



*Dedicated to Professor Bogdan C. Simionescu  
on the occasion of his 65<sup>th</sup> anniversary*

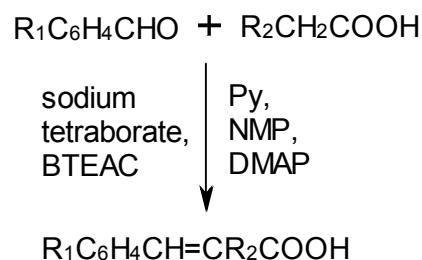
## SODIUM TETRABORATE/BENZYLTRIEETHYLAMMONIUM CHLORIDE-MEDIATED SYNTHESIS OF SUBSTITUTED CINNAMIC ACIDS FROM AROMATIC ALDEHYDES AND ALIPHATIC CARBOXYLIC ACIDS

Marioara NECHIFOR,\* Constantin I. CHIRIAC and Fulga TANASA

“Petru Poni” Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda Alley, Iași, Roumania

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A simple, efficient, and cost-effective method has been developed for the synthesis of some cinnamic acid derivatives in moderate to high yields (63-86%) by a one-pot condensation reaction of benzaldehyde and aliphatic carboxylic acids in the presence of sodium tetraborate and benzyltriethylammonium chloride, and *N*-methyl-pyrrolidinone as solvent. The reaction requires high temperatures (reflux at 180-190°C) and strong basic conditions, which have been generated by pyridine and 4-dimethylaminopyridine added to the reaction medium.



### INTRODUCTION

Cinnamic acid and its derivatives are important reagents in organic synthesis, both as intermediates and final products. They are important in flavors, perfumes, cosmetics, graphics, and pharmaceutical industries, and also as building blocks in the structures of photosensitive polymers, working as negative photoresists in microelectronics. The most common synthetic methods to produce cinnamic acids are Perkin reaction (benzaldehydes with acetic anhydride in the presence of sodium acetate),<sup>1</sup> Knoevenagel-Doebner condensation (benzaldehydes with malonic acid and subsequent decarboxylation or with alkoxymalonates),<sup>2</sup> Heck coupling reaction (iodoarenes with acrylates with subsequent hydrolysis),<sup>3</sup> Claisen-Schmidt condensation (aromatic aldehydes and esters of

carboxylic acids in the presence of sodium),<sup>4</sup> and Wittig-Horner reaction (olefination reaction of benzaldehydes with the stabilized phosphoranes).<sup>5</sup> Cinnamic acid derivatives are most frequently synthesized by Perkin reaction, but the presence of electron-donor substituents significantly decreases the yield of the target products. Routinely, in this case, they are obtained by Knoevenagel-Doebner condensation. Various non-classical methods dealing with the synthesis of cinnamic acid derivatives have been reported in the literature. They have been performed under unconventional reaction media, such as enzymatic conditions,<sup>6</sup> microwave heating conditions,<sup>7</sup> solventless<sup>8</sup> or in ionic liquids,<sup>9</sup> etc. Alternative routes to some above mentioned reactions employ phase transfer catalysts. Cinnamic acids are obtained from aromatic aldehydes or ketones and malonic acid in

\* Corresponding author: [nechifor@icmpp.ro](mailto:nechifor@icmpp.ro)

the presence of tetrabutylammonium bromide and  $K_2CO_3$ .<sup>10</sup> The same ammonium salt and  $Na_2CO_3$  are used in the reaction between different aryl halides and methyl acrylate in the presence of  $PdCl_2$  to afford cinnamic acid esters.<sup>11</sup> Benzyltriethylammonium chloride (BTEAC) has also been investigated as phase transfer catalyst in the reaction of benzaldehyde and ethyl cyanomalonate using hydroxy/fluoroapatite.<sup>12,13</sup>

In this communication we have been evaluating a new synthetic route to cinnamic acid derivatives starting from (substituted)benzaldehyde and aliphatic carboxylic acids, in the presence of a soluble complex produced from sodium tetraborate and benzyltriethylammonium chloride, under basic conditions generated by pyridine and *N*-methyl-2-pyrrolidinone used as solvents.

## RESULTS AND DISCUSSION

It is well-known that the Perkin reaction involves aromatic aldehydes and aliphatic anhydrides under base catalysis (particularly in the presence of sodium or potassium salts of the carboxylic acids corresponding to the anhydrides employed), and it cannot be performed if the aliphatic carboxylic anhydrides are replaced by the corresponding aliphatic carboxylic acids. We have been evaluating a new synthetic route to the synthesis of cinnamic acid derivatives from (substituted)benzaldehydes and aliphatic carboxylic acids, circumventing the use of their corresponding anhydrides. Therefore we wish to report the use of a new catalytic agent, sodium tetraborate-benzyltriethylammonium chloride (BTEAC) complex, which exhibits a significant importance in the generation of an active methylene group within the carboxylic acid structure (Scheme 1).

Sodium tetraborate, a salt of boric acid, has a wide variety of applications, but it is scarcely encountered in the preparative organic chemistry. Borax is a challenging reagent due to its special chemical structure, where boron atoms have both tetrahedral and trigonal planar stereochemistry. That explains its *co*-complexing ability with different compounds. In addition, boric acid is a monoprotic acid, not triprotic as expected, because it exhibits withdrawing electron ability rather than proton releasing. Both peculiar features aforementioned were exploited in our experiments. Sodium tetraborate generates a complex with BTEAC under the strongly basic conditions

produced by pyridine (Py) and *N*-methylpyrrolidinone (NMP) used as solvents and 4-dimethyl-aminopyridine (DMAP) employed as nucleophilic agent. BTEAC, one of commonly used phase transfer catalysts in organic synthesis, was selected as the most appropriate due to its small molecular weight, availability and price. The addition of the quaternary ammonium salt as phase-transfer catalyst in the reaction system is essential because it enhances the solubility of sodium tetraborate in less polar pyridine and facilitates their interaction, and provokes the activation of the last one. In this case, the high reactivity of sodium tetraborate can be explained by the presence of the methylene group from aliphatic carboxylic acids, activated by the boron atom, which is electron deficient.

The formation of sodium tetraborate-BTEAC complex takes place in a 1:1 molar ratio and an equimolar amount of the aromatic aldehyde was used (structure (A) in Scheme 2). Taking into consideration that activation of CH-acid component is favored by base catalysis, DMAP was added into reaction mixture. Concomitantly, aliphatic carboxylic acids can easily react with DMAP, resulting in a carboxylate anion, which is a stronger nucleophilic reagent than the parent carboxylic acid (structure (B) in Scheme 2). The resulted organic salt can interact with sodium tetraborate-BTEAC complex, leading to an activated methylene compound (C). As a consequence, the addition of the alkyl group to the aromatic aldehydes happens and cinnamic acids are produced.

Concerning the solvent we have chosen for this reaction system, NMP proved to be a good solvent for all products involved in this synthesis. Generally, addition of dipolar aprotic solvents, especially NMP, to a system often increases the reaction rate and the yield.

As Perkin reaction, this synthesis occurs at high temperatures (reflux at 180-190°C) and it is not suitable for aromatic aldehydes carrying electron donating substituents. Unlike Perkin reaction, the major advantages associated with our protocol are shorter time intervals (5-9 h, unlike 8-20 h duration of Perkin reaction) and higher yields (63-86%, unlike 30-75% reported for the same compounds in Perkin synthesis) (Table 1). It is worth mentioning that *p*-methoxybenzaldehyde resulted in *p*-methoxycinnamic acid in a good yield, even if it was the lowest, its value was double in comparison with Perkin procedure.



Table 2  
Spectroscopic data of the cinnamic acids III(a-j)

Cinnamic acid	$\lambda_{\max}$ (nm)	$\nu$ (cm <sup>-1</sup> )		$\delta$ (ppm)	
		C=O	HC=CH	Ar-CH=	=CH-COO
IIIa	277	1686	1630, 981	7.80	6.46
IIIb	305	1694	1632, 988	7.70	6.75
IIIc	311	1699	1635, 977	7.73	6.75
IIId	309	1697	1638, 983	7.72	6.78
IIIe	265	1701	1626, 985	7.62	6.60
IIIf	269	1699	1633, 982	7.60	6.65
IIIg	271	1695	1640, 970	7.58	6.69
IIIh	310	1683	1645, 974	7.84	6.81
IIIi	260	1682	1627, 980	7.30	-
IIIj	296	1689	1628, 978	7.23	-

## EXPERIMENTAL

The reagents and solvents are commercially available. All of the products are known compounds and identified by melting point, elemental analysis and spectroscopic data. Spectral measurements of <sup>1</sup>H-NMR were performed using a Bruker Avance DRX spectrometer at 400 MHz, in DMSO-*d*<sub>6</sub> as solvent. The chemical shifts were expressed in  $\delta$  values compared to Me<sub>4</sub>Si, which was used as an internal standard. Infrared spectra were recorded on a Bruker Vertex 70 Fourier transform infrared spectrometer. Electronic absorption spectra were measured using a SPECORD M42 spectrophotometer in DMF solution. Elemental analyses were run in a Perkin Elmer 2400 CHNSO analyzer. Melting points of the monomers were measured on a Melt-Temp II (Laboratory Devices) apparatus without correction.

### General procedure

A 100 mL, round-bottomed flask was charged with Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10H<sub>2</sub>O (5 mmol, 1.9 g) and heated at 160-180°C for 3-4 h until constant weight. Benzyl-triethylammonium chloride (5 mmol, 1.14 g), DMAP (5 mmol, 0.61 g), Py (20 mmol, 1.61 mL) and NMP (3 mL) were added. This mixture was heated at reflux, under stirring for 2-2.5 h, when benzyltriethylammonium-sodium tetraborate complex resulted *in situ*. The solution temperature was decreased to 70°C and acetic acid (50 mmol, 2.85 mL), and *p*-chlorobenzaldehyde (5 mmol, 0.70 g) were added. A condenser was fitted to the flask and the excess of acetic acid was removed by distillation until the temperature in the flask reached 185-187°C. The obtained solution was finally heated under reflux at 185-190°C for 6-10 h (see Table 1). After cooling down, the solution was treated with water (5-7 mL) and aqueous NaOH (20%) to pH=9-10, and the unreacted aromatic aldehyde was distilled as azeotropic mixture with water, until the distillate was clear. The final solution was filtered off and the filtrate was treated with HCl solution 15-20% until pH=1-2, under cooling on ice and stirring for 2-3 h, when cinnamic acid precipitated. The resulted product was filtered off, washed with cold water (15-20 mL) and dried in a vacuum oven. Recrystallization from aqueous EtOH or EtOAc:petroleum ether gave pure products as white or yellowish crystals. In all cases, a good *trans*-selectivity for the cinnamic acids was observed.

## CONCLUSIONS

The work summarizes our recent work in the field of cinnamic acid synthesis. We introduced an

efficient one-pot synthesis of cinnamic acids from (substituted)benzaldehydes and aliphatic carboxylic acids, which proved to be an efficient alternative route to the Perkin reaction. Our experimental results evidenced that sodium tetraborate activated with benzyltriethylammonium chloride led to a significant increase in the yield of the target compounds and a shorter reaction time. The work-up in all experiments didn't involve extractions with organic solvents or chromatographic separation using organic solvents as eluents.

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