Pergamon

Tetrahedron 55 (1999) 12557–12562

TETRAHEDRON

Chemoselective *N*-Oxidation of Picolinaldehydes with Dimethyldioxirane

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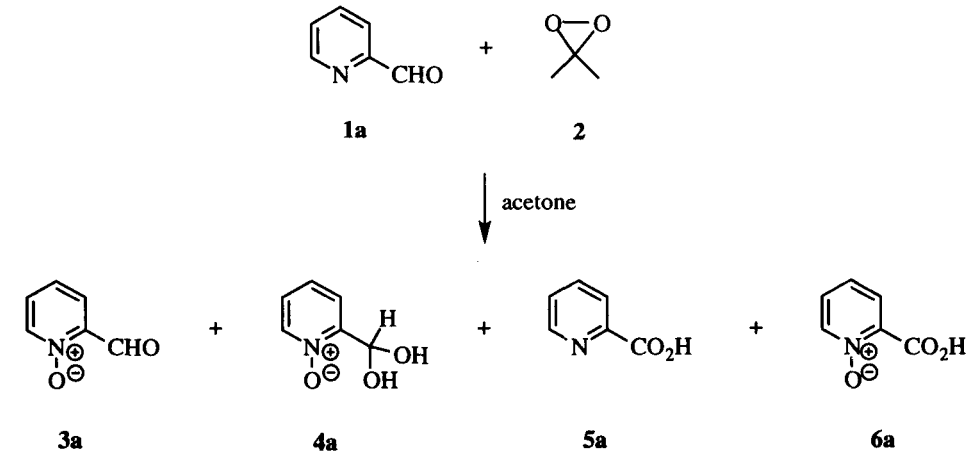
Received 23 July 1999; accepted 27 August 1999

Abstract: The N-oxidation of picolinaldehydes with dimethyldioxirane proceeds with remarkable selectivity. Especially the *N*-oxides of 3- and of 4-picolinaldehyde are isolated in high yields. The aldehyde-hydrate 3-dihydoxymethylpyridin-*N*-oxide was fully characterized.

Chiral *N*-oxides recently were found to be valuable catalysts, useful for instance for the enantioselective reduction of ketones[1] and for the enantioselective addition of allyltrichlorosilanes to aldehydes[2]. In this respect we became interested in the synthesis of the *N*-oxides of picolinaldehydes as potential building blocks for the construction of chiral *N*-oxides.

Two independent pathways are known from literature: the oxidation of alkyl-substituted pyridine-N-oxides at the alkyl group[3] and the N-oxidation of acetals of picolinaldehydes[4]. Both pathways suffer from only moderate yields and from being somewhat tedious. Dimethyldioxirane (**2**) is able to oxidize pyridines[5, 6] and exhibited an extraordinary selectivity in several oxidation reactions[7]; therefore we decided to try this reagent for the direct *N*-oxidation of picolinaldehydes **1** without any protecting groups. First we focused on the oxidation of 2-pyridinecarboxaldehyde (**1a**), anticipated as the most difficult case since the two reactive functional groups are in close proximity.



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PII: S0040-4020(99)00746-2

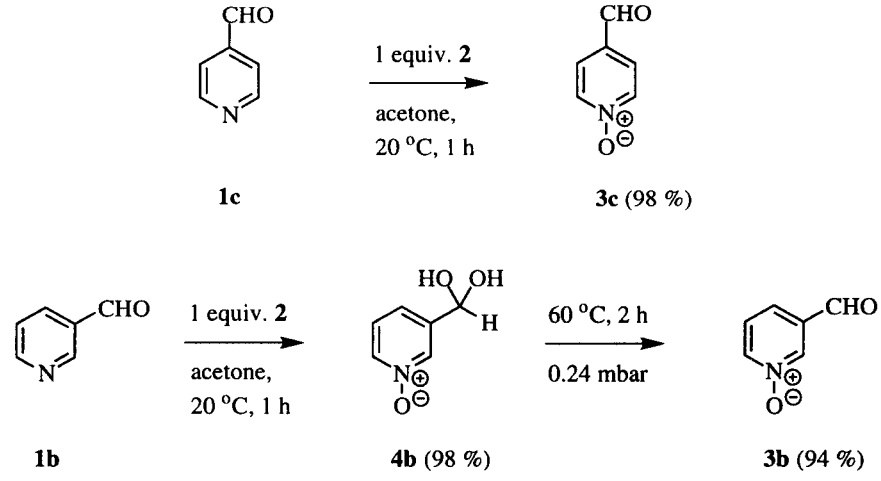
Tab. 1: Oxidation of **1a** with dimethyldioxirane (**2**)

entry	equiv. **2**	T [°C]	t [h]	proportion [%] : **1a**	**3a+4a**	**5a**	**6a**
1	1.0	0	2	58	42	--	--
2	1.0	0	4	40	56	2	2
3	1.0	0	8	25	68	5	2
4	2.0	0	2	28	65	--	7
5	1.0	-20	12	33	67	--	--
6	1.5	-20	12	21	79	--	--
7	2.0	-20	12	14	80	3	3
8	1.0	20	1	15	79	3	3

The proportion of the components was determined by ^{1}H NMR spectroscopy (300 MHz, DMSO-d_6); diagnostic signals: for **1a**: δ = 9.97 (s, 1H, CHO); for **3a**: δ = 10.36 (s, 1H, CHO); for **4a**: δ = 6.07 (t, J = 5.8 Hz, 1H); for **5a**: δ = 8.69 (m, 1H); for **1a**: δ = 8.73 ("d", "J" = 7.1 Hz, 1H).

The oxidation of **1a** was investigated on a 500 µmol scale in the temperature range from -20 to +20 °C (Table 1). After evaporating solvent and remaining **2** (at 40 °C/400 mbar) the product ratio was determined by ^{1}H NMR spectroscopy. The target aldehyde **3a** turned out to be the main product, accompanied with its hydrate **4a**[3a, 8]. The aldehyde/hydrate ratio was found between 3:7 and 9:1, the latter as equilibrium reached after 12 h in DMSO-d_6. As the result from table 1 we concluded, that a large excess of **2** (entries 4 and 7) should be avoided, otherwise substantial amounts of the carboxylic acids **5a** and **6a** were formed. A low temperature (entries 5-7) caused a prolonged reaction time. For a reaction on a preparative scale (7 mmol of **1a**) we chose conditions in analogy to entry 8 (20 °C, 1 h) and isolated a 60 % yield of *N*-oxide **3a** after flash chromatography (TLC: silica, ethyl acetate/triethylamine 4:1; R_f = 0.87 for **1a**, 0.26 for **3a**, 0.00 for **5a** and **6a**; **4a** is dehydrated on silica to give **3a**).

The oxidation of the regioisomers 3-picolinaldehyde (**1b**) and 4-picolinaldehyde (**1c**) revealed an astonishing difference in aldehyde-hydrate formation of the corresponding *N*-oxides **3b** and **3c**. While **3c** was obtained in an almost quantitative yield and did not show any tendency for the formation of an aldehyde-



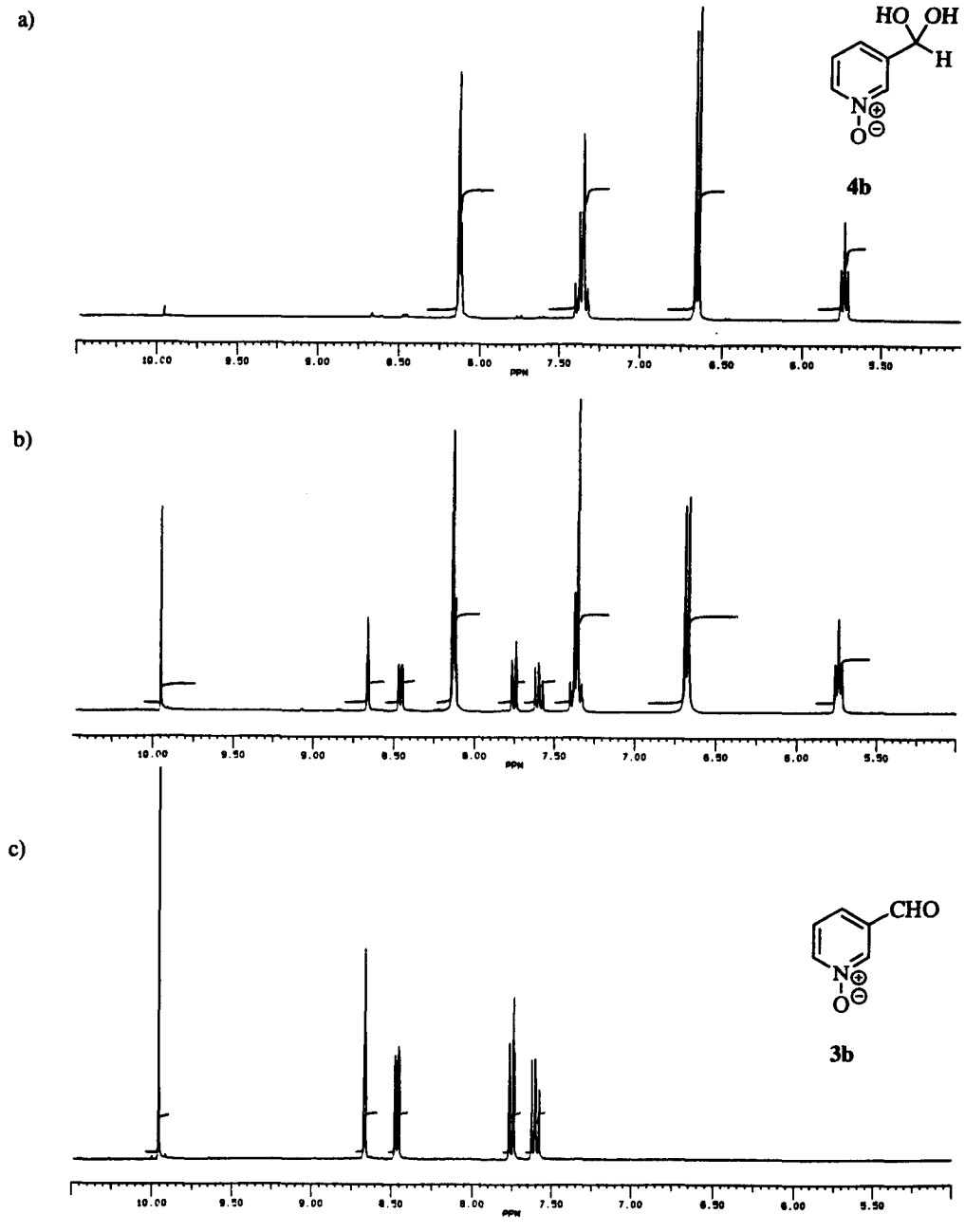


Fig. 1: ^{1}H NMR spectra (300 MHz) of 3-picolinaldehyde-*N*-oxide **3b** and its aldehyde-hydrate **4b** in DMSO-d_6: a) **4b** immediately after solubilization; b) after 1h a **4b/3b** ratio of 70:30 is observed (equilibrium at a **4b/3b** ratio of 8:92 with unknown concentration of water after one week); c) ^{1}H NMR spectrum of pure **3b**.

hydrate, the dihydroxymethyl-substituted *N*-oxide **4b** was obtained as the exclusive oxidation product of **1b**. **4b** was analytically pure according to ^{1}H NMR and to elemental analysis; its dehydration can be monitored by ^{1}H NMR in DMSO-d_6 (Figure 1) and is preparatively achieved at 60 °C/0.24 mbar.

In conclusion, based on dimethyldioxirane (**2**) as highly reactive but nevertheless extraordinary selective oxidizing agent we have developed an efficient procedure for the direct *N*-oxidation of picolinaldehydes, thus eliminating the need of any protecting groups.

Experimental Section

General: m.p. (uncorrected): Reichert Thermovar. – IR: Perkin Elmer 983. – UV: Perkin Elmer 554. – NMR: Bruker DRX 500, Bruker WM 300; ^{1}H-NMR spectra (300 MHz) were recorded in $CDCl_3$ (if not mentioned otherwise) with TMS as the internal standard. ^{13}C-NMR spectra (75.5 MHz) were measured by using $CDCl_3$ as the solvent and the internal standard. – MS: MAT 311A (70 eV). – For analytical TLC precoated plastic sheets "POLYGRAM SIL G/UV254" from "Macherey-Nagel" were used.

Pyridine-2-carboxaldehyde-*N*-oxide (3a): A mixture of 762 mg (7.05 mmol) of 2-picolinaldehyde (**1a**) and 133 ml of a 0.08 M solution of dimethyldioxirane (**2**) in acetone was stirred for 1 h at room temperature. The solvent was removed at the rotatory evaporator at 40 °C/300 mbar and the yellow residue dried for 1 h at room temperature/0.24 mbar (TLC: silica, ethyl acetate/triethylamine 4:1; R_f = 0.87 for **1a**, 0.26 for **3a**, 0.00 for **5a** and **6a**). Flash chromatography (silica, ethyl acetate/triethylamine 4:1) gave 54 mg (7 %) of starting material **1a** and 521 mg (60 %) of **4a** as a colourless solid with mp 67-70 °C. – IR (KBr): ν = 3425 cm^{-1} (w), 3076 (m), 3053 (m), 1686 (s), 1601 (m), 1549 (w), 1482 (w), 1435 (s), 1367 (m), 1296 (s), 1252 (m), 1212 (m), 1184 (s), 1154 (m), 1067 (w), 1041 (w), 884 (w), 859 (s), 812 (w), 779 (s), 708 (w), 635 (m). – ^{1}H NMR (DMSO-d_6): δ = 7.43 ppm ("t","*J*" = 7.7 Hz, 1H), 7.66 ("t", "*J*" = 7.1 Hz, 1H), 7.76 (dd, *J* = 7.9, 2.2 Hz, 1H), 8.34 ("d", "*J*" = 6.5 Hz, 1H), 10.36 (t, *J* = 0.9 Hz, 1H, CHO). – ^{13}C NMR (DMSO-d_6): δ = 125.38 ppm (d), 125.51 (d), 131.03 (d), 140.36 (d), 143.46 (s), 186.40 (d, CHO). – MS (70 eV, 70 °C); *m/z* (%): 123 (17, M^+), 106 (30), 105 (12), 95 (37), 79 (13), 78 (100), 52 (12), 51 (37), 39 (11). $C_6H_5NO_2$ (123.1): calcd. C 58.54, H 4.09, N 11.38; found C 58.50, H 4.23, N 11.17.

3-(Dihydroxymethyl)pyridine-*N*-oxide (4b): A mixture of 749 mg (7.00 mmol) of 3-picolinaldehyde (**1b**) and 116 ml of a 0.06 M solution of dimethyldioxirane (**2**) in acetone was stirred for 1 h at room temperature. The solvent was removed at the rotatory evaporator at 40 °C/300 mbar and the residue dried for 1 h at room temperature/0.24 mbar: 971 mg (98 %) N-oxide **4b** as a colourless, analytically pure solid with mp 110 °C. – IR (KBr): ν = 3125 cm^{-1} (w), 2893 (m), 1704 (w), 1608 (ww), 1573 (w), 1464 (m), 1427 (s), 1338 (w), 1307 (m), 1299 (m), 1277 (m), 1247 (m), 1230 (m), 1156 (s), 1070 (s), 1045 (s), 1021(m), 954 (s), 929 (m), 889 (m), 824 (m), 773 (s), 702 (m), 665 (w). – ^{1}H NMR (DMSO-d_6): δ = 5.74 ppm (t, *J* = 6.5 Hz, 1H), 6.65 (d, *J* = 6.5 Hz, 2H, OH),7.32-7.40 (m, 2H), 8.11-8.14 (m, 2H). – ^{13}C NMR (DMSO-d_6): δ = 87.49 ppm (d), 123.54 (d), 126.19 (d), 136.73 (d), 137.80 (d), 144.00 (s). – MS (70 eV, 70 °C); *m/z* (%): 123 (100, $M^+ - H_2O$), 107 (35), 106 (22), 78 (34), 66 (10), 52 (12), 51 (14); virtually identical with the MS of aldehyde **3b**. $C_6H_7NO_3$ (141.1): calcd. C 51.06, H 5.00, N 9.92; found C 51.25, H 5.02, N 9.90.

Pyridine-3-carboxaldehyde-*N*-oxide (3b): 971 mg of aldehyde-hydrate **4b** were heated for 2 h at 60 °C/0.24 mbar to give 795 g (92 %) of **3b** as a slightly yellow, analytically pure solid with mp 130 °C (ref.[3b]: mp 138 °C). – IR (KBr): ν = 3421 cm^{-1} (w), 3111 (w), 3032 (m), 3013 (m), 2873 (w), 2767 (w), 1841 (w), 1747 (w), 1697 (s), 1602 (w), 1558 (w), 1483 (w), 1448 (m), 1396 (w), 1319 (w), 1277 (s), 1168 (m), 1071 (w), 1045 (w), 1017 (m), 1004 (w), 959 (w), 931 (w), 915 (w), 890 (w), 815 (w), 795 (m), 669 (w). – ^{1}H NMR (DMSO-d_6): δ = 7.60 ppm ("t", "*J*" = 6.5 Hz, 1H), 7.75 ("d", "*J*" = 7.8 Hz, 1H), 8.46 ("d", "*J*" = 6.4 Hz, 1H), 8.66 ("s", 1H), 9.95 (s, 1H, CHO). – ^{13}C NMR (DMSO-d_6): δ = 124.39 ppm(d), 127.33 (d), 135.01 (s), 140.19 (d), 143.33 (d), 190.56 (d, CHO). – MS (70 eV, 70 °C); *m/z* (%): 123 (100, M^+), 107 (17), 106 (12), 78 (19), 79 (13), 66 (11), 63 (9), 51 (18), 50 (9), 39 (34). $C_6H_5NO_2$ (123.1): calcd. C 58.54, H 4.09, N 11.38; found C 58.55, H 4.08, N 11.34.

Pyridine-4-carboxaldehyde-*N*-oxide (3c): A mixture of 749 mg (7.00 mmol) of 4-picolinaldehyde (**1c**) and 116 ml of a 0.06 M solution of dimethyldioxirane (**2**) in acetone was stirred for 2 h at room temperature. The solvent was removed at the rotatory evaporator at 40 °C/300 mbar and the residue dried for 1 h at room temperature/0.24 mbar: 845 mg (98 %) of **3c** as a colourless, analytically pure solid with mp 145 °C (ref.[3b]: mp 152 °C). – IR (KBr): ν = 3430 cm^{-1} (w), 3107 (m), 3033 (m), 3018 (m), 2862 (w), 2761 (w), 1685 (s), 1629 (w), 1606 (s), 1551 (m), 1492 (w), 1479 (w), 1449 (m), 1396 (m), 1313 (w), 1265 (s), 1224 (s), 1164 (s), 1028 (m), 867 (s), 851 (w), 843 (w), 712 (w), 663 (w), 617 (s), 531 (w). – ^{1}H NMR (DMSO-d_6): δ = 7.86 ppm ("d", "*J*" = 7.2 Hz, 2H), 8.38 ("d", "*J*" = 7.1 Hz, 2H), 9.94 (s, lH, CHO). – ^{13}C NMR (DMSO-d_6): δ = 126.35 ppm (d), 130.96 (s), 140.12 (d), 189.87 (d, CHO). – MS (70 eV, 70 °C); *m/z* (%): 123 (100, M^+), 122 (42), 95 (10), 94 (16), 78 (10), 63 (11), 51 (15), 50 (11), 39 (31). $C_6H_5NO_2$ (123.1): calcd. C 58.54, H 4.09, N 11.38; found C 58.50, H 4.11, N 11.30.

Acknowledgement: Financial support of the *Deutsche Forschungsgemeinschaft* and of the *Fonds der Chemischen Industrie* is gratefully acknowledged.

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