IMPROVEMENT OF THE ULLMANN'S CONDENSATION METHOD FOR THE SYNTHESIS OF 2-ANILINONICOTINIC ACIDS

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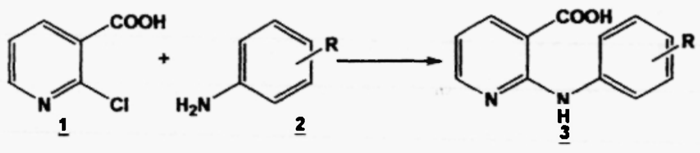
Abstract

Several 2-anilinonicotinic acid derivatives were prepared under the Ullmann's reaction conditions by condensation of 2-chloronicotinic acid and various substituted anilines. Improvement of the procedure based on the effect of the catalyst and that of the solvent on the reaction yields is reported.

Introduction

Ullmann's reaction is mostly used in arylanthranilic acids synthesis. For example, the title reaction can be used for preparing 2-arylaminonicotinic acids 3 which are key intermediates in the benzo[*b*]-1,8-naphthyridin-5-ones synthesis[1,2]. These compounds are potentially active on parasitic diseases and multidrug resistance in tumour cells [3,4]. However, the Ullmann's reaction conditions are vigorous with generally average yields[5,6]. Considerable deactivation is obtained when amine branched with electron-withdrawing substituent is the reagent; moreover, tar formation is observed during the reaction[7]. Thus we tried to optimize the synthesis of anilinonicotinic acid derivatives which are usually obtained by refluxing during 24 hr 2-chloronicotinic acid 1 with substituted anilines 2, in a solvent with high boiling point in the presence of copper as catalyst[5].



2a = aniline
2b = 2-methoxyaniline
2c = 2-nitroaniline
2d = 2-cyanoaniline
2e = 2-carbomethoxyaniline
2f = 3,4-dimethoxyaniline
2g - 5-aminoindazole

Results and discussion

Experiments were performed with substituted anilines 2 (20 mmol). On the one hand, xylene, n-amyl alcohol, DMF, DMSO and pyridine were used as solvents at 140-150°C in quantities from 50 mL to 150 mL. On the other hand, the role of copper was evaluated. Results are given in the Table.

Compounds	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Yields (xylene, 150 mL with Cu)	87%	10%	7%	60%	20%	5%	0%
Yields (xylene, 150 mL without Cu)	0%	90%	93%	0%	80%	89%	0%
Yields (pentanol, 50 mL with Cu)	0%	0%	0%	39%	0%	0%	67%
Yields (pentanol, 50 mL without Cu)	-	-	-	-	-	-	70%

Apart from the synthesis of **3g**, it can be noted that xylene is much more better than n-amyl alcohol as solvent on the condition that a large excess be used. Actually, **3g** was not obtained in xylene because reagents are not soluble in this solvent whilst there are in n-amyl alcohol. In addition, xylene allows to isolate easily the reaction products due to their low solubility in this solvent. The other solvents, like DMF, DMSO and pyridine, do not work at all. Moreover, the greater the quantity of solvent, the better the yield: compound **3a** is obtained in 87% yield when 150 mL of xylene is used whereas the reaction yield fell to 53% when only 50 mL of xylene was used. In the presence of copper **3a**, **3d** and **3g** are obtained in good yields whereas **3b**, **3c**, **3e** and **3f** are only obtained in very low yields with tar formation. However, yields significantly increase in the absence of catalyst except that of **3g** which is almost the same whatever are the conditions. In addition, no purification is needed for compounds obtained without use of catalyst. Actually, copper is capable to catalyse efficiently carbon-carbon bonding, specially in case of aromatic compounds[8]. Referring to the involvement of copper in the metal-promoted coupling of aryl halides[9] and owing to the fact that 2-chloronicotinic acid is concerned in the reaction under evaluation it could be assumed that the Ullmann's reaction conditions induce side reactions such as dimerization of aromatic nucleus. Thus, low yields obtained in case of compounds **3b**, **3c**, **3e** and **3f** could be attributed to these side products which compete directly with the desired anilinonicotinic derivatives although no coupling products were isolated probably because of the tar formation.

In conclusion, the great majority of anilinonicotinic acids can be easily prepared in xylene on the sole condition that reagents be soluble in this solvent and, in many cases, yield is strongly improved when no catalyst is used.

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