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Selective Ring Closure to Substituted Pyrido[1,2-b]-as-triazinium Salt

György Hajós*, Zsuzsanna Riedl, Eszter Gács-Baitz and András Messmer
Central Research Institute for Chemistry, H-1525 Budapest POB 17

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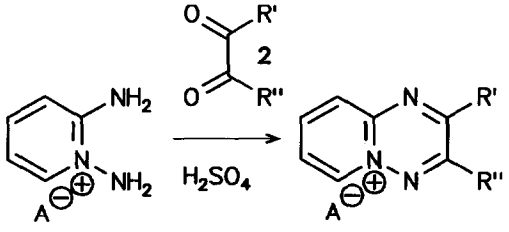
Abstract: Reaction of arylglyoxal with 1,2-diaminopyridinium salt **1** under acidic conditions afforded 2-aryl-pyrido[1,2-b]-as-triazinium salt **9** selectively, whereas cyclization of the same dioxo compound with 1-amino-2-iminopyridine **5** under neutral conditions - due to "umpolung" of the exo nitrogen atom - led exclusively to the 3-aryl isomer **8**.

In the course of our extended research on fused 1,2,4-triazines[1] we became interested in the synthesis of the pyrido[1,2-b]-as-triazinium ring system **3**. Survey of the pertinent literature showed, interestingly, that fairly little has been published[2] in this area. The first synthesis was described by Kost et al.[3,4]; these authors reported that 1,2-diaminopyridinium salt **1** when reacted with different α-dioxo compounds **2** in acidic media afforded the fused pyridotriazinium salt **3** in good yields. These authors claimed, furthermore, that unsymmetrically substituted α-dioxo compounds (e.g. phenylglyoxal: **2**, R'=Ph; R"= H) gave selectively the 2-substituted product (**3**, R'=Ph; R"=H) which was found to be identical with the reaction product obtained from 1-amino-2-iminopyridine **5** and phenacyl bromide.

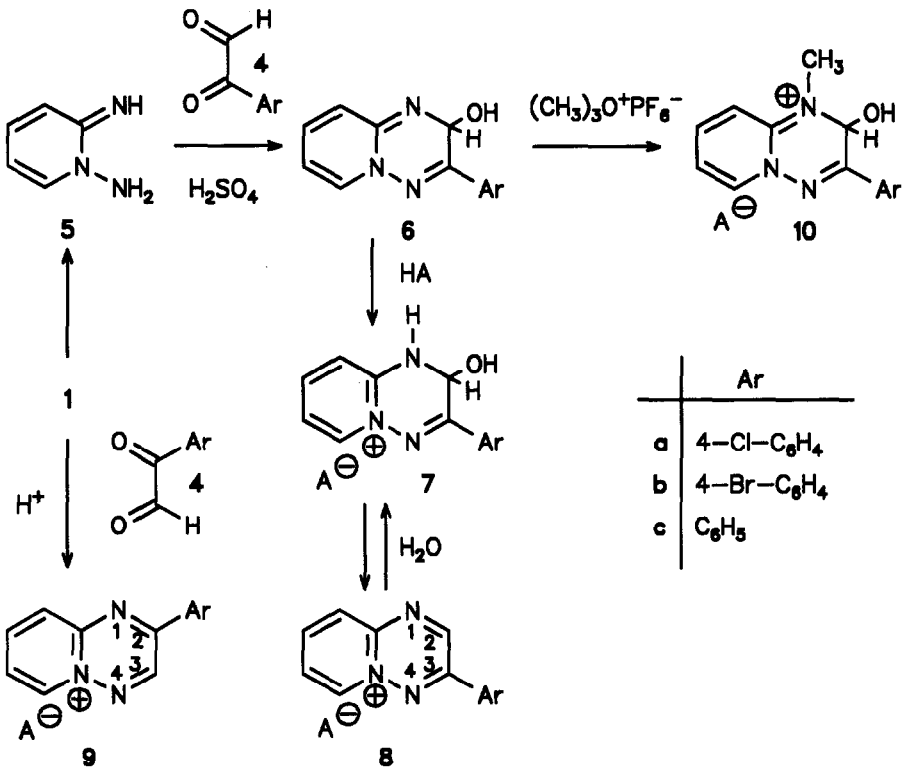


1 **3**

Upon reinvestigation of these conversions we found now that, in accordance with this publication[4], reaction of phenylglyoxal with diaminopyridinium salt **1** affords indeed one crystalline yellow product only, the structure of which, however, should be questioned. All of our efforts to obtain this compound by reacting the imino-amino compound **5**[5] and phenacyl bromide failed (this supposed conversion should involve also an oxydation process) and, instead of the expected ring closure, a multi-component mixture was obtained which could not be separated.

Additional experiments with the imino-amino compound **5** showed however, that this compound also reacts with arylglyoxal, even more easily than the protonated **1**: a cream colored solid precipitated from the reaction mixture which, upon acidification, afforded a new colorless salt. This product when dissolved in trifluoroacetic acid resulted in a yellow solution, the ^{1}H-NMR spectra of which was compared with that of the product obtained according to Kost et al. (claimed to be **9**)[4].

This comparison revealed that the two spectra are very similar but still distinctly different and thus we assumed that they can be assigned to the two differently substituted pyrido-as-triazinium salts **8** and **9**. If one accepts the structural supposition of Kost (i.e. structure **9**) formation of the isomeric 3-aryl structure **8** should be assumed for the second (neutral) reaction route.



A further support for the presence of structure **8** in trifluoroacetic acid solution was provided by the investigation of the primary product isolated directly from the reaction mixture: IR spectra (no carbonyl band, presence of intense OH band) of this cream-colored crystalline product which precipitated upon addition of the reagent to the solution of the imino-amino compound revealed that the addition-condensation product **6** was formed which can be considered as a pseudo base of the target cation **8**. Treatment of this adduct **6** with aqueous acid gave protonated salt **7** which is a covalent hydrate[6] of **8**. Hydrate salt **7** obviously afforded the heteroaromatic form **8** when treated with the dehydrating trifluoroacetic acid. It is interesting to note that quite recently, regioselective ring closures to quinoxalines[7] have been published; in contrast to this, in our case the presence of the bridge-head nitrogen seems to play a decesive role (see Fig. 1.).

The two different synthetic pathways accomplished under acidic and neutral conditions were successfully extended for two additional aryl-glyoxals (i.e., **4**, Ar = C_6H_4Br and Ar = C_6H_5) and, in each case, the corresponding pairs of ring closed compounds (**7** and **9**) were obtained. The final verification for the supposed structures was provided by a thorough NMR measurement with derivative of **6a**. Although the structure of **6a** could not be proved unambigouosly by NMR experiments, its methylation product **10** allowed to observe HetCor long-range couplings which revealed that three protons: the methyl proton, H-2 (attached to the saturated carbon atom), and H-6 are in equally in a three-bond distance from the annelation carbon atom C-9a. The most pertinent NMR data of the ^1H- and ^{13}C-spectra of **6a**, **7a**, **8a**, **9a** and **10a** are summarized in Table 1 and 2, respectively.

The chemical behaviour of the two differently substituted new heteroaromatic salts proved to be surprisingly different. While the 2-aryl compound **9** did not give any covalent hydrate and proved to be fairly stable towards basic conditions, 3-aryl isomer **8** could be isolated only under specific conditions

Table 1. ^{1}H NMR Data for Compounds **6a, 7a, 8a, 9a, 10a**[#].
(values in ppm from internal TMS)

	H2	H3	H6	H7	H8	H9	H2',6'	H3',5'	N-CH_3	J Values (Hz)
6a	5.89	-	7.74	6.19	7.12	6.65	7.96	7.56	-	$J_{6,7}$=7.0; $J_{7,8}$=6.5; $J_{8,9}$=9.0
7a	6.28	-	8.62	7.24	8.09	7.38	8.16	7.72	-	$J_{6,7}$=6.9; $J_{7,8}$=7.0; $J_{8,9}$=9.2
8a[*]	9.71	-	9.33	8.34	8.77	8.63	8.19	7.68	-	$J_{6,7}$=6.6; $J_{7,8}$=7.0; $J_{8,9}$=8.8
8a[**]	9.80	-	9.38	8.38	8.82	8.62	8.33	7.76	-	$J_{6,7}$=6.5; $J_{7,8}$=7.2; $J_{8,9}$=8.8
9a	-	10.33	9.63	8.35	8.87	8.68	8.62	7.85	-	$J_{6,7}$=6.8; $J_{7,8}$=7.0; $J_{8,9}$=8.8
9a[*]	-	9.69	9.17	8.17	8.71	8.49	8.39	7.67	-	$J_{6,7}$=6.8; $J_{7,8}$=7.0; $J_{8,9}$=8.8
9a[**]	-	9.88	9.30	8.27	8.81	8.57	8.52	7.80	-	$J_{6,7}$=6.5; $J_{7,8}$=7.0; $J_{8,9}$=8.5
10a[**]	6.16	-	8.49	7.30	8.20	7.51	8.10	7.68	3.54	$J_{6,7}$=6.8; $J_{7,8}$=7.0; $J_{8,9}$=8.3

Table 2. ^{13}C NMR Data for Compounds **6a, 7a,8a, 9a, 10a**[#].(ppm from internal TMS)

	C2	C3	C6	C7	C8	C9	C9a	C1'	C2',C6'	C3',C5'	C4'	N-CH_3
6a	68.61	146.79	136.12	105.57	133.71	122.59	144.39	132.50	129.05	128.83	135.29	-
7a	63.65	154.95	138.11	114.46	142.96	114.73	144.55	129.48	129.70	129.22	137.72	-
8a[*]	151.78	154.13	141.11	128.47	145.21	129.34	145.31	127.41	130.41	131.12	142.50	-
9a	155.34	145.67	140.39	125.99	145.02	128.11	145.72	130.30	131.13	130.00	140.36	-
9a[*]	156.43	144.80	140.07	126.02	145.16	128.68	146.15	129.12	130.97	130.75	143.76	-
10a[**]	72.36	155.72	140.32	115.97	145.05	114.37	146.17	130.18	130.58	130.53	139.35	37.14

[#]Numbering is given on the formula. Solvent DMSO-d_6 unless otherwise specified.
[*]$CDCl_3$+ TFA; [**]CD_3CN

(under rigorous exclusion of water in TFA) and gave spontaneously hydrate **7** even in the presence of traces of water (e.g. on standing in commercial organic solvents).

The difference between the reactivities of the diaminopyridinium salt **1** and its conjugate base: the imino-amino compound **5**, which led to the selective formation of isomers **9** and **8**, respectively, can probably be interpreted by the different charge distribution in the two starting compounds **1** and **5** as shown in Fig 1.

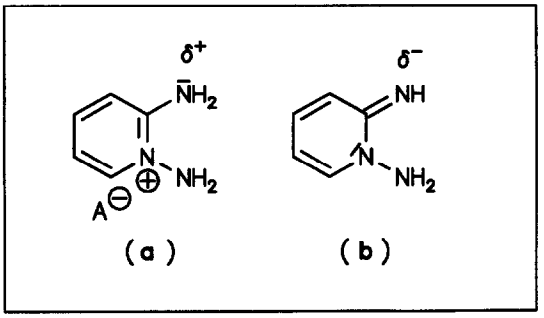


Fig. 1. Qualitative comparison of the electronic densities on the C-NH_2 nitrogen atom in 1,2-diaminopyridinium salt (**a**) and 1-amino-2-iminopyridine (**b**).

Fig. 1. shows that the lone pair of the ring nitrogen atom in **b** can take part in a three-center delocalization and thus the imino-nitrogen becomes negatively charged. In **a**, also a delocalization through the same three atoms can be formed by participation, however, of the positive charge of the ring-nitrogen as shown in the figure. This electron shift renders the C-nitrogen atom considerably positively charged and therefore its nucleophilicity decreases significantly. This qualitative picture, in other words, expresses that deprotonation of **1** to **5** (i.e. of **a** to **b** in Fig. 1.) involves an "umpolung" regarding the exo nitrogen atom and this effect can account for the entirely different selectivity of the ring closure reactions carried out under acidic and neutral conditions.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Nicolet 205 FT apparatus. The NMR spectra were registered on Varian EM-360 and XL-400 equipments. TMS was used as internal standard.

General procedure for preparation of 3-arylpyrido[1,2-b]-as-triazinium salts

A solution of 1,2-diaminopyridinium perchlorate (2.2 g; 1 cmol) in acetonitrile (10 ml) while stirred at room temperature was treated with a sodium hydroxide solution (0.8 g in 2 ml water). A red mixture was formed immediately which was treated with the appropriate arylglyoxale hydrate (1.2 cmol). In a few minutes, the pseudobase **6** separated as yellow crystals. When the reaction mixture obtained as above was treated with 70 % perchloric acid (2 ml), covalent hydrate salt **7** as a colorless precipitate was formed which was filtered off and recrystallized from acetonitrile-water.

2,5-Dihidro-2-hydroxi-3-(4'-chlorophenyl)-pyrido[1,2-b]-as-triazin (6a, Ar=p-Cl-C_6H_4)

mp. 166-170 °C, IR (KBr): 3450, 2923, 2724, 1650, 1570, 1550, 1540, 1360, 1170, 1090, 1030, 970, 840, 755, 720 cm^{-1}.^{1}H-NMR and ^{13}C-NMR 400 MHz,) see Table 1 and Table 2 . EIMS, m/z: 259 (M+). Anal. Calcd. for $C_{13}H_{10}N_3ClO$ (259.70): C, 60.12; H, 3.88; N, 16.18. Found: C, 60.18; H, 3.94; N, 16.13.

1,2-Dihydro-2-hydroxi-3-(4'-chlorophenyl)-pyrido[1,2-b]-as-triazinium perchlorate (7a: Ar=p-Cl-C_6H_4)

Yield: 77 %, m.p. 251-257 °C. IR (KBr): 3110, 3070, 1623, 1616, 1602, 1590, 1550, 1460, 1450, 1400, 1380, 1270, 1180, 1110, 941, 830, 780, 790, 610, 620 cm^{-1}. ^1H NMR and ^{13}C NMR(400 MHz,) see Table 1 and Table 2. Anal. Calcd. for $C_{13}H_{11}N_3Cl_2O_5$ (360.15): C, 43.35; H, 3.08; N, 11.67. Found: C, 43.22; H, 3.11; N, 11.53.

1,2-Dihydro-2-hydroxi-3-(4'-bromophenyl)-pyrido[1,2-b]-as-triazinium perchlorate (7b, Ar=p-Br-C_6H_4)

Yield: 65 %, mp. 166-169 °C. IR (KBr): 3300-2900 (broad NH,OH),1630, 1610, 1580, 1530, 1390, 1260, 1100 cm^{-1}.Anal. Calcd. for $C_{13}H_{11}N_3BrClO_5$ (404.61): C, 38.59; H, 2.74; N, 10.39. Found: C, 38.65; H, 2.69; N 10.44.

1,2-Dihydro-2-hydroxi-3-phenylpyrido[1,2-b]-as-triazinium perchlorate (7c, Ar=C_6H_5)

Yield: 78 %, m.p. 271-74 °C. IR (KBr): 3060, 1610, 1580, 1550, 1440, 1880, 1260, 1100 cm^{-1}. Anal. Calcd. for $C_{13}H_{12}N_3ClO_5$ (325.70): C,47.94; H, 3.71; N, 12.90. Found : C, 48.11; H, 3.66; N, 12.83.

Detection of aromatic salts 8

Covalent hydrate salts **7** when dissolved in trifluoroacetic acid underwent dehydratation and the heteroaromatic fused as-triazinium salts could be detected by ^1H-NMR. 3-(4'-chloro-phenyl)pyrido[1,2-b]-as-triazinium perchlorate (**8a**, Ar= p-Cl-C_6H_4): ^1H NMR and ^{13}C NMR(400 MHz,) see Table 1 and Table 2.

3-(4'-bromo-phenyl)pyrido[1,2-b]-as-triazinium perchlorate (8b, Ar= p-Br-C_6H_4)

^1H NMR (60 MHz, TFA): δ 9.9 (s, 1H, H-2); 9.5 (d, 1H, H-6); 9.1-8.3 (m, 3H, H-7,8,9); 8.2 and 7.9 (dd, 4H, H-4'-Br-phenyl).

3-Phenylpyrido[1,2-b]-as-triazinium perchlorate (8c, Ar=C_6H_5)

^1H NMR (60 MHz, TFA):δ 9.9 (s, 1H, H-2); 9.5 (d, 1H, H-6); 9.0-7.7 (m, 1H, H-7,8,9 and H-phenyl).

General procedure for preparation of 2-arylpyrido[1,2-b]-as-triazinium salts

A mixture of suspension of 1,2-diaminopyridinium tosylate (2.8 g) in methanol (5 ml) and 70 % perchloric acid (2.5 ml) was treated with the appropriate arylglyoxal hydrate (1.2 cmol) at room temperature with stirring. Clear solution was first formed and upon standing for several hours colorless crystals separated. The reaction mixture was allowed to stand at room temperature for one day, the precipitate was collected and recrystallized from acetonitrile.

2-(4'-chloro-phenyl)pyrido[1,2-b]-as-triazinium perclorate (9a, Ar=p-Cl-C_6H_4)

Yield: 82 %, m.p. 267-270 °C. IR (KBr): 3060, 3000, 2960, 1610, 1590, 1550, 1450, 1380, 1300, 1290, 1100 cm^{-1}. ^1H NMR and ^{13}C NMR(400 MHz) see Table 1 and Table 2. Anal.Calcd. for $C_{13}H_9N_3Cl_2O_4$ (342.15): C, 45.63; H, 2.65; N, 12.28. Found: C, 45.48; H, 2.57; N, 12.34.

2-(4'-bromo-phenyl)pyrido[1,2-b]-as-triazinium perchlorate (9b, Ar=p-Br-C_6H_4)

Yield: 70 %, m.p. 296-298 °C. IR (KBr): 3060, 3000, 2950, 1610, 1600, 1590, 1450, 1370, 1100 cm^{-1}. ^1H NMR (60 MHz): δ 9.9 (s, 1H, H-3); 9.3 (d, 1H, H-6); 8.9-8.2 (m, 3H, H-7,8,9); 8.45 and 7.9 (dd, 4H, H-4'-bromo-phenyl). Anal. Calcd. for $C_{13}H_9N_3BrClO_4$ (386.61): C, 40.39; H, 2.35; N, 10.87. Found : C, 40.44; H, 2.37; N, 10.72.

2-Phenylpyrido[1,2-b]-as-triazinium perchlorate (9c, Ar=C_6H_5)

Yield: 75 % m.p. 255-260 °C. IR (KBr): 3050,1610,1590, 1580, 1550, 1450, 1360, 1300, 1260, 1100 cm^{-1}. ^1H NMR (60 MHz, TFA): δ 9.97 (s, 1H, H-3); 9.4 (d, 1H, H-6); 9.0-7.7 (m, 8H, H-7,8,9 and H-phenyl). Anal. Calcd. for $C_{13}H_{10}N_3ClO_4$ (307.70): C, 50.74; H, 3.28; N, 13.65. Found: C, 50.65; H, 3.22; N, 13.68.

1,2-Dihydro-1-methyl-2-hydroxi-3-(4'-chlorophenyl)-pyrido[1,2-b]-as-triazinium hexafluorophosphate (10)

To a suspension of the pseudobase **6** (260 mg; 1.0 mmol) in abs. dichloromethane (10 ml), trimethyloxonium hexafluorophosphate (200 mg; 1.15 mmol) was added and it was stirred at room temperature for 24 hours. Diethyl ether was then added, the solid precipitate was filtered off and recrystallized from acetonitrile-diethyl ether, to give **10** (280 mg, 66.7% yield): m.p. 120-124 °C. IR (KBr): 3660, 3590, 3190, 3140, 3110, 2950, 2930, 1650, 1590, 1570, 1540, 1095, 1035, 840, 765, 560 cm^{-1}. ^1H NMR and ^{13}C NMR(400 MHz,) see Table 1 and Table 2. Anal.Calcd. for $C_{14}H_{13}ClN_3OPF_6$ (419.71): C, 40.06; H, 3.12; N, 10.01. Found: C, 40.11; H, 3.22; N, 9.95.

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