Yield [%]
conc. H_2SO_4	-3.0	140	**98**	63
CH_3SO_3H	-2.6	140	**98**	56
CF_3COOH	-0.25	72	**98**	56
HCOOH	3.77	101	**98**	67
AcOH	4.76	118	**108**	85
Ac_2O		140	**108**	87
glycol		140	**108**	80



Scheme 7. Possible mechanism of formation of imidazodiquinoxaline **98**

for the structure (**Table 3**). The structure was supported by an independent synthesis, the imidazole ring being formed via Buchwald–Hartwig amination.[33]

After the structure of **55** had been established, we carried out studies to evaluate the effects of the acid strength and temperature on the course of the transformation. Yields and reaction conditions are listed in **Table 3**. Stirring azoxyquinoxaline **96** at 72-140 °C for 10 min in various strong mineral and organic acids uniformly furnished **98** in moderate yields of 56-67%. A possible interpretation of the formation of **98** was proposed. The pentacyclic skeleton may be formed through [1,5]-electrocyclization (**Scheme 7**).

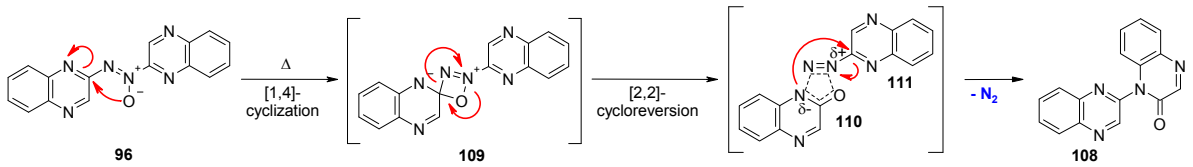
4.2.2. Thermal transformation of azoxyquinoxaline 96

When pK_a 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 N_2 from **96**. 2D NMR measurements suggested the structure 1-(quinoxalin-2-yl)quinoxalin-2(1*H*)-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 N_2 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 N_2 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**).

[33] Bogányi, B.; Kámán, J. *J. Heterocycl. Chem.* **2009**, *46*, 33.
[34] Heating of quinoxaline *N*-oxide with acetic anhydride resulted in the formation of **108** in 4% yield, among others: Iijima, C. *Yakugaku Zasshi* **1967**, *87*, 942.
[35] Moskalenko, G. G.; Sedova, V. F.; Mamaev, V. P. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (English Trans.)* **1987**, *36*, 642. (Translated from *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, *3*, 701.)



Scheme 8. Possible mechanism of formation of quinoxalone **108**

5. Summary of the new findings

1. A productive one-pot synthesis was developed for the preparation of halogenated 4*H*-pyrido[1,2-*a*]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(1*H*)-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]-cyclodimerization 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 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton at position C(6): 6-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was synthesized from 4*H*-pyrido[1,2-*a*]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-4*H*-pyrido[1,2-*a*]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 *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 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton was investigated, and was found to be: posn. C(8) ≥ C(2) > C(9) > C(7) > C(3). With the use of comparatively cheaper chloro derivatives under simple conditions, 17 new derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one were synthesized in good to excellent yields.[3]

6. Preliminary investigations of the Hiyama cross-coupling of halogenated 4*H*-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 4*H*-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(1*H*)-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

[1] Molnár, A.; Faigl, F.; Podányi, B.; Finta, Z.; Balázs, L.; Hermecz, I.: *Synthesis of Halogenated 4H-Pyrido[1,2-a]pyrimidin-4-ones – Heterocycles* **2009**, *78*, 2477-2488 (IF: 0.98).

[2] Molnár, A.; Mucsi, Z.; Vlád, G.; Simon, K.; Holczbauer, T.; Podányi, B.; Faigl, F.; Hermecz, I.: *Ring Transformation of Unsaturated N-Bridgehead Fused Pyrimidin-4(3H)-ones: Role of Repulsive Electrostatic Nonbonded Interaction – J. Org. Chem.* **2011**, *76*, 696-699 (IF: 4.219; 2009).

[3] Molnár, A.; Kapros, A., Párkányi, L.; Mucsi, Z.; Vlád, G.; Hermecz, I.: *Suzuki–Miyaura Cross-coupling Reactions of Halo Derivatives of 4H-Pyrido[1,2-a]pyrimidin-4-ones* – submitted (*Org. Biomol. Chem.*).

[4] Molnár, A.; Hermecz, I.: *Hiyama Cross-coupling Reactions of Halo Derivatives of 4H-Pyrido[1,2-a]pyrimidin-4-ones* – under preparation.

[5] Hermecz, I.; Molnár, A.; Boros, S.; Simon, K.; Gönczi, Cs.: *Unexpected Ring Transformations of an Azoxyquinoxaline – Eur. J. Pharm. Sci., Suppl.* **2009**, *38*, S187-S189.

[6] Molnár, A.; Boros, S.; Simon, K.; Hermecz, I.; Gönczi, Cs.: *Unexpected Transformations of an Azoxyquinoxaline – ARKIVOC* **2010**, *x*, 199-207 (IF: 1.090, I: 1; 2009).

6.2. Oral presentations

[7] Molnár, A.: *Synthesis of Halogenated Derivatives of 4H-Pyrido[1,2-a]pyrimidin-4-ones – Sanofi-aventis Thesis Day*, Budapest, 4 December, 2008.

[8] Molnár, A.; Boros, S.; Simon, K.; Faigl, F.; Hermecz, I.; Gönczi, Cs.: *Unexpected Transformations of an Azoxyquinoxaline – Sanofi-aventis Thesis Day*, Budapest, 18 November, 2009.

[9] Molnár, A.; Boros, S.; Simon, K.; Hermecz, I.; Gönczi, Cs.: *Acid Catalyzed and Thermal Ring Transformations of an Azoxyquinoxaline – YoungChem2009 – VII International Congress of Young Chemists*, Warsaw, Poland, 14-18 October, 2009.

[10] Molnár, A.: *Synthesis of Halogenated 4H-Pyrido[1,2-a]pyrimidin-4-ones and Their Cross-coupling Reactions – Sanofi-aventis Thesis Day – LaLonde Conference*, Arles, France, 31 Septrember - 1 October, 2010.

[11] Molnár A.: *NITROGÉNHÍDFŐS GYŰRŰRENDSZEREK HALOGÉNSZÁRMAZÉKAINAK SZERKEZET-MÓDOSÍTÁSA ÁTMENETIFÉMEK KATALIZÁLT REAKCIÓKBAN – Sanofi-aventis Thesis Day*, Budapest, 26 March, 2008.

[12] Molnár, A.: *4H-PIRIDO[1,2-a]PIRIMIDIN-4-ONOK HALOGÉNSZÁRMAZÉKAINAK ELŐÁLLÍTÁSA – XXXI. Kémiai Előadói Napok*, Szeged, 27-29 October, 2008.

[13] Mucsi, Z.; Molnár, A.; Vlád, G.; Finta, Z.; Podányi, B.; Hermecz, I.: *[N-(2-PIRIDIL)-IMINOMETILÉN]KETÉNEK GYŰRŰZÁRÁSI REAKCIÓIRÓL – Elméleti Szerves Kémiai Munkabizottsági Ülés*, Budapest, 1 December, 2008.

[14] Molnár, A.; Boros, S.; Hermecz, I.; Gönczi, Cs.: *EGY AZOXIKINOXALIN ÁTRENDEZŐDÉSI REAKCIÓI – Heterociklusos Munkabizottsági Ülés*, Balatonszemes, 20-22 May, 2009.

[15] Molnár, A.; Mucsi, Z.; Vlád, G.; Finta, Z.; Balázs, L.; Faigl, F.; Hermecz, I.: *[2-(PIRIDIL-AMINO)METILÉN]MALONÁTOK GYŰRŰZÁRÁSI REAKCIÓIRÓL – Heterociklusos Munkabizottsági Ülés*, Balatonszemes, 20-22 May, 2009.

6.3. Poster presentations

[16] Molnár, A.; Mucsi, Z.; Vlád, G.; Finta, Z.; Hermecz, I.; Faigl, F.: *SYNTHESIS OF HALOGENATED DERIVATIVES OF 4H-PYRIDO[1,2-a]PYRIMIDIN-4-ONES – 2nd International Symposium on Organic Chemistry*, Sofia, Bulgaria, 13-16 December, 2008.

[17] Molnár, A.; Boros, S.; Simon, K.; Hermecz, I.; Gönczi, Cs.: *UNEXPECTED RING TRANSFORMATIONS OF AN AZOXYQUINOXALINE – 3rd BBBB International Conference on Pharmaceutical Sciences*, Antalya, Turkey, 26-28 October, 2009.

[18] Molnár, A.; Finta, Z.; Hermecz, I.; Faigl, F.: *KERESZTKAPCSOLÁSI REAKCIÓK 4H-PIRIDO[1,2-a]PIRIMIDIN-4-ONOK KÖRÉBEN – Vegyészkonferencia*, Hajdúszoboszló, 19-21 June, 2008.

[19] Molnár, A.; Kapros, A.; Faigl, F.; Hermecz, I.: *4H-PIRIDO[1,2-a]PIRIMIDIN-4-ON HALOGÉNSZÁRMAZÉKOK SUZUKI–MIYAURA ÉS HIYAMA REAKCIÓJA – Vegyészkonferencia*, Hajdúszoboszló, 31 June - 2 July, 2010.