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AMIDE REACTIONS OF IZONICOTINE ACID WITH SOME AROMATIC AMINES

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Abstract

Corresponding amides were synthesized from the reactions of isonicotinic acid with o-toluidine, m-toluidine, p-toluidine 2,4-xylidine 2,5-xylidines. The influence of the nature of the solvent on the course of reactions was studied and the results obtained were compared. It was found that isonicotinic acid reacts with some aromatic amines to form amides when heated in non-polar solvents. The physical constants of the synthesized amides were determined. The structure of the reaction products was analyzed using IR- and ^{1}H and ^{13}C NMR spectroscopy methods.

Keywords: *Isonicotinic acid, o-toluidine m-toluidine, p-toluidine 2,4-xylidine, 2,5-xylidine, amide, organic solvent*

Introduction

It can be seen from the analysis of literature data that it is possible to obtain acid amides with high yields from N-acylation (benzoylation) reactions of amines, especially aromatic amines with anhydrides and halogen anhydrides of carboxylic acids. However, finding ways to synthesize any organic substance through low-level reactions using ready-made reagents is one of the important tasks for chemists. It should be noted that special attention is paid to these aspects in the synthesis of acid amides. As a result, effective methods of product synthesis with high yield are being developed by direct use of carboxylic acids as acylating agents in the synthesis of amides. Below is an analysis of relevant literature data.

The results of research related to the study of the reactions of carboxylic acids with amines show that the reactions proceed with the formation of intermediate protonated quaternary ammonium salts, as a result of condensation when heated under certain conditions, acid amides are formed.

The ligand N, N´-(2,5-dimethyl-1,4-phenylene)diisonicotinamide was synthesized by reacting 2,5-dimethyl-1,4-phenylenediamine with isonicotinyl chloride hydrochloride in pyridine for 5 days at 25 °C (Pingwah Tang. 2012).

The acid amide was synthesized in high yield in 40 min by reacting heteroaromatic isonicotinic acid with aniline, 2,4-dimethylaniline and n-propylamine under ultrasonic bath using rGO-SO3H (sulfonated reduced graphene oxide) catalyst (Baevsky A. M., Tsikalov V. V., Baevsky M. Yu., Sheludko A. B., 2011).

Nicotinic acid was first reacted with oxalyl chloride to form nicotinic anhydride, then nicotinic anhydride was reacted with amines to synthesize acid amides in high yield (Yoshikawa M. et al. 2008).

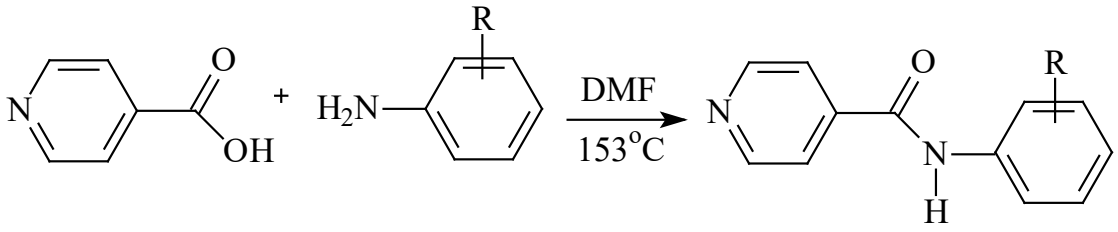
In other literature, the formylation of aliphatic, aromatic, heterocyclic, primary and secondary amines with DMF in the presence of nickel (II) quinazolone was brought out with high efficiency, and the mechanism of the reaction was shown with a catalytic cycle (Sonawane R. B., Rasal N. K., Jagtap S. V., 2017).

In recent years, research has been developing on the use of nitrogen heterocyclic compounds in acid-amine condensation reactions. For example, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholine chloride (Kunishima M., Kawachi C., Hioki K., Terao K., Tani S., 2001), 2,4,6-trichloro-1,3,5-triazine (Gholap S., Gunjal N. 2017), and nitrogen heteropolyanions (Jaita S., Phakhodee W., Chairungsi N., Pattarawarapan M., 2018) are used as active condensation catalysts. Also, N, N-diisopropylcarbodiimide showed catalytic activity in the reaction of carboxylic acids with amines in an aqueous medium at room temperature. This method is important because it ensures environmental safety and, in particular, reveals new aspects of organic synthesis in water (Fattahi N., Ayubi M., Ramazani A. 2018). When the reaction of substituted phenylacetic acids with benzylamine derivatives was carried out in the presence of various nickel compounds, the following series of catalytic activity was determined: $NiCl_2$ > $(CH_3COO)_2Ni$ > $NiCl_2(PPh_3)_2$ > $NiCl_2$ H_2O > without catalyst. Solvents – diethyl ether, TGF, toluene, fluorobenzene, acetonitrile, DMF and DMSO were used in this process, and the highest yield (80% in 10 hours, 99.2% in 20 hours) was achieved in toluene (Cheng L., Ge X., Huang L., 2018).

Research methods

Initially devoted to studying the reaction of isonicotinic acid with o-toluidine. The reaction of isonicotinic acid with o-toluidine was carried out in a flask equipped with a reflux condenser at the boiling temperature of DMF on a magnetic stirrer for 7 hours.

The reaction equation is:



R = o-Toluidin, R = m-Toluidin, R = p-Taluidin, R = 2,4-xylidine, R = 2,5-xylidine

The obtained product was recrystallized from a 40% ethanol-water mixture and dried in a desiccator with calcium chloride. The melting temperature was determined, the IR and NMR spectra were taken, and the purity was checked using the TLC method.

Experimental part

IR spectra were recorded on a FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system. ^{1}H and ^{13}C NMR spectra were recorded on a JNM-EC-Z400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD3OD solutions. TMS (0 ppm) was used as an internal standard in ^{1}H NMR spectra. In 13C NMR spectra, the chemical shift of the solvent (CD3OD, 49.00 ppm relative to TMS) was used as an internal standard.

N-(o-tolylphenyl)isonicotinamide is a white crystalline substance**,** yield 45%, $T_{melting}$= 158 °C, Rf = 0.61 (benzene-acetone system 3: 1). IR spectrum sm^{-1} 3198 (NH), 2917 (–CH2-), 1680 (C=O), 1281 (C-N), 1586 (C=C aromatic ring).NMR^{1}H-spectr (400 MHz, METHANOL-D_4) δ 9.12–9.07 (m, 1H), 8.71

(dd, *J* = 5.0, 1.6 Hz, 1H), 8.35 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.57 (dd, *J* = 8.1, 5.0 Hz, 1H), 7.37–7.12 (m, 4H), 2.28 (s, 3H), 1.36–1.24 (m, 1H).^{13}C NMR (101 MHz, METHANOL-D_4) δ 166.03, 162.13, 150.96, 136.10, 132.08, 131.83, 131.55, 128.03, 127.38, 126.84, 125.09, 124.74, 123.57, 18.00, 17.81.

N-(м-tolylphenyl)isonicotinamide is a white crystalline substance, yield 43%, $T_{melting}$=122 ˚C, Rf = 0.58 (benzene-acetone system 3: 1). IR spectrum sm^{-1} 3138 (NH), 1674 (C=O), 1306 (C-N), 1612 (C=C aromatic ring).^{1}H NMR (600 MHz, METHANOL-D_4) δ 9.05 (dd, *J* = 2.7, 1.5 Hz, 1H), 8.71–8.66 (m, 1H), 8.34–8.28 (m, 1H), 7.59–7.53 (m, 1H), 7.50 (s, 1H), 7.49–7.44 (m, 1H), 7.22 (td, *J* = 8.5, 3.5 Hz, 1H), 7.00–6.95 (m, 1H), 2.33 (dd, *J* = 5.5, 2.7 Hz, 3H).^{13}C NMR (101 MHz, METHANOL-D_4) δ 164.88, 161.59, 150.96, 136.36, 135.82, 135.34, 131.10, 130.38, 124.77, 121.10, 119.87, 20.80.

N-(p-tolylphenyl)isonicotinamide is a pink crystalline substance, 55%, $T_{melting}$= 130 ˚C, Rf = 0.56 (benzene-acetone system 3: 1). IR spectrum sm^{-1} 3308 (NH), 2921 (–CH2-), 1673 (C=O), 1290 (C-N), 1592 (C=C aromatic ring).^{1}H NMR (600 MHz, METHANOL-D_4) δ 9.04 (d, *J* = 2.3 Hz, 1H), 8.69 (dd, *J* = 4.3, 2.3 Hz, 1H), 8.34–8.29 (m, 1H), 7.59–7.54 (m, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.19–7.14 (m, 2H), 5.00–4.92 (m, 1H), 4.60 (s, 1H), 2.31 (d, *J* = 1.8 Hz, 3H).^{13}C NMR (151 MHz, METHANOL-D_4) δ 164.98, 151.36, 147.99, 135.99, 135.56, 134.51, 131.45, 129.03, 129.00, 128.98, 123.87, 121.13, 121.02, 48.23, 48.10, 47.96, 47.81, 47.77, 47.75, 47.67, 47.63, 47.60, 47.53, 47.48, 47.44, 47.39, 47.34, 47.32, 47.29, 47.25, 19.65, 0.64.

N-(2,4-dimethylphenyl)isonicotinamide is a white powdery substance, 42%, $T_{melting}$= 102 ˚C, Rf = 0.52 (benzene-acetone system 3: 1). IR spectrum sm^{-1} 3272 (NH), 2920 (–CH2-),1653 (C=O), 1230 (C-N), 1591 (C=C aromatic ring).^{1}H NMR (400 MHz, METHANOL-D_4) δ 9.08 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.70 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.39–8.30 (m, 1H), 7.57 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.12––7.06 (m, 1H), 7.02 (dd, *J* = 8.1, 2.1 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H).^{13}C NMR (101 MHz, METHANOL-D_4) δ 165.21, 162.07, 134.43, 131.07, 130.17, 129.49, 128.69, 126.08, 125.27, 124.54.

N-(2,5-dimethylphenyl)isonicotinamide is a white crystalline substance, 46%, $T_{melting}$= 108 ˚C, Rf = 0.56 (benzene-acetone system 3: 1). IR spectrum sm^{-1} (KBr, ν, см$^{-1}$): : 3243 (NH), 2918 (–CH2-),1645 (C=O), 1289 (C-N), 1592 (C=C aromatic ring).^{1}H NMR (400 MHz, METHANOL-D_4) δ 8.24 (s, 1H), 7.47–7.41 (m, 1H), 7.08 (t, *J* = 8.0 Hz, 2H), 6.98–6.86 (m, 2H), 2.30–2.09 (m, 9H).^{13}C NMR (101 MHz, METHANOL-D_4) δ 166.06, 162.16, 137.21, 131.91, 131.44, 128.64, 128.05, 127.58, 125.61, 124.16, 21.05, 20.90, 17.57, 17.37.

Results and discussion

Initially, the reaction with isonicotinic acid and o-toluidine, m-toluidine, p-toluidine, 2,4-xylidine, 2,5-xylidine in different molar ratio was carried out in a flask with a reflux condenser in a magnetic stirrer for 7 hours at the boiling point of DMF. As a result of the studies, arylamides were synthesized in high yields using a 1:1 molar ratio reaction, which is the most alternative of the reactions obtained in different molar ratios. Initially, reactions carried out at the boiling point of a non-polar organic solvent in the presence of isonicotinic acid and aromatic amines in equal molar ratios gave unique results.

Table 1.

Primary amen	The proportions of the mol	Time,	Product yield in solvent, %		Reaction product
			DMF (144 °C)	TS, °C	R_f
o-Toluidin	1:1	7	**45**	158–160	0.60
	1: 2	7	38		
	1: 3	7	34		
	1: 1	7	42		

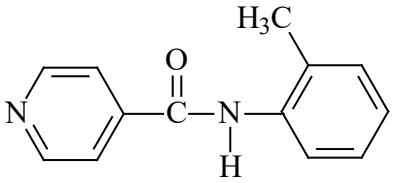
Primary amen	The proportions of the mol	Time,	Product yield in solvent, %		Reaction product
			DMF (144 °C)	TS, °C	R_f
m-Toluidin	1: 2	7	36	**152–154**	0.5
	1: 3	7	27		
p-Toluidin	1: 1	7	52		
	1: 2	7	44	**135–137**	0.56
	1: 3	7	40		
2,4-xylidine	1: 1	7	38		
	1: 2	7	33	102–104	0.5
	1: 3	7	31		
2,5-xylidine	1: 1	7	41		
	1: 2	7	36	108–110	0.56
	1: 3	7	32		

The reason is that as a result of experiments m-toluidine, 2,4-xylidines with relatively lower basicity gave amide products with lower yield, on the contrary, basicity in reactions with o-toluidine, p-toluidine, 2,5-xylidines with higher basicity arylamides of isonicotinic acid were synthesized with high yield compared to lower aromatic amines.

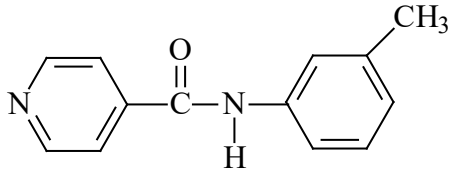
The result of the reaction of arylamides with isonicotinic acid and aromatic amines in molar ratios of 1:1, 1:2 and 1:3.

From the values presented in the table, it is evident that arylamides were formed in the presence of the solvent used for the reactions. Moreover, the yield of products increases depending on the basicity of the amines.

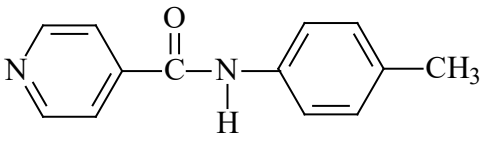
Synthesized amides



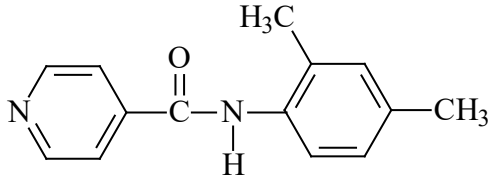
1a



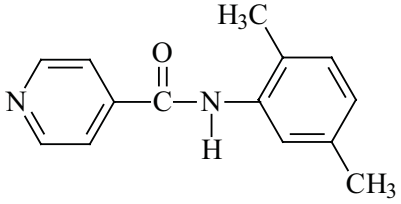
2b



3d



4e



5f

Conclusion

As a result of the experiments, arylamides of isonicotinic acid were synthesized. The physical constants of the reaction products were determined and their structure was confirmed by IR spectroscopy and NMR spectra. It was possible to obtain quaternary ammonium salts of isonicotinic acid and aromatic amines in an organic solvent at At high temperature.

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