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AN IMPROVED SOLVENT-FREE PREPARATION OF 2-IMIDOYLPHENOLS

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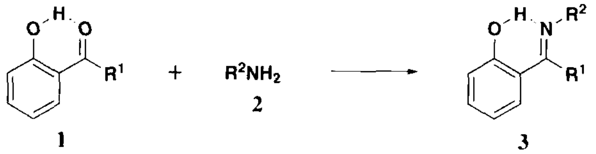
2-Imidoylphenols (**3**) are heterofunctionally substituted organic compounds used in several applications and as precursors for some classes of molecules. They serve as ligands[1] in the preparation of rhodium complex catalysts, possess interesting antifungal properties,[2] and are starting materials for the synthesis of 4H-chromen-4-ylidenamines.[3] Moreover, the stereoselective reduction of imidoyl phenols is a convenient synthetic pathway to aminophenols, another class of ligands extremely efficient in catalytic reactions such as the synthesis of optically active secondary alcohols by enantioselective addition of organozinc compounds to aldehydes.[4]



During the course of our studies on aminophenols and 4H-chromen-4-ylidenamines, we needed to prepare imidoylphenols (**3**) in a multigram scale as starting materials. These compounds are commonly prepared by condensation of primary amines with 2-acylphenols (**1**). The reaction protocol reported in the literature[5] consists of dissolving the starting materials in benzene, toluene or xylene and refluxing the mixture for prolonged time (some hours) with azeotropic removal of water through a Dean-Stark apparatus. In some cases, Brønsted[6] or Lewis acids ($ZnCl_2$[7]) are used as catalysts. Extraction of the mixture affords the crude product in variable yields and these products normally required further purification, either by distillation or crystallization. The main drawbacks of this method are the use of toxic aromatic solvents, and the difficulty to obtain pure liquid products; purification by chromatographic separation is not convenient because of the partial decomposition of the imidoyl phenol on silica gel. We now report an improved route to the preparation of imidoyl phenols (**3**).

This new methodology produces the desired products without any need of heating, solvent, or acid catalyst. When 2-acylphenol (**1**, R^1 = Me, Et, Ph) is mixed with a slight excess of primary aliphatic amine [**2**, R^2 = Me, Pr^i, Bn, (*R*)-$CHCH_3Ph$)] in a 1.1 molar ratio, an immediate yellow coloration of the mixture and evolution of heat are observed. After a few seconds the water produced separates as droplets. The reaction mixture became more viscous during the course of the reaction until an oil or a solid is obtained. This final mixture contains the product in a 91-98% yield and purification is carried out by washing the reaction mixture with water to remove the excess amine.

The speed and efficacy of the reaction is probably due to carbonyl activation by the acidic phenolic proton; acetophenone does not react with amines under the same conditions. Moreover, the presence of the hydroxy function in the *ortho* position helps stabilize the final imidoylphenol. For example, when 4-hydroxyacetophenone and isopropylamine are mixed, a bright yellow color develops immediately, but the final product is isolated in poor yield and rapidly loses isopropylamine to give back 4-hydroxyacetophenone. This method is especially suitable for low boiling amines, which can be used as hydrochlorides. In this case, a larger excess of amine is used to circumvent the volatility problem, and the reaction takes place only when 30% aqueous sodium hydroxide is added dropwise at 0° to the mixture of amine hydrochloride and 2-acylphenols. Aniline does not react, probably because it is less nucleophilic than the aliphatic amines.

Table 1. Synthesis of 2-Imidoylphenols (3)

Product	R^1	R^2	Time (h)	Yield (%)	mp [bp] (°C)	Lit. (°C)
3a	Me	Me	4.00[a]	98	65-66	68[5a]
3b	Me	Pr^i	0.75	98	[120 (3 mm)]	[123 (3 mm)][5a]
3c	Me	Bn	2.00	97	118-119	118-119[8]
3d	Et	Me	5.00[a]	93	[118 (3 mm)]	-[8]
3e	Et	Pr^i	1.00	96	[132 (3 mm)]	-[8]
3f	Me	(*R*)-$CHCH_3Ph$	2.00	96[b]	[179 (3 mm)]	-[8]
3g	Et	(*R*)-$CHCH_3Ph$	5.00	94	78-80	79-81[8]
3h	Ph	(*R*)-$CHCH_3Ph$	8.00	91	129-131	128-130[4a]

a) Methylamine hydrochloride was used; b) The reaction performed starting from 20 g of acetophenone gave a 94% yield.

In summary, this preparation does not involve any complex procedure, use of toxic aromatic solvents is avoided, as is the need for acid catalysis and heating. The brief work-up procedure affords the products directly in high purity and the reaction can be easily scaled up. The very mild conditions makes this procedure especially suitable for use with low boiling amines, more practically as their hydrochlorides.

EXPERIMENTAL SECTION

^1H and ^{13}C-NMR spectra were recorded with a Varian VXR 300 instrument. IR spectra were obtained with a Perkin-Elmer 257 spectrometer. GC-MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. All melting points are uncorrected. All reagents and solvents were distilled prior to use or were of commercial quality from freshly opened containers.

Procedure for High-boiling Amines.- To 5 mmol of 2-acylphenols **1** (R^1 = Me, Et, Ph) in a 25 mL round bottom flask, equipped with a stir bar at 0° (ice bath) under inert atmosphere, was added dropwise 5.5 mmol of the amine **2** (R^2 = Pr^i, Bn, (*R*)-$CHCH_3Ph$) (20 min). The reaction mixture immediately turned to bright yellow and heat was evolved. The reaction mixture was stirred at ambient temperature and monitored by GC or NMR methods until the starting 2-acylphenol disappeared. It was then diluted with *n*-hexane (50 mL) and washed with water (50 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting oil or solid was the pure 2-imidoylphenol (**3**) in 91-98% yields, whose structure was confirmed on the basis of spectroscopic data according to literature.[8] The purity of imidoylphenol (**3**) (95-98 %) was determined by HPLC (*n*-hexane - ethyl acetate, 95:5).

The reactions of 4-hydroxyacetophenone and acetophenone with isopropylamine were performed in the same ratios and under the same conditions.

Procedure for Low-boiling Amines.- To a mixture of 5 mmol of 2-acylphenols **1** (R^1 = Me, Et) and 15 mmol of the methylamine hydrochloride (R^2 = Me) in a round bottom flask equipped with a stir bar at 0° (ice bath) under inert atmosphere, was added dropwise 2.5 mL of 30% wt. NaOH aqueous solution. The reaction mixture became bright yellow and developed heat with the first drop of base. The reaction mixture, stirred at 0°, was monitored by GC or NMR methods until the starting 2-acylphenol desappeared. Work-up was performed by washing the reaction mixture diluted in *n*-hexane (50 mL) with water (50 mL). The organic layer was then dried with Na_2SO_4 and evaporated under reduced pressure. The resulting oil or solid was the pure 2-imidoylphenol **3** in 93-98% yields, whose structure was assigned on the basis of spectroscopic data according to literature.[8]

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