

## A NEW SYNTHESIS OF CINNAMIC ACIDS FROM AROMATIC ALDEHYDES AND *N,N*-DIMETHYLACETAMIDE HYDROCHLORIDE

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Cinnamic acids have been prepared in 61-85% yields by a new synthesis from aromatic aldehydes and *N,N*-dimethylacetamide hydrochloride as reagent and solvent, at reflux (190-200°C), for 8-12 hours. Without *N,N*-dimethylacetamide hydrochloride this reaction is not possible.

### INTRODUCTION

Thorough studies of organic chemistry have emphasized the important role of reactive solvents in some condensation reactions, such as ethynylation of carbonylic compounds.<sup>1,2</sup> Some of the most widely used reactive solvents for these reactions are *N,N*-dialkylacetamides, among which *N,N*-dimethylacetamide is prominent due to its particular reactivity. This is the reason why it had been used not only as solvent and reaction medium,<sup>3,4</sup> but also as a very effective catalyst<sup>5</sup> and, in the case of *N,N*-dimethylacetamide hydrochloride, even as a reagent.<sup>6-9</sup> As a general feature, these reactive solvents are able to yield in compounds which result from a condensation reaction at the methylene group in  $\alpha$  position towards amide moiety, position activated by the presence of an electron withdrawing functional group (-E). The reactions of *N,N*-dimethylacetamide with aromatic ketones in the presence of strong bases such as potassium hydroxide (KOH) or sodium amide (NaNH<sub>2</sub>) as condensing agents are known.<sup>2</sup> Therefore, we considered of interest to study the condensation reaction of *N,N*-dimethylacetamide and aromatic aldehydes in the presence of a strong acid, such as hydrochloric acid (HCl).

On the other hand, the cinnamic acid and its derivatives, as reagents for organic and macromolecular chemistry,<sup>10-14</sup> due to their photoreactive

character determined by the presence of the cinnamoyl group, as well as key components of a wide variety of pharmacological formulations, due to their flavouring abilities, antibacterial, antifungal and parasite fighting properties, still attract much attention from the scientific community.

Despite of the great variety of well-known and tried methods (Perkin reaction,<sup>15</sup> Knoevenagel condensation,<sup>16</sup> Claisen condensation,<sup>17</sup> and Heck reaction<sup>18</sup>), the development of new general synthetic protocols for cinnamic acids is still an active field, where we do have some recent contributions concerning designed syntheses of cinnamic acids.<sup>19-21</sup>

In this paper, we present a new approach of the cinnamic acids synthesis, starting from aromatic aldehydes and *N,N*-dimethylacetamide hydrochloride as reagent and solvent. The protocol of this new method and a study of optimization on reaction parameters are presented herein.

### RESULTS AND DISCUSSION

As generally known, amides are weak bases, even weaker than the amines due to the fact that the doublet from nitrogen atom is delocalized on many atoms. As result, they can react with acids, yielding in amides preferably protonated at the oxygen atom, stabilized by conjugation, as presented in Scheme 1.

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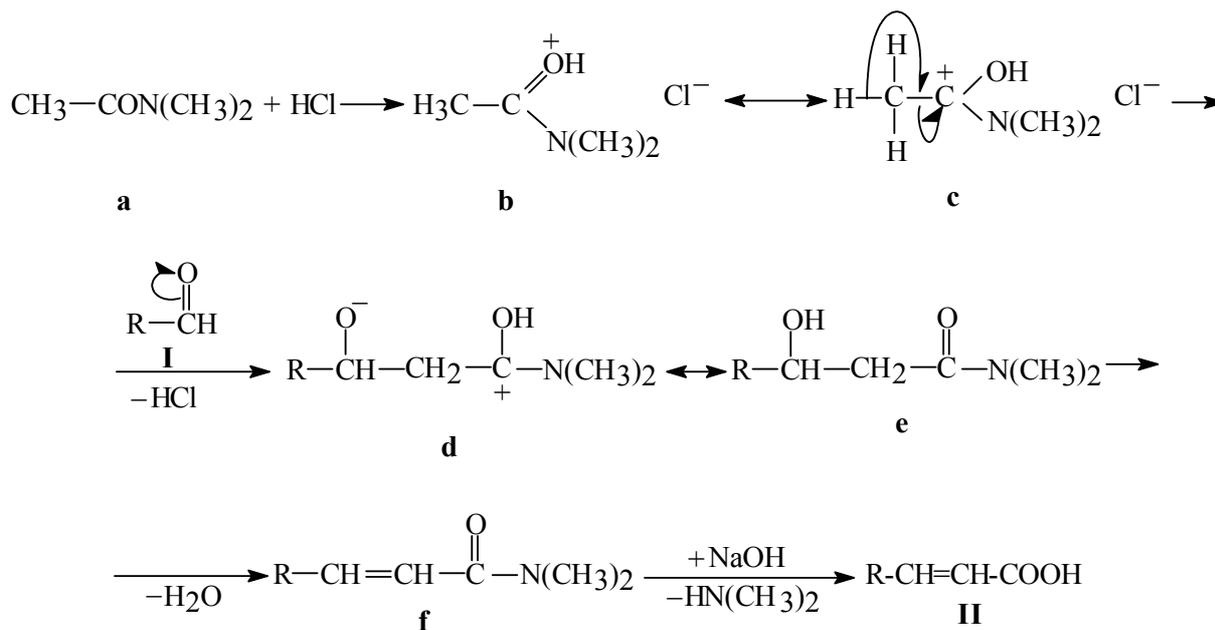


This synthesis requires high temperatures (reflux at 190-200°C), during 8-12 hours (Table 1). At lower temperatures, the yield decreases. For example, the yield for product **IIb** decreased to 45% when the reaction was performed at 130-140°C. Same decrease was observed when the reaction time was reduced to 7 h.

As presented in Table 1, we obtained cinnamic acids **II** in yields which ranged from 61 to 85%, yields determined by the reaction conditions and

structure of the aromatic aldehydes **I** employed. The cinnamic acid **IIc** has been obtained in the lowest yield due to the presence of *p*-CH<sub>3</sub>O group which has an electron-donating (+E) effect. Cinnamic acids with electron-withdrawing (-E) substituents were obtained in good yields.

Taking into account the theoretic features presented herein, it is possible to suggest a mechanism for this synthesis, presented in Scheme 3.



Scheme 3 – Mechanism of the synthesis of cinnamic acids using *N,N*-dimethylacetamide hydrochloride.

It involves the reaction of *N,N*-dimethylacetamide (**a**) with the hydrochloric acid, when *N,N*-dimethylacetamide hydrochloride (**b**) results *in situ*, reagent which has a reactive methylene group activated by the adjacent carbon atom (structure **c**) deficient in electrons, an interesting phenomenon yet insufficiently studied in the case of protonated amides. This reagent reacts with the aromatic aldehydes **I**, resulting in cinnamic acids **II**, after the alkaline hydrolysis of intermediate (**f**) in the presence of NaOH solution, as presented in Scheme 3.

## EXPERIMENTAL

### Reagents and materials

All reagent-grade aromatic aldehydes were purchased from Sigma Aldrich Co. and used as received. *N,N*-dimethylacetamide is commercially available (Fluka) and it was anhydridized prior to use by vacuum distillation over calcium hydride and stored over molecular sieves (4Å).

### Measurements

The IR absorption spectra were recorded on a Carl Zeiss Jena SPECORD M80 spectrophotometer on KBr pellets. The <sup>1</sup>H-NMR spectra were run using a Jeol C60-HL spectrometer with DMSO-d<sub>6</sub> as solvent and tetramethylsilane as internal standard. The melting points were measured with a Gallenkamp hot-block melting point apparatus.

### General procedure for the synthesis of cinnamic acids

In a 100 mL three-necked Claisen flask, 3.72 mL (0.04 mole) *N,N*-dimethylacetamide and 7 mL benzene were added. Then, gaseous hydrogen chloride was passed through this solution for 45-60 min, when *N,N*-dimethylacetamide hydrochloride precipitated. 0.01 Mole of aromatic aldehyde **I** was added and the obtained mixture was heated for 8-12 h at 190-200°C, while benzene distilled (see Table 1). At the end of the reaction, the final solution was treated with 50-60 mL water and then with NaOH solution 20% to pH=9-10. From this solution, the unreacted aromatic aldehyde **I** was distilled with water under vacuum (30-40 mmHg) until the distillate was no longer cloudy. The solution was diluted with water until a volume of 70-80 mL; then, 10-15 mL NaOH solution 20% was added. This mixture was refluxed until the amide precipitate disappeared by hydrolysis (5-6 h). After cooling at room temperature, this solution was filtered and the filtrate

was treated with HCl solution 15-20%, until pH=1-2, when the cinnamic acid **II** precipitated. The obtained product was filtered, washed with 10-15 mL cold water and dried. Yields ranged from 61 to 85% (Table 1).

## CONCLUSION

A novel synthetic pathway for obtaining cinnamic acids in good yields from aromatic aldehydes and *N,N*-dimethylacetamide hydrochloride has been identified. The key compound of this synthesis, *N,N*-dimethylacetamide hydrochloride, is not only a solvent for this reaction system, but a very effective reagent, fact proved by the impossibility to perform this reaction in its absence. This new alternative route is not suitable for aliphatic aldehydes. The synthesis yield depends on the reaction conditions. The mechanism we propose evolves through an intermediate which has a reactive methylene group activated by the adjacent carbon atom of the protonated amide. This method is a very effective alternative to the classic Perkin synthesis.

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