

A Simple Method for Synthesis of Active Esters of Isonicotinic and Picolinic Acids

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Abstract: A method for preparation of the p-nitrophenyl-, N-hydroxysuccinimidyl- and pentafluorophenyl esters of isonicotinic and picolinic acids from the corresponding acids is reported.

Keywords: Active esters, pyridine carboxylic acids.

Introduction


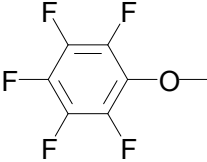
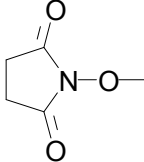
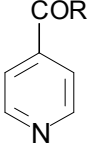
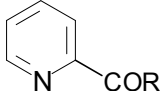
In connection with ongoing synthetic work, we needed access to good acylating reagents based on isonicotinic and picolinic acids. Acylations with isonicotinoyl and picolinoyl chlorides were found to be troublesome, because the acid chlorides are only prepared or available as the corresponding hydrochlorides, which are only sparingly soluble in inert solvents. A further complication was, that upon reaction with polyamines such as poly(propyleneimine) dendrimers incomplete reactions occurred due to extensive salt formation. Therefore we turned our attention to the so called active esters [1].

Results and Discussion

Searching the literature we found references to the p-nitrophenyl esters of isonicotinic [2,3] and picolinic acid [2,3,4], which have been used for the synthesis of potent antagonists of the luteinizing hormone-releasing hormone (LHRH) [4,5]. The only other ester reported was the pentachlorophenyl

ester of isonicotinic acid [6], however in the latter case, no experimental details were given. All the procedures were based on the DCC coupling of the acids with the corresponding phenol, however especially in the case of picolinic acid the coupling reaction was hampered by the well known rearrangement of the intermediate O-acylureas to N-acylureas [2]. This problem could be solved by performing the coupling reaction in CH_2Cl_2 , but again no experimental details were given [2]. We were primarily interested in obtaining the more reactive [1] N-hydroxysuccinimidyl and pentafluorophenyl esters, and since DCC-coupling mainly gave the corresponding N-acyl-N,N'-dicyclohexylureas, the present method was developed. Reaction of the corresponding pyridinecarboxylic acid with SOCl_2 catalyzed by DMF [7] at room temperature gives the acid chlorides as their hydrochlorides. These were reacted with 4-nitrophenol, pentafluorophenol and N-hydroxysuccinimide in THF with triethylamine as base to give the corresponding active esters. The compounds prepared are shown Table 1.

Table 1.
Isonicotinic (**1**) and Picolinic (**2**) acid esters prepared.

R (yield):			
	1a (54%)	1b (97%)	1c (84%)
	2a (39%)	2b (92%)	2c (67%)

Conclusions

A convenient method has been developed for the synthesis of a variety of active esters of isonicotinic and picolinic acids.

Experimental

General

^1H - and ^{13}C -NMR spectra were obtained using a Varian Gemini 300 NMR or a Varian Unity 400 NMR. Mass spectra were obtained using a Jeol JMS-HX 110 A Tandem Mass Spectrometer. IR-spectra were recorded on a Perkin Elmer 1760 X. All melting points are uncorrected. The elemental analyses were performed by Mrs. Karin Linthoe, Department of Organic Chemistry, University of Copenhagen. All chemicals were used as received.

Isonicotinoylchloride hydrochloride

Thionylchloride (60 mL) was added carefully to a stirred mixture of isonicotinic acid (24.6 g; 0.2 mol) and DMF (1 mL). A lively gas evolution started, and after 30 minutes all of the acid had gone into solution and the temperature had risen to about 40°C. Excess thionyl chloride was removed *in vacuo*, and diethyl ether (200 mL) was stirred into the residue. The crude product was filtered, washed with diethyl ether and dried *in vacuo* at 40°C. Yield: 35.0 g (98%) of white crystals sufficiently pure for the preparation of the activated esters.

Picolinoylchloride hydrochloride

Prepared analogously to isonicotinoylchloride hydrochloride.

General procedure for the preparation of active esters

Isonicotinic acid pentafluorophenyl ester

To a stirred suspension of isonicotinoylchloride hydrochloride (8.9 g; 0.05 mol) and pentafluorophenol (9.2 g; 0.05 mol) in THF (100 mL) was added triethylamine (20 mL; 0.14 mol) over 10 minutes. The suspension was stirred at room temperature for 12 hrs, filtered and concentrated *in vacuo*. The residue was dissolved in hexane (300 mL), treated with activated carbon and filtered. The hexane was removed to give the pentafluorophenyl ester as a slightly brownish oil, which crystallized to give a creme colored solid melting 52-54°C. Yield: 14.0 g (97%); ¹H-NMR (300 MHz; CDCl₃) δ: 8.93 (m; 2 H); 8.01 (m; 2 H). ¹³C-NMR (100 MHz; CDCl₃) δ: 161.2; 150.9; 142.3 (m); 141.1 (m); 139.8 (m); 139.2 (m); 138.5 (m); 136.6 (m); 134.2; 123.3. MS (EI): M/Z: 290 (M⁺); 155; 106; 78; 51. IR (KBr pellet): 3132, 3087, 3063, 2644, 2132, 1765, 1741, 1651, 1592, 1520, 1457, 1436, 1391, 1298, 1241, 1163, 1098, 1067, 1042, 980, 865, 821, 787, 785, 714, 691, 621, 608. An analytical sample was recrystallized from hexane. Found: C: 49.31; H: 1.40 ; N: 4.79. (Calcd. for C₁₂H₄F₅NO₂: 49.84% C; 1.39% H; 4.84% N.)

Isonicotinic acid 4-nitrophenyl ester

This compound was prepared according to the general procedure with the exception, that the crude product was crystallized from 2-propanol to give the ester in 54% yield. Mp. 137-138°C (137-139°C [5]). ¹H-NMR (300 MHz; CDCl₃) δ: 8.88 (m; 2 H); 8.35 (m; 2 H); 7.99 (m; 2 H); 7.44 (m; 2H). ¹³C-NMR (63 MHz; CDCl₃) δ: 162.80; 154.91; 150.88; 146.0; 135.76; 125.31; 123.05; 122.32. MS(EI): M/Z: 245 (M⁺); 106; 78; 51. IR (KBr pellet): 3462, 3116, 3086, 3053, 3024, 1746, 1615, 1594, 1567, 1525, 1489, 1408, 1357, 1326, 1312, 1272, 1210, 1163, 1109, 1087, 1061, 1012, 884, 864, 847, 833, 750, 699, 677, 624.

Isonicotinic acid N-hydroxysuccinimidyl ester

Prepared according to the general procedure with the exception that the crude product was crystallized from 2-propanol to give the ester in 84% yield. Mp. 140-141°C. ¹H-NMR (300 MHz; CDCl₃) δ: 8.81 (m; 2 H); 7.87 (m; 2 H); 2.88 (d; J = 8.6 Hz; 4 H). ¹³C-NMR (63 MHz; CDCl₃) δ: 168.54; 160.62; 150.79; 132.39; 122.95; 25.46. MS(EI): M/Z: 220 (M⁺); 106; 78; 51. Found C: 54.14; H: 3.80; N: 12.49. IR (KBr pellet): 3501, 3064, 2991, 2939, 1806, 1779, 1736, 1596, 1563, 1409, 1367, 1326, 1238, 1201, 1074, 1018, 844, 806, 747, 698, 651, 603. (Calcd. for C₁₀H₈N₂O₂: 54.55% C; 3.66% H; 12.72 % N.)

Picolinic pentafluorophenyl ester

Prepared according to the general procedure, and crystallized twice from hexane. Transparent crystals. Yield: 92%. Mp. 61-63°C. ¹H-NMR (300 MHz; CDCl₃) δ: 8.78 (m; 1 H); 8.21 (m; 1 H); 7.89 (m; 1 H); 7.56 (m; 1 H). ¹³C-NMR (100 MHz; CDCl₃) δ: 160.93; 150.14; 144.89; 140.75; 139.80; 139.00; 138.20; 137.29; 136.50; 128.11; 126.38. MS(EI): M/Z: 290 (M⁺); 242; 212; 183; 155; 106; 78. IR (KBr pellet): 3518, 3054, 2467, 1768, 1715, 1654, 1616, 1593, 1520, 1473, 1411, 1330, 1263, 1212, 1161, 1078, 1056, 995, 857, 845, 806, 764, 748, 728, 699, 622, 576.

Picolinic acid p-nitrophenyl ester

Prepared according to the general procedure, and crystallized from 2-propanol. White needles. Yield: 39%. Mp. 147-149°C (dec.). (155-157°C [5]). ¹H-NMR (300 MHz; CDCl₃) δ: 8.86 (m; 1 H); 8.31 (m; 3 H); 7.96 (m; 1 H); 7.60 (m; 1 H); 7.45 (m; 2 H). ¹³C-NMR (63 MHz; CDCl₃) δ: 162.87; 155.44; 150.13; 146.40; 145.48; 137.25; 127.78; 126.01; 125.16; 122.56; MS (EI): M/Z: 245 (M⁺); 200; 106; 78. IR (KBr pellet): 3455, 3114, 3079, 1764, 1740, 1615, 1591, 1520, 1489, 1437, 1350, 1293, 1245, 1218, 1160, 1094, 1072, 1045, 995, 887, 865, 836, 749, 740, 712, 696, 681, 617.

Picolinic acid N-hydroxysuccinimidyl ester

Prepared according to the general procedure, and crystallized from 2-propanol. White crystals. Yield: 67%. Mp. 172-174°C. ¹H-NMR (300 MHz; CDCl₃) δ: 8.84 (m; 1 H); 8.23 (m; 1 H); 8.12 (m; 1 H); 7.82 (m; 1 H); 2.91 (s; 4 H). ¹³C-NMR (63 MHz; CDCl₃) δ: 169.04; 150.06; 143.5; 137.4; 128.5; 126.2; 25.4. MS (EI): M/Z: 220 (M⁺); 106; 78. IR (KBr pellet): 3493, 3093, 2955, 1799, 1776, 1742, 1587, 1471, 1440, 1419, 1359, 1265, 1236, 1200, 1066, 1009, 851, 814, 744, 698, 642, 620, 598.

References

1. Bodanzsky, M. *Peptide Chemistry*, 2nd ed., Springer-Verlag, Berlin-Heidelberg-New York **1993**, pp. 60.
2. Folkers, K.; Ljungqvist, A. The Reaction of Pyridinecarboxylic Acids with Dicyclohexylcarbodiimide and p-Nitrophenol. *Acta Chem. Scand.* **1988**, B42, 408.

3. Fife, T. H.; Przystas, T. J. Divalent Metal Ion Catalysis in the Hydrolysis of Esters of Picolinic Acid. Metal Ion Promoted Hydroxide Ion and Water Catalyzed Reactions. *J. Am. Chem. Soc.* **1985**, *107*, 1041.
4. Flouret, G.; Mahan, K.; Majewski, T. Decreased Histamine Release by Luteinizing Hormone-Releasing Hormone Antagonists Obtained upon Translocation of the Cationic Amino Acid from Position 8 to Position 7. *J. Med. Chem.* **1992**, *35*, 636.
5. Janecka, A.; Janecki, T.; Shan, S.; Bowers, C.; Folkers, K. Novel, Potent Luteinizing Hormone-Releasing Antagonist with Improved Solubility in Water. *J. Med. Chem.* **1994**, *37*, 2238.
6. Solárzano, C.; Davis, M. A. Preparation of Arene Ruthenium(II) Complexes with Activated Ligands for Protein Labeling. *Inorg. Chim. Acta* **1985**, *97*, 135.
7. Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. Eine Methode zur katalysierten Herstellung von Carbonsäure- und Sulfosäure-chloriden mit Thionylchlorid. *Helv. Chim. Acta* **1959**, *42*, 1653.

Sample Availability: Available from the author.

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