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SHORT COMMUNICATIONS

Effect of Hydrochloric Acid on the Reductive Amination of 1-(3-Nitropyridin-2-yl)pyridinium Salts

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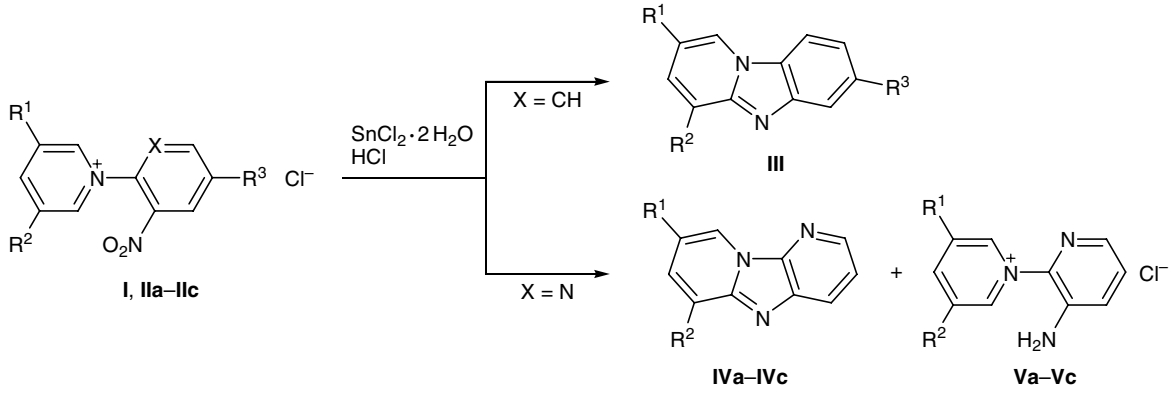
We previously reported on the reductive amination of pyridinium salts, which led to the formation of fused systems with a bridgehead nitrogen atom, benzo[4,5]imidazo[1,2-*a*]pyridines **III** and pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines **IV** [1–3]. However, unlike *N*-arylpyridinium salts **I**, 1-(3-nitropyridin-2-yl)pyridinium chlorides **II** did not always undergo cyclization under the reduction conditions [3]. The main difference between structures **I** and **II** is that the latter contain a nitrogen atom capable of taking up a proton. Therefore, it may be presumed that the reduction of compounds **IIa**–**IIc** with a solution of $SnCl_2 \cdot 2H_2O$ in hydrochloric acid involves formation of the corresponding hydrochloride via protonation of the nitrogen atom. As a result, nucleophilicity of the amino group formed by reduction of the nitro group is weakened, and the cyclization is hindered. With a view to verify the above assumption we examined the effect of hydrochloric acid concentration on the reductive amination process (see table).

We found that the reductive amination of salts **II** with a solution of $SnCl_2 \cdot 2H_2O$ in 2% hydrochloric acid gave in all cases the corresponding cyclization products **IVa**–**IVc**. Raising the concentration of HCl in the reaction mixture led to appearance of amino derivatives **V** in addition to pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines **IV**. Taking into account that the concentration of unprotonated pyridine sharply decreases as the concentration of electrophile (proton in our case) increases [4], the assumption implying formation of chlorides **V** due to protonation of the pyridine nitrogen atom seems to be quite reasonable.

Thus the concentration of hydrochloric acid is a factor affecting the reductive amination of 1-(3-nitropyridin-2-yl)pyridinium chlorides **II**. By varying the concentration of HCl in the reaction mixture, the process can be forced to yield either 1-(3-aminopyridin-2-yl)pyridinium chlorides **V** or cyclization products **IV**.

The structure of the isolated compounds was confirmed by the analytical data and ^{1}H NMR and mass spectra.

Pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines IVa–IVc (*general procedure*). A solution of 0.03 mol of



I, **III**, $R^1 = R^2 = H$, $R^3 = CF_3$, COOH, NO_2, NH_2, CN; **II**, **IV**, **V**, $R^1 = R^2 = H$ (**a**), $R^1 = H$, $R^2 = Me$ (**b**), $R^1 = R^2 = Me$ (**c**).

$SnCl_2 \cdot 2H_2O$ in 15 ml of 2% hydrochloric acid was added under stirring to a mixture of 0.01 mol of 1-(3-nitropyridin-2-yl)pyridinium chloride **IIa–IIc** in 20 ml of ethanol. After10 min, the mixture was adjusted to pH 7–8 by adding 25% aqueous ammonia and extracted with several portions of chloroform (total of 150 ml). The products were isolated by removal of the solvent from the extract.

Pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine (IVa). Yield 90%, mp 120–122°C; published data [5]: mp 130°C. ^{1}H NMR spectrum, δ, ppm: 7.08 t (1H, 8-H, J = 9.5 Hz), 7.59 m (1H, 3-H), 7.65–7.75 m (2H, 6-H, 7-H), 8.24 d (1H, 4-H, J = 10.0 Hz), 8.51 d (1H, 2-H, J = 7.0 Hz), 8.95 d (1H, 9-H, J = 8.5 Hz). Mass spectrum, m/z (I_{rel}, %): 169 (100) $[M]^+$, 142 (7), 78 (28), 51 (12). Found, %: C 70.81; H 4.17; N 25.02. $C_{10}H_7N_3$. Calculated, %: C 71.09; H 4.24; N 24.89. M 169.18.

6-Methylpyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine (IVb). Yield 85%, mp 111–113°C; published data [5]: mp 117°C. ^{1}H NMR spectrum, δ, ppm: 2.61 s (3H, CH_3), 6.83 t (1H, 8-H, J = 9.5 Hz), 7.30–7.45 m (2H, 3-H, 7-H), 8.20 d (1H, 4-H, J = 10.0 Hz), 8.42 d (1H, 2-H, J = 7.0 Hz), 8.59 d.d (1H, 9-H, J = 8.0, 1.5 Hz). Mass spectrum, m/z (I_{rel}, %): 183 (100) $[M]^+$, 169 (8), 157 (26), 78 (31), 51 (10). Found, %: C 71.79; H 5.16; N 23.31. $C_{11}H_9N_3$. Calculated, %: C 72.10; H 4.97; N 23.09. M 183.21.

6,8-Dimethylpyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine (IVc). Yield 79%, mp 95–97°C. ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, 8-CH_3), 2.59 s (3H, 6-CH_3), 7.55 m (1H, 3-H), 7.64 d (1H, 7-H, J = 1.0 Hz), 8.24 d.d (1H, 4-H, J = 10.0, 1.5 Hz), 8.46 d.d (1H, 2-H, J = 8.0, 1.0 Hz), 8.61 d (1H, 9-H, J = 1.5 Hz). Mass spectrum, m/z (I_{rel}, %): 197 (100) $[M]^+$, 182 (30), 169 (7), 155 (5), 77 (16), 51 (12), 39 (20). Found, %: C 72.93; H 5.39; N 21.24. $C_{12}H_{11}N_3$. Calculated, %: C 73.11; H 5.62; N 21.36. M 197.24.

1-(3-Aminopyridin-2-yl)pyridinium chlorides Va–Vc (*general procedure*)**.** A solution of 0.03 mol of $SnCl_2 \cdot 2H_2O$ in 15 ml of 12% hydrochloric acid was added under stirring to a mixture of 0.01 mol of 1-(3-nitropyridin-2-yl)pyridinium chloride **IIa–IIc** in 20 ml of ethanol. After 10 min, the mixture was adjusted to pH 7–8 by adding 25% aqueous ammonia and extracted with several portions of chloroform (total of 200 ml). The solvent was distilled off, and compounds **IVa** and **Va** were separated by treatment with boiling hexane where the latter is insoluble.

Effect of HCl concentration on the yield of reduction products **IV** and **V**

Concentration of HCl, %	Yield, %					
	IVa	**Va**	**IVb**	**Vb**	**IVc**	**Vc**
2	90	0	85	0	79	0
3	91	0	82	0	11	83
6	88	6	16	63	0	89
12	49	37	0	84	0	88

1-(3-Aminopyridin-2-yl)pyridinium chloride (Va). Yield 37%, mp 182–185°C. ^{1}H NMR spectrum, δ, ppm: 6.05 s (2H, NH_2), 7.44–7.50 m (2H, 4′-H, 5′-H), 7.86 d.d (1H, 6′-H, J = 7.5, 1.5 Hz), 8.35 t (2H, 3-H, 5-H, J = 8.5 Hz), 8.81 t (1H, 4-H, J = 9.0 Hz), 9.31 d (2H, 2-H, 6-H, J = 8.0 Hz). Mass spectrum, m/z (I_{rel}, %): 172 (28) $[M]^+$, 169 (100), 142 (11), 119 (19), 78 (65), 64 (18), 51 (38), 39 (41), 36 (42). Found, %: C 57.91; H 5.03; Cl 17.17; N 20.15. $C_{10}H_{10}ClN_3$. Calculated, %: C 57.83; H 4.82; Cl 17.11; N 20.24. M 172.21.

1-(3-Aminopyridin-2-yl)-3-methylpyridinium chloride (Vb). Yield 84%, mp 161–164°C. ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 6.05 s (2H, NH_2), 7.44–7.50 m (2H, 4′-H, 5′-H), 7.85 d.d (1H, 6′-H, J = 8.0, 1.5 Hz), 8.23 m (1H, 5-H), 8.65 d.d (1H, 4-H, J = 8.5, 2.0 Hz), 9.09 d (1H, 6-H, J = 8.0 Hz), 9.19 d (1H, 2-H, J = 1.5 Hz). Mass spectrum, m/z (I_{rel}, %): 186 (42) $[M]^+$, 183 (100), 170 (28), 120 (23), 92 (25), 78 (13), 65 (19), 39 (29). Found, %: C 59.62; H 5.33; Cl 16.27; N 18.79. $C_{11}H_{12}ClN_3$. Calculated, %: C 59.59; H 5.42; Cl 16.03; N 18.96. M 186.24.

1-(3-Aminopyridin-2-yl)-3,5-dimethylpyridinium chloride (Vc). Yield 88%, mp 204–206°C. ^{1}H NMR spectrum, δ, ppm: 2.51 s (6H, CH_3), 6.05 s (2H, NH_2), 7.44–7.50 m (2H, 4′-H, 5′-H), 7.85 d (1H, 6′-H, J = 6.5 Hz), 8.50 s (1H, 4-H), 9.05 s (2H, 2-H, 6-H). Mass spectrum, m/z (I_{rel}, %): 200 (50) $[M]^+$, 198 (100), 184 (34), 120 (39), 108 (17), 77 (10), 36 (26). Found, %: C 61.09; H 6.01; Cl 15.13; N 18.01. $C_{12}H_{14}ClN_3$. Calculated, %: C 61.15; H 5.95; Cl 15.07; N 17.83. M 200.26.

The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra were obtained on an MKh-1310 instrument. The elemental compositions were determined on a CHN-1 analyzer.

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