# Reactions of 3-Chloropropeniminium Salts with Aminopyridines. Synthesis of *N*-Pyridylpyridinium and Pyrido[1,2-*a*]pyrimidinium Salts*

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*N*-(Pyridyl)pyridinium salts **7** and **8** as well as 4-phenylpyrido[1,2-*a*]pyrimidinium salts **4** and **12** have been prepared by reactions of 3-aryl-3-chloropropeniminium salts **5** with aminopyridines (**6**) using glacial acetic acid as solvent. 2-Phenylpyrido[1,2-*a*]pyrimidinium salts **2** are formed when ethanol is used as the solvent. The condensation of 2-aminopyridine (**6a**) with 3-chloro-2,3-dehydromorpholino-2-carbiminium salt **13** is described. The HSAB principle of Pearson is discussed to explain the different regioselective ring closure reactions.

*Key words:* 3-Chloropropeniminium Salts, Pyridinium Salts, Phenylpyrido[1,2-*a*]pyrimidinium Salts, Iminium Cyclization

## Introduction

Recently, we synthesized novel 3-benzoyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidinium salts [1] **1** by condensation of 2-aminopyridine (**6a**) with enone Mannich bases, which are easily accessible through heating of aryl methyl ketones, paraformaldehyde, and *N*,*N*-dimethylamine hydrochloride in DMF [2]. Later on, the ability of **1** to inhibit the catalytic activity of the inducible NO synthase enzyme was characterized *in vitro* and the *p*-bromo substituted derivative **1b** was shown to exhibit increased potency [3]. In order to gain more insight into structure-activity relationships concerning the position of the aryl group as well as the requisite for the carbonyl function and the necessity of a partially hydrogenated heterocyclic system, we decided to synthesize pyrido[1,2-*a*]pyrimidinium salts **2b – 4b** substituted by the aromatic residue in the pyrimidine moiety of the molecule (Fig. 1). Whereas methods for the preparation of pyrido[1,2-*a*]pyrimidines **2** [4] and **4** [5] are known in the literature, to our knowledge 3-aryl substituted heterocycles **3** are not described. Compounds **2** had been synthesized by G. W. Fischer [4] using condensation of aminopyridines with 3-chloro-3-phenylpropenals

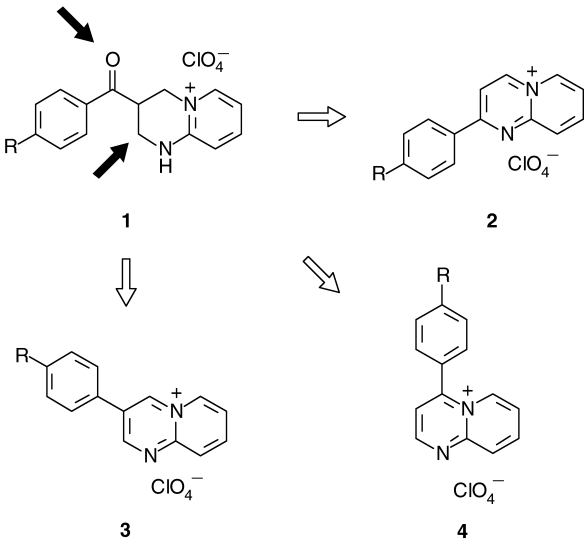


Fig. 1. Constitutions of 1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidinium perchlorate **1** and phenylpyrido[1,2-*a*]pyrimidinium perchlorates **2 – 4**.

which are the products of hydrolysis of the corresponding 3-chloropropeniminium salts **5** [6]. These salts are easily accessible by formylating aromatic methylketones with dimethylformamide/phosphorous oxychloride and play an important role as reactive intermedi-

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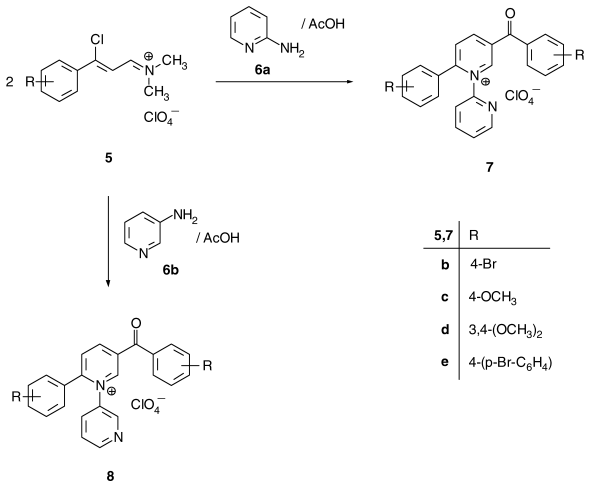
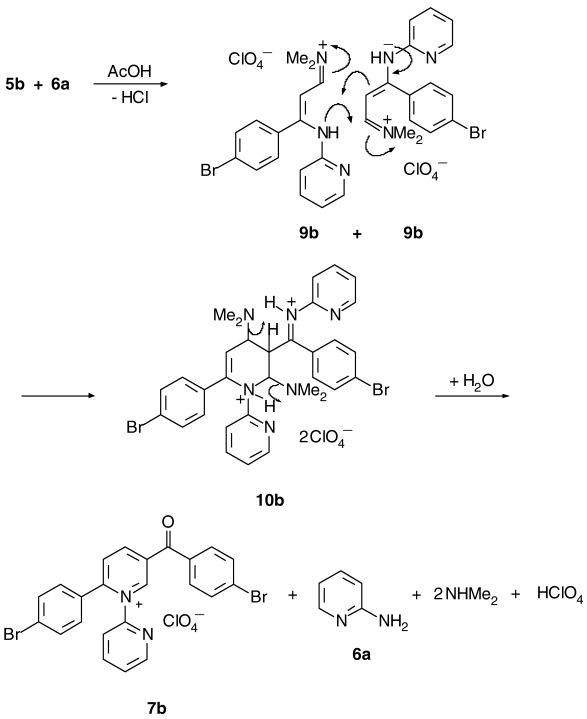



Scheme 1. *N*-Pyridylpyridinium salts **7** and **8** by condensation of 3-chloropropeniminium salts **5** with aminopyridines **6**.

ates in the synthesis of heterocyclic compounds [7]. Substitution reactions of **5** with *N*-nucleophiles have been intensively studied [8], but not their reactions with ambifunctional nucleophilic reagents such as 2-aminopyridine **6a**. Indeed, for our investigations concerning the synthesis of pyrido[1,2-*a*]pyrimidines **2** as potential NO-synthase inhibitors the iminium salts **5** should be expected to give just the same synthetic result as the application of 3-chloro-3-phenylpropenals [4].

## Results and Discussion

Surprisingly, first experiments with the iminium salt **5b** and 2-aminopyridine (**6a**) in glacial acetic acid did not give rise to the formation of **2b** or even **4b**. The analytical and spectroscopic data of the reaction product, namely IR, $^{1}$H and $^{13}$C NMR data (*cf.* Experimental Section) indicated that even equimolar amounts of the educts **5b** and **6a** had reacted in a molar ratio of 2:1, with formation of the N-(2-pyridyl)pyridinium salt **7b** (Scheme 1). The structure of this unexpected product was established using two-dimensional NMR techniques such as H,H-COSY, H,H-NOESY, and C,H correlation spectra. MS spectroscopic data (EI, ESI) were also in accordance with the structure of **7b**. According to the reaction mechanism suggested in Scheme 2 the condensation is initiated by substitution of the chloro atom in position 3 of the iminium salt **5b** by the primary amino group of **6a** to give the trimethinium salt **9b**.




Scheme 2. Reaction mechanism suggested for the formation of the *N*-pyridylpyridinium salts **7** and **8**.

Such a start usually accounts for the nucleophilic substitution observed for reactions of 3-chloropropeniminium salts **5** with primary and secondary amines [8]. The following nucleophilic attack of a carbanion at the electrophilic carbiminium ion of a second molecule of **9b** to form the tetrahydropyridine **10b** may be considered as key step of the cyclization reaction. Subsequent elimination of two equivalents of dimethylamine and one equivalent of 2-aminopyridine **6a** completes the reaction sequence. The condensation of the methoxy substituted iminium salts **5c**–**e** with **6a** gave the corresponding pyridinium salts **7c**–**e**. Since the ambifunctional character of 2-aminopyridine **(6a)** is not required for this mode of ring closure, other amino substituted *N*-heterocycles should also afford such a cyclization. As expected, 3-aminopyridine **(6b)** reacted with the iminium salt **5b** in glacial acetic acid to yield the pyridinium salt **8b** (Scheme 1). It is a surprising synthetic result on account of which the salts **7** and **8** are only formed when the reactions were carried out with the iminium salts **5b**–**e** bearing a substituted phenyl ring. Otherwise, using the unsubstituted iminium salt **5a** for the procedure in glacial acetic acid the pyridinium salt **7a** could not be isolated but might

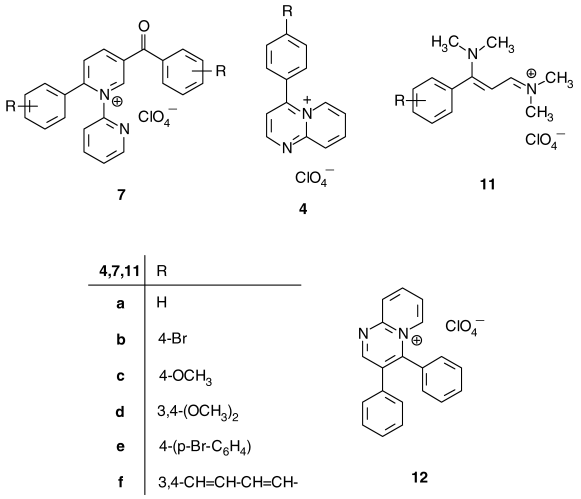
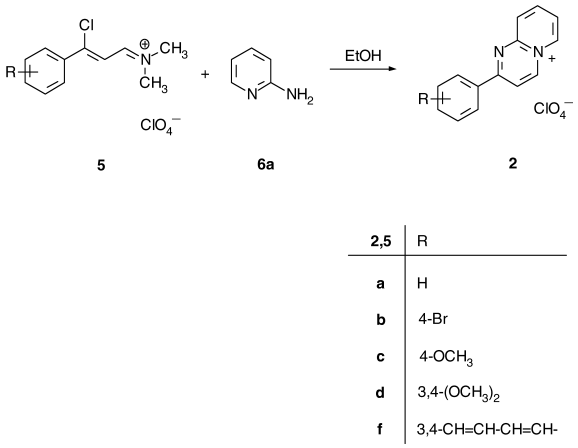



Fig 2. Products from the reactions of 3-chloropropeniminium salts **5** with 2-aminopyridine (**6a**) in glacial acetic acid.

be present in the reaction mixture as minor component. Instead, the 4-phenylpyrido[1,2-*a*]pyrimidinium salt **4a** was the major product (Fig. 2). The synthesis of such compounds by condensation of 2-aminopyridine with 3,3-dimethoxy-1-phenyl-1-propanone were described by Nesmejanow und Rybinskaja [5]. It is noteworthy to point out that all reactions described above resulted in low yields of about 15 – 30%. In order to find the reasons we examined the reaction mixtures by tlc in search of further products. It turned out that dimethylamine, eliminated during the formation of the pyridinium salts **7** (Scheme 2), undergoes nucleophilic attack on another iminium ion **5** to afford 3-dimethylaminopropeniminium salts **11** which are stable toward condensation with 2-aminopyridine (**6a**). Thus, all experiments in solvents like ethanol or glacial acetic acid failed, even upon prolonged refluxing. Furthermore, we found variable amounts of 4-phenylpyrido[1,2-*a*]pyrimidinium salts **4** in all condensations and isolated **4c** and **4f** (Fig. 2).

Changing the solvent to ethanol had a drastic effect on the reaction course (Scheme 3) as equimolar amounts of the educts **5** and **6a** afforded the 2-phenylpyrido[1,2-*a*]pyrimidinium salts **2** in analogy to the investigations of G. W. Fischer [4]. Structural assignment and discrimination of the 2- and 4-arylpyrido[1,2-*a*]pyrimidinium salts **2** and **4** in Scheme 1 and 3 are based on appropriate $^1$H NMR data. In [D6]-DMSO solution the phenyl ring of **2a** exhibits an $^1$H NMR multiplet at $\delta = 7.69 - 7.80$ for 3-, 4-, and 5-H and a doublet at $\delta = 8.51$ for 2-H/6-H, the

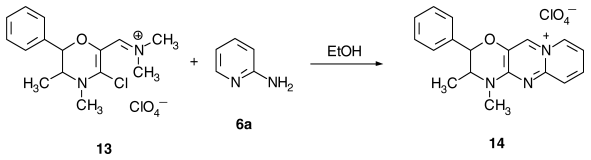



Scheme 3. Reactions of the 3-chloropropeniminium salt **5** with 2-aminopyridine (**6a**) in ethanolic solution.

corresponding protons of **4a** show only a broad singlet at $\delta = 7.77$. Another characteristic difference are the signals for 7-H with a single triplet at $\delta = 8.13$ for **2a** and a double triplet at $\delta = 8.06$ ($J = 6.9$ and 2.0 Hz) for **4a**. Depending on the substitution of the phenyl ring all spectra recorded show a corresponding pattern thus facilitating the attachment.

These synthetic results demonstrate that reactions of 3-chloropropeniminium salts with aminopyridines are to a high degree dependent on the substitution of the educts as well as on the solvent employed. Nucleophilic attack of the primary amino group of 2-aminopyridine (**6a**) at either C-1 or C-3 of the 3-chloropropeniminium salt **5** is responsible for the different reaction pathways described above. The reason of this high sensitivity towards solvent and substitution requires further studies. As described above, the preparation of pyridinium salts **7** in glacial acetic acid requires an unsubstituted carbon atom in position 2 of the propeniminium moiety which should be blocked by either integrating into a cyclic system (see the iminium salts **13** in Scheme 4) or by substitution with a phenyl ring. Recently, we described the *Vilsmeier* formylation of desoxybenzoin [9] to produce a 2,3-diphenyl substituted iminium salt which reacted with 2-aminopyridine (**6a**) to give a 2,3-diphenylpyrido[1,2-*a*]pyrimidinium salt (**12**) (Fig. 2). It is remarkable that identical products were formed according to the same mode of cyclization no matter whether ethanol or glacial acetic acid was used as solvent, which is the reaction pathway to compounds **4**.

Moreover, we studied the reaction behavior of cyclic iminium salts. Thus, the dehydromorpholine **13**,




Scheme 4. Condensation of 3-chloro-2,3-dehydromorpholino-2-carbiminium salt **13** with 2-aminopyridine (**6a**).

prepared from ephedrine in two steps [10], was condensed with 2-aminopyridine (**6a**) in glacial acetic acid to afford a mixture of unidentified compounds. The $^1$H NMR spectrum of such a mixture revealed that any cyclization reaction can be excluded. No high field signals above $\delta = 8.10$ ppm were recorded, which are typical for the pyrido[1,2-a]pyrimidine ring system. On the other hand, using ethanol as solvent the cyclization took place and the anellated pyrido[1,2-*a*]pyrimidinium salt **14** was isolated, solutions of which are characterized by a blue fluorescence.

## Conclusions

In order to explain the different regioselective ring closure reactions described in this study, Pearson's concept of hard and soft acids and bases (the HSAB principle) can be considered. Generally, *S*-nucleophiles as typical soft bases attack at the carbon atom C-3 of the 3-chloropropeniminium salt **5** and substitute the chlorine atom (Fig. 3). On the contrary, *O*-nucleophiles as hard bases hydrolyse the carbiminium group at C-1 [7].

It is rather difficult to apply this HSAB principle to reactions of the iminium salts **5** with aminopyridines **6**. Supposing that the condensation is initiated by the exocyclic amino group, *e.g.* the formation of the pyridinium salt **8** (Scheme 1), the $NH_2$-group is preferably acting as soft base according to the literature [8] and in this study it is the case always in ethanol and partially in glacial acetic acid (Scheme 5).

On the other hand, there is one exception from this rule, namely the 4-phenylpyrido[1,2-*a*]pyrimidinium

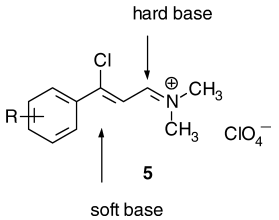
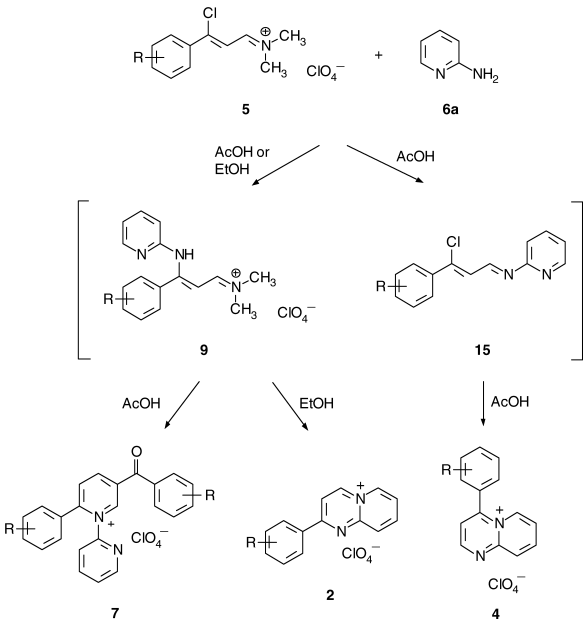



Fig. 3. Attack of hard and soft bases at 3-chloropropeniminium salts **5**.




Scheme 5. Summary of all reaction sequences.

salts **4**, which can only be formed by attack of the amino group at C-1 of the propeniminium moiety of the salts **5**. Supposing that in acidic solution the exocyclic nitrogen is protonated, the endocyclic nitrogen atom attacks as soft base in the usual manner at C-3, followed by cleavage of dimethylamine. This type of reaction of pyridine at position 3 of chloropropeniminium salts has been reported in the literature [11, 12]. Scheme 5 represents a summary of the reaction pathways.

## Experimental Section

*General methods:* Melting points are uncorrected and were recorded with a Büchi 510 melting point apparatus, $^1$H and $^{13}$C NMR spectra (internal $Me_4Si$) were recorded using a Bruker ARX 300 spectrometer ($\delta$ given in ppm, *J* in Hz), IR spectra (KBr pellet) were measured on a Perkin-Elmer FT-IR 16 PC spectrometer, ESI-MS spectra were taken on a Bruker LC esquire mass spectrometer (ESI /EI) in a MeOH/water mixture by direct infusion; elemental analysis was performed by the Microanalytical laboratory of the Institute of Inorganic Chemistry, University of Kiel. Macherey-Nagel Polygram® SIL G/$UV_{254}$ on plastic sheets was used for TLC monitoring.

### Synthesis of 2-arylpyrido[1.2-*a*]pyrimidinium salts (2a – f)

A mixture of 3-chloropropeniminium salts (**5a – f**) (1 mmol) and 2-aminopyridine (**6a**) (1 mmol) in ethanol (5 ml) was refluxed for 3 h. The reaction mixture was con-

centrated under reduced pressure, isopropanol (10 ml) was added to the residue and the mixture was stirred in an ice bath for 30 minutes. The solid formed was collected by filtration and purified by crystallization from methanol to give the 2-arylpyrido[1.2-*a*]pyrimidinium salts (**2a – d, f, 14**), respectively.

*2-Phenylpyrido[1,2-a]pyrimidinium perchlorate (**2a**)*

M. p. 215 °C (MeOH); yield 77 mg (25%). – IR: $\nu = 1634$ (C=N), 1097 ($ClO_4^-$) $cm^{-1}$. – $^1$H NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.69 - 7.80$ (m, 3H, 3'-H, 4'-H, 5'-H), 8.13 (t, 1H, 7-H), 8.51 (m, 3H, 2'-H, 6'-H, 9-H), 8.62 (t, 1H, 8-H), 8.85 (d, 1H, 3-H), 9.22 (d, 1H, 2-H), 9.69 (d, 1H, 6-H). – $^{13}$C NMR (75 MHz, [$D_6$]-DMSO): $\delta = 115.51$, 123.28, 127.31, 128.77, 129.63, 133.67, 133.95, 136.73, 142.04, 144.47, 148.33, 164.44 (all $C_{arom}$). – MS: *m/z* 207 ($M^+$). – $C_{14}H_{11}N_2O_4Cl$ (306.70): calcd. C 54.83, H 3.61, N 9.13; found C 54.72, H 3.57, N 9.19.

*2–(p–Bromophenyl)pyrido[1,2–a]pyrimidinium perchlorate (**2b**)*

M. p. > 250 °C (MeOH); yield 120 mg (31%). – IR: $\nu = 1628$ (C=N), 1074 ($ClO_4^-$) $cm^{-1}$. – $^1$H NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.95$ (d, $J = 8.6$ Hz, 2H, 3'-H, 5'-H), 8.16 (t, $J = 6.8$ Hz, 1H, 7-H), 8.45 (d, $J = 8.6$ Hz, 2H, 2'-H, 6'-H), 8.54 (d, $J = 8.4$ Hz, 1H, 9-H), 8.65 (t, $J = 7.4$ Hz, 1H, 8-H), 8.86 (d, $J = 7.3$ Hz, 1H, 3-H), 9.24 (d, $J = 6.6$ Hz, 1H, 6-H), 9.72 (d, $J = 7.3$ Hz, 1H, 4-H). – $^{13}$C NMR (75 MHz, [$D_6$]-DMSO): $\delta = 115.41$, 123.49, 127.35, 128.32, 130.61, 132.74, 132.88, 136.82, 142.21, 144.67, 148.27, 163.49 (all $C_{arom}$). – MS: *m/z* 285 ($M^+$, $^{79}$Br). – $C_{14}H_{10}N_2O_4BrCl$ (385.60): calcd. C 43.61, H 2.61, N 7.26; found C 43.83, H 2.59, N 7.27.

*2-(p-Methoxyphenyl)pyrido[1,2-a]pyrimidinium perchlorate (**2c**)*

M. p. 246 °C (MeOH); yield 61 mg (18%). – IR: $\nu = 1634$ (C=N), 1086 ($ClO_4^-$) $cm^{-1}$. – $^1$H NMR (300 MHz, [$D_6$]-DMSO): $\delta = 3.93$ (s, 3H, $OCH_3$), 7.26 (d, $J = 8.9$ Hz, 2H, 3'-H, 5-H), 8.04 (t, $J = 6.8$ Hz, 1H, 7-H), 8.42 (d, $J = 8.7$ Hz, 1H, 9-H), 8.51 (d, $J = 8.9$ Hz, 2H, 2'-H, 6'-H), 8.56 (t, $J = 7.6$ Hz, 1H, 8-H), 8.76 (d, 1H, $J = 7.4$ Hz, 3-H), 9.14 (d, $J = 6.7$ Hz, 1H, 6-H), 9.57 (d, $J = 7.4$ Hz, 1H, 4-H). – $^{13}$C NMR (75 MHz, [$D_6$]-DMSO): $\delta = 55.85$ ($OCH_3$), 114.86, 115.21, 122.52, 125.97, 126.96, 131.12, 136.56, 141.78, 143.84, 148.44, 163.73, 164.28 (all $C_{arom}$). – MS: *m/z* 237 ($M^+$). – $C_{15}H_{13}N_2O_5Cl$ (336.73): calcd. C 53.50, H 3.89, N 8.32; found C 52.37, H 3.76, N 8.08.

*2-(3,4-Dimethoxyphenyl)pyrido[1,2-a]pyrimidinium perchlorate (**2d**)*

M. p. 224 °C (MeOH); yield 99 mg (27%). – IR: $\nu = 1621$ (C=N), 1094 ($ClO_4^-$) $cm^{-1}$. – $^1$H NMR (300 MHz, [$D_6$]-DMSO): $\delta = 3.81$ (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 7.35 (m, 3H, arom-H), 8.04 (t, $J = 6.9$ Hz, 1H, 7-H), 8.14 (d, $J = 4.3$ Hz, 1H, 3-H), 8.62 – 8.70 (m, 2H, 8-H, 9-H), 9.16 (d, $J = 6.9$ Hz, 1H, 6-H), 9.52 (d, $J = 4.3$ Hz, 1H, 4-H). – $^{13}$C NMR (75 MHz, [$D_6$]-DMSO): $\delta = 55.72$, 55.85 (all $OCH_3$), 112.43, 112.51, 120.36, 121.39, 122.89, 124.15, 128.09, 134.09, 141.84, 149.20, 149.37, 151.60, 153.27, 159.58 (all $C_{arom}$). – MS: *m/z* 267 ($M^+$). – $C_{16}H_{15}N_2O_6Cl$ (366.76): calcd. C 52.40, H 4.12, N 7.64; found C 52.58, H 4.12, N 7.65.

*2-(2-Naphthyl)pyrido[1,2-a]pyrimidinium perchlorate (**2f**)*

M. p. 219 °C (MeOH); yield 125 mg (35%). – IR: $\nu = 1641$ (C=N), 1096 ($ClO_4^-$) $cm^{-1}$. – $^1$H NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.68 - 7.82$ (m, 2H, arom-H), 8.07 – 8.24 (m, 4H, 3 arom-H, 7-H), 8.57 (m, 3H, arom-H), 8.65 (t, $J = 7.5$ Hz, 1H, 8-H), 8.99 (d, $J = 7.2$ Hz, 1H, 3-H), 9.21 – 9.25 (m, 2H, 5-H, 7-H), 9.73 (d, $J = 7.2$ Hz, 1H, 4-H). – $^{13}$C NMR (75 MHz, [$D_6$]-DMSO): $\delta = 115.61$, 123.26, 123.86, 127.29, 127.45, 127.82, 129.32 (two overlapping signals), 129.57, 130.85, 130.99, 132.55, 135.25, 136.74, 142.09, 144.22, 148.33, 164.25 (all $C_{arom}$). – MS: *m/z* 257 ($M^+$). – $C_{18}H_{13}N_2O_4Cl$ (356.76): calcd. C 60.60, H 3.67, N 7.85; found C 60.61, H 3.66, N 7.85.

*2,3-Dihydro-1,2-dimethyl-3-phenyl-1H-oxazino[3,2-d]-pyrido[1,2-a]pyrimidinium perchlorate (**14**)*

M.p. > 250 °C (MeOH); yield (26%). – IR: $\nu = 1617$ (C=N), 1084 ($ClO_4^-$) $cm^{-1}$. – $^1$H NMR (300 MHz, [$D_6$]-DMSO): $\delta = 0.84$ (d, 3H, $CH_3$), 3.30 (s, 3H, N-$CH_3$), 4.10 (qd, $J = 6.9/2.4$ Hz, 1H, 3-H), 5.41 (d, $J \approx 2$ Hz, 1H, 2-H), 7.43 (t, $J = 7.2$ Hz, 1H, arom-H), 7.52 (t, $J = 7.5$ Hz, 2H, arom-H), 7.62 (d, $J = 7.5$ Hz, 2H, arom-H), 8.01 (td, $J = 6.5/1.8$ Hz, 1H, 8-H), 8.34 – 8.43 (m, 2H, 6-H, 7-H), 9.07 (d, $J = 7.0$ Hz, 1H, 9-H), 9.38 (s, 1H, 11-H). – $^{13}$C NMR (75 MHz, [$D_6$]-DMSO): $\delta = 11.62$ (C$CH_3$), 42.32 ($NCH_3$), 57.41 (CHO), 73.91 (OCH), 122.25, 125.71, 128.07, 128.18, 128.49, 130.24, 135.92, 137.23, 138.29, 140.73, 145.31, 149.16 ($C_{arom}$) – MS: *m/z* 292 ($M^+$). – $C_{18}H_{18}N_3ClO_5$ (391.81): calcd. C 55.18, H 4.63, N 10.72; found C 55.33, H 4.69, N 10.58.

**Synthesis of 4-arylpyrido[1.2-a]pyrimidinium perchlorates (4a, c, e, 12)**

A mixture of 3-aryl-3-chloropropeniminium perchlorates **5** (1 mmol) and 2-aminopyridine (**6a**) (1 mmol) in glacial acetic acid (10 ml) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure. Isopropanol (10 ml) was added to the residue and heated to 50 – 60 °C for a few minutes. The solid formed was collected by filtration and purified by crystallization from methanol to give the

4-arylpyrido[1,2-*a*]pyrimidinium salts **4a,c,e,f**, respectively. For **12** instead of isopropanol 10 ml of glacial acetic acid was used for crystallization as well as recrystallization.

*4-Phenylpyrido[1,2-a]pyrimidinium perchlorate (**4a**)*

M. p. 189 °C (MeOH); yield 86 mg (28%). – IR: $\nu = 1634$ (C=N), 1097 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.77$ (bs, 5H, arom-H), 8.06 (td, $J = 6.9/2.0$ Hz 1H, 7-H), 8.16 (d, $J = 4.4$ Hz, 1H, 3-H), 8.65 – 8.72 (m, 2H, 8-H, 9-H), 8.99 (d, $J = 7.0$ Hz, 1H, 6-H), 9.56 (d, $J = 4.4$ Hz, 1H, 2-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 120.50$, 124.39, 128.21, 129.42, 129.54, 129.68, 131.90, 133.88, 141.95, 149.27, 153.06, 159.82 (all $C_{arom}$). – MS: *m/z* 207 ($M^+$). – $C_{14}H_{11}N_2O_4Cl$ (306.70): calcd. C 54.83, H 3.61, N 9.13; found C 55.10, H 3.62, N 9.03.

*4-(p-Methoxyphenyl)pyrido[1,2-a]pyrimidinium perchlorate (**4c**)*

M. p. 199 °C (MeOH); yield 67 mg (20%). – IR: $\nu = 1623$ (C=N), 1083 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 3.91$ (s, 3H, $OCH_3$), 7.31 (d, $J = 8.8$ Hz, 2H, arom-H), 7.72 (d, $J = 8.6$ Hz, 2H, arom-H), 8.05 (dt, $J = 7.0/2.1$ Hz, 1H, 7-H), 8.11 (d, $J = 4.5$ Hz, 1H, 3-H), 8.61 – 8.74 (m, 2H, 8-H, 9-H), 9.09 (d, $J = 6.9$ Hz, 1H, 6-H), 9.51 (d, $J = 4.5$ Hz, 1H, 2-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 55.64$ ($OCH_3$), 115.18, 120.38, 121.46, 124.14, 128.16, 131.37, 133.81, 141.78, 149.44, 153.31, 159.57, 161.95 ($C_{arom}$). – MS: *m/z* 237 ($M^+$). – $C_{15}H_{13}N_2O_5Cl$ (336.73): calcd. C 53.50, H 3.89, N 8.32; found C 53.75, H 3.94, N 8.38.

*4-(2-Naphthyl)pyrido[1,2-a]pyrimidinium perchlorate (**4f**)*

M.p. 243 °C (MeOH); yield 79 mg (22%). – IR: $\nu = 1620$ (C=N), 1090 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.73 - 7.82$ (m, 3H, arom-H), 8.05 – 8.14 (m, 3H, 2 arom-H, 7-H), 8.28 – 8.38 (m, 3H, 2 arom-H, 3-H), 8.69 (bs, 2H, 8-H, 9-H), 9.11 (d, $J = 6.2$ Hz, 6-H), 9.61 (d, $J = 2.8$ Hz, 1H, 2-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 120.75$, 124.39, 125.09, 126.94, 127.56, 127.97, 128.21, 128.58, 128.78, 129.41, 130.40, 132.47, 133.96, 134.21, 142.00, 149.32, 153.11, 159.80 (all $C_{arom}$). – MS: *m/z* 257 ($M^+$). – $C_{18}H_{13}N_2O_4Cl$ (356.76): calcd. C 60.60, H 3.67, N 7.85; found C 60.59, H 3.67, N 7.73.

*3,4-Diphenylpyrido[1,2-a]pyrimidinium perchlorate (**12**)*

M. p. 222 °C (AcOH); yield 176 mg (46%). – IR: $\nu = 1635$ (C=N), 1098 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.27 - 7.30$ (m, 2H, arom-H), 7.36 – 7.39 (m, 3H, arom-H), 7.53 – 7.62 (m, 5H, arom-H), 8.09 (dt, $J = 6.7/2.3$ Hz, 1H, 7-H), 8.68 – 8.76 (m, 3H, 6-H, 8-H, 9-H), 9.69 (s, 1H, 2-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 124.81$, 128.10, 128.13, 128.53, 128.96, 129.60, 129.64, 130.05, 131.29, 132.12, 132.54, 133.96, 141.68, 148.21, 150.13, 160.87 (all $C_{arom}$). – MS: *m/z* 283 ($M^+$). – $C_{20}H_{15}N_2O_4Cl$ (382.80): calcd. C 62.75, H 3.95, N 7.32; found C 62.38, H 3.95, N 7.17.

**Synthesis of *N*-pyridylpyridinium salts (7b – d)**

A mixture of 3-chloropropeniminium salts (**5b – d**) (2 mmol) and aminopyridines (**6a**, **b**) (1 mmol) in glacial acetic acid (20 ml) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure. Isopropanol (10 ml) was added to the residue and stirred under ice cooling for 30 minutes. The solid formed was collected by filtration, washed with isopropanol and subsequently diethyl ether and purified by crystallization from methanol to give the *N*-pyridylpyridinium salts (**7b, 7d, 7e, 8b**), respectively. The crude product of **7c** was purified by chromatography on silica gel (dichloromethane/methanol, 9:1).

*5-(p-Bromobenzoyl)-2-(p-bromophenyl)-N-pyrid-2-ylpyridinium perchlorate (**7b**)*

M. p. 243 °C (MeOH); yield 180 mg (30%). – IR: $\nu$ = 1669 (C=O), 1089 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.36$ (d, $J = 8.2$ Hz, 2H, arom-H), 7.66 – 7.76 (m, 4H, arom-H, 3'-H, 5'-H), 7.91 (bs, 4H, arom-H), 8.10 (t, $J = 7.5$ Hz, 1H, 4'-H), 8.58 (m, 2H, 6'-H, 5-H), 9.14 (d, $J = 7.8$ Hz, 1H, 4-H), 9.72 (s, 1H, 6-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 122.32$, 125.29, 126.69, 128.86, 130.50, 130.52 131.64, 131.90, 132.15, 132.16, 134.07, 135.49, 140.20, 146.72, 147.12, 149.44, 152.46, 155.31 (all $C_{arom}$), 189.46 (C=O). – MS: *m/z* 493 ($M^+$, $^{79}Br$). – $C_{23}H_{15}N_2O_5Br_2Cl$ (594.64): calcd. C 46.46, H 2.54, N 4.71; found C 46.52, H 2.54 N 4.70.

*5-(p-Methoxybenzoyl)-2-(p-methoxyphenyl)-N-pyrid-2-ylpyridinium perchlorate (**7c**)*

M. p. 214 °C (MeOH); yield 90 mg (18%). – IR: $\nu = 1664$ (C=O), 1100 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 3.79$ (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 7.01 (d, $J = 8.6$ Hz, 2H, arom-H), 7.19 (d, $J = 8.4$ Hz, 2H, arom-H), 7.35 (d, $J = 8.5$ Hz, 2H, arom-H), 7.66 – 7.70 (m, 2H, 3'-H, 5'-H), 7.98 (d, $J = 8.5$ Hz, 2H, 2"-H, 6"-H), 8.07 (t, $J = 7$ Hz, 1H, 4'-H), 8.49 (d, $J = 8.4$ Hz, 1H, 3-H), 8.64 (d, $J = 3.5$ Hz, 1H, 6'-H), 9.02 (d, $J = 7.8$ Hz, 1H, 4-H), 9.57 (s, 1H, 6-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 55.52$, 55.83 (all $OCH_3$), 114.47 (two overlapping signals), 122.20, 123.25,126.45, 127.77, 130.22, 131.77, 132.90, 135.39, 140.05, 146.01, 146.28, 149.48, 152.98, 156.11, 161.47, 164.31 (all $C_{arom}$), 188.53 (CO). – MS: *m/z* 397 ($M^+$). – $C_{25}H_{21}N_2O_7Cl$ (496.90): calcd. C 60.43, H 4.26, N 5.64; found C 60.52, H 4.24, N 5.60.

*5-(3,4-Dimethoxybenzoyl)-2-(3,4-dimethoxyphenyl)-N-pyrid-2-ylpyridinium perchlorate (**7d**)*

M.p. 217 °C (EtOH); yield 128 mg (23%). – IR: $\nu = 1647$ (C=O), 1086 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 3.58$ (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 3.92 (s, 3H, $OCH_3$), 6.88 (s, 1H, arom-H), 7.07 (s, 2H, arom-H), 7.19 (d, $J = 8.4$ Hz, 1H, arom-H), 7.57 (m, 2H, arom-H), 7.69 (m, 2H, 3'-H, 5'-H), 8.08 (t, $J = 7.1$ Hz, 1H, 4'-H), 8.54 (d, $J = 8.4$ Hz, 1H, 3-H), 8.66 (d, $J = 4.3$ Hz, 1H, 6'-H), 9.04 (d, $J = 8.3$ Hz, 1H, 4-H), 9.60 (s, 1H, 6-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 55.45$, 55.70, 55.76, 56.02 (all $OCH_3$), 111.06, 111.71 (two overlapping signals), 112.87, 122.19, 123.08, 123.91, 126.38, 126.45, 127.69, 130.19, 135.28, 140.10, 146.10, 146.24, 148.37, 149.06, 149.48, 151.24, 153.13, 154.39, 156,07 (all $C_{arom}$), 188.49 (C=O). – MS: *m/z* 457 ($M^+$). – $C_{27}H_{25}N_2O_9Cl$ (556.96): calcd. C 58.23, H 4.52, N 5.03; found C 58.29, H 4.54, N 5.01.

*2-(p-Bromobiphenylyl)-5-[4-(p-bromophenyl)benzoyl]-N-pyrid-3-ylpyridinium perchlorate (**7e**)*

M. p. > 250 °C (EtOH); yield 65 mg (15%). – IR: $\nu = 1670$ (C=O), 1096 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.52$ (d, 2H, arom-H), 7.68 – 7.82 (m, 12H, arom-H, 3'-H, 5'-H), 7.96 (d, 2H, 3"-H, 5"-H), 8.07 – 8.12 (m, 3H, 2"-H, 6"-H, 4'-H), 8.63 (d, 2H, 3-H, 6'-H), 9.16 (dd, $J = 8.2/1.3$ Hz, 1H, 4-H), 9.75 (d, $J = 1.3$ Hz, 1H, 6-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 122.15$, 122.37, 122.44, 126.64, 126.75, 127.09, 128.91, 129.19, 129.38, 130.55, 130.61, 131.15, 131.98, 132.07, 134.12, 135.58, 137.22, 137.58, 140.14, 141.20, 144.44, 146.64, 146.88, 149.47, 152.75, 155.93 (all $C_{arom}$), 189.71 (C=O). – MS: *m/z* 645 ($M^+$, $^{79}Br$). – $C_{36}H_{23}N_2O_5Br_2Cl$ (746.84): calcd. C 64.93, H 3.59, N 4.33; found C 64.85, H 3.56 N 4.35.

*5-(p-Bromobenzoyl)-2-(p-bromophenyl)-N-pyrid-3-ylpyridinium perchlorate (**8b**)*

M. p. > 250 °C (EtOH); yield 90 mg (15%). – IR: $\nu = 1670$ (C=O), 1090 ($ClO_4^-$) $cm^{-1}$. – $^1H$ NMR (300 MHz, [$D_6$]-DMSO): $\delta = 7.38$ (d, 2H, 3"-H, 5"-H), 7.58 (dd, 1H, $J = 8.0/4.9$ Hz, 5'-H), 7.71 (d, 2H, 2"-H, 6"-H), 7.92 (bs, 4H, arom-H), 8.06 (d, $J = 8.1$ Hz, 1H, 4'-H), 8.56 (d, 1H, $J = 8.2$ Hz, 3-H), 8.72 (d, 1H, $J = 4.3$ Hz, 6'-H), 8.80 (bs, 1H, 2'-H), 9.13 (d, $J = 8.0$ Hz, 1H, 4-H), 9.70 (s, 1H, 6-H). – $^{13}C$ NMR (75 MHz, [$D_6$]-DMSO): $\delta = 124.10$, 125.17, 128.99, 130.24, 130.34, 131.87, 131.96, 132.17, 132.20, 134.03, 134.71, 135.69, 138.29, 146.89, 147.01, 147.69, 151.53, 156.33 (all $C_{arom}$), 189.48 (C=O). – MS: *m/z* 493 ($M^+$, $^{79}Br$). – $C_{23}H_{15}N_2O_5Br_2Cl$ (594.64): calcd. C 46.46, H 2.54, N 4.71; found C 46.55, H 2.56, N 4.74.


[1] U. Girreser, D. Heber, M. Schütt, Synlett 263 (1998).
[2] U. Girreser, D. Heber, M. Schütt, Synthesis 715 (1998).
[3] B. Clement, D. Heber, U. Bluhm, unpublished results.
[4] G. W. Fischer, J. Prakt. Chem. **316**, 474 (1974).
[5] A. I. Nesmejanow, O. A. Rybinskaja, Dokl. Chem. (engl. transl.) **43**, 118 (1958).
[6] a) Z. Arnold, J. Zemlicka, Proc. Chem. Soc. 227 (1958); b) Z. Arnold, J. Zemlicka, Coll. Czech. Chem. Commun. **24**, 2385, 2378 (1959).
[7] J. Liebscher, H. Hartmann, Synthesis 241 (1979).
[8] a) J. Zemlicka, Z. Arnold, Coll. Czech. Chem. Commun. **26**, 2838 (1961); b) Z. Arnold, J. Zemlicka, Coll. Czech. Chem. Commun. **28**, 869 (1963); c) A. Holý, J. Krupicka, Z. Arnold, Coll. Czech. Chem. Commun. **30**, 4127 (1965); d) J. Liebscher, Dissertation, TU Dresden (1966); e) K. Bredereck, S. Humburger, Chem. Ber. **99**, 3227 (1966); f) A. E. Nikolajewski, S. Dähne, B. Hirsch, Chem. Ber. **100**, 2616 (1967); g) C. Jutz, R. Kirchlechner, H.-J. Seidel, Chem. Ber. **102**, 2301 (1969); h) A. Holý, Z. Arnold, Coll. Czech. Chem. Commun. **38**, 1371 (1973).
[9] A. J. Hopfinger, D. Heber, M. Klingmüller, K. Mohr, C. D. P. Klein, J. Med. Chem. **42**, 3874 (1999).
[10] D. Heber, M. Schütt, unpublished results.
[11] J. Liebscher, H. Hartmann, J. Prakt. Chem. **318**, 705, 731 (1976).
[12] G. W. Fischer, J. Prakt. Chem. **317**, 779 (1975).