

*Dedicated to the memory of
Professor Ecaterina Ciorănescu-Nenitzescu (1909–2000)*

A NOVEL DIRECT BORON-MEDIATED SYNTHESIS OF CINNAMIC ACIDS FROM AROMATIC ALDEHYDES AND ALIPHATIC CARBOXYLIC ACIDS

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Cinnamic acids have been prepared in 64-85% yields by a new direct synthesis from aromatic aldehydes and aliphatic carboxylic acids in the presence of anhydrous sodium tetraborate and lithium chloride, bases as pyridine (Py) and 4-dimethylaminopyridine (DMAP), and *N*-methyl-2-pyrrolidinone (NMP) as solvent, at reflux (180-190°C), for 8-12 hours. Without sodium tetraborate-lithium chloride this reaction is not possible.

INTRODUCTION

Organo-boron compounds have been known for over a century and nowadays they are among the most widely used reagents and intermediates in organic synthesis due to their chemical properties and reactivity. Despite some early discoveries, however, the real potential of some of the more versatile and chemically stable organo-boron compounds was not understood until recently. Indeed, the growing list of valuable organo-boron compounds in addition to organoboranes¹ includes organoboronic acids and boronates² and more recently organo-trifluoroborates.³⁻⁵ Many of these molecules have increasingly been used in a variety of newly discovered chemical processes, in organic synthesis as reagents and as key functional components in other areas, including molecular receptors, molecular sensors, novel materials, as well as biological probes and pharmaceuticals.

It is not surprising that organo-boron compounds exhibit unique, versatile and tunable reactivity. The electronic structure of boron and its position in the periodic table adjacent to carbon makes trivalent boron compounds behave as electrophilic molecules with trigonal planar structures that are neutral yet

isoelectronic to carbocations. However, formation of an additional bond to boron generates anionic tetravalent boron compounds that have tetrahedral structures and behave as nucleophilic molecules. Most notably, both of these types of boron compounds can be stable while retaining significant reactivity that defines their peculiar and tunable chemical behaviour. Nearly every common type of boron bond (B–H, B–B, B–C, B–N, B–O, B–F, etc.) has distinctive reactivity features that can be exploited. An additional advantage of many of these processes is that their major boron by-product is boric acid, an environmentally friendly substance. As a result of their unique reactivity and other attractive features, organo-boron compounds have contributed to a number of new reactions (asymmetric synthesis, metal-catalysis, acid-catalysis, multicomponent reactions) already applied in various areas of chemistry, from pharmaceuticals to materials.

This paper introduces a new boron-containing reagent, namely sodium tetraborate-lithium chloride, not yet known as reagent in synthetic chemistry, which proved to be unexpectedly efficient for the direct synthesis of cinnamic acids by the reaction of aromatic aldehydes and aliphatic carboxylic acids.

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RESULTS AND DISCUSSION

Cinnamic acids can be prepared from aromatic aldehydes and aliphatic anhydrides in the presence of bases, particularly with sodium or potassium salts of the carboxylic acids corresponding to the anhydrides used in the reaction (the Perkin reaction).⁶

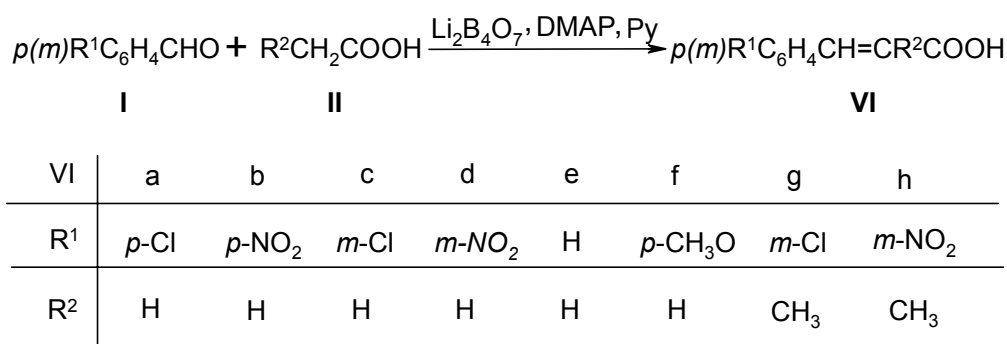
It is commonly known that potassium acetate is used in the reaction between acetic anhydride and benzaldehyde when yields, at 180°C for 8h, are up to 70-72%. Using sodium acetate, the yields are lower under the same conditions.⁷ This reaction cannot be performed in the case of aliphatic aldehydes.⁸ Same when aliphatic carboxylic anhydrides are replaced by the corresponding acids. Alternative novel synthetic approaches have been described in the literature in last decades. We do have some recent contributions in the field of direct synthesis of cinnamic acids, particularly in boron-mediated reactions.⁹ Due to its particular structure and electron deficiency, boron induces enhanced reactivity to its derivatives and makes them fit for condensation reactions as activating agents (*e.g.*, sodium borohydride,^{9a} boron tribromide,^{9b} sodium tetramethoxyborate-lithium chloride^{9c} used for cinnamic acids direct synthesis, and boric acid in the direct synthesis of aromatic esters¹⁰).

Now we have found that the reaction of aromatic aldehydes and aliphatic carboxylic acids is possible, in an one-pot procedure, in the presence

of a boron-containing reagent, namely anhydrous lithium tetraborate, obtained *in situ* from sodium tetraborate and lithium chloride, in the molar ratio 1:2. Lithium tetraborate is the key reagent in this synthesis because it activates the methylene group adjacent to COOH function in the carboxylic acid, making possible the direct reaction with the aromatic aldehyde employed in the reaction. It is noteworthy that the literature is poor in reports on the use of this reagent in organic synthesis.

The addition of amines has a positive influence on this reaction, especially DMAP due to its particular structure which enables it to be involved into the generation of reactive intermediate in this type of condensation. When DMAP is replaced with other tertiary amines, such as triethylamine, tripropyl amine, etc., the yield decreases (to 40-50%), although these tertiary amines are more basic than DMAP (triethylamine has pKa=10.65 and DMAP has pKa=9.70). This shows the evident superiority of DMAP in comparison with other tertiary amines in this synthesis, superiority proved in many other reactions.¹¹

By stepwise investigations, we established that aromatic aldehydes (I) can react with aliphatic carboxylic acids (II) in the presence of lithium tetraborate (III) (prepared *in situ*), DMAP (IV) and pyridine (V), in the molecular ratio 1:1:0.5:0.5:2, resulting in cinnamic acids (VI), as presented in Scheme 1.

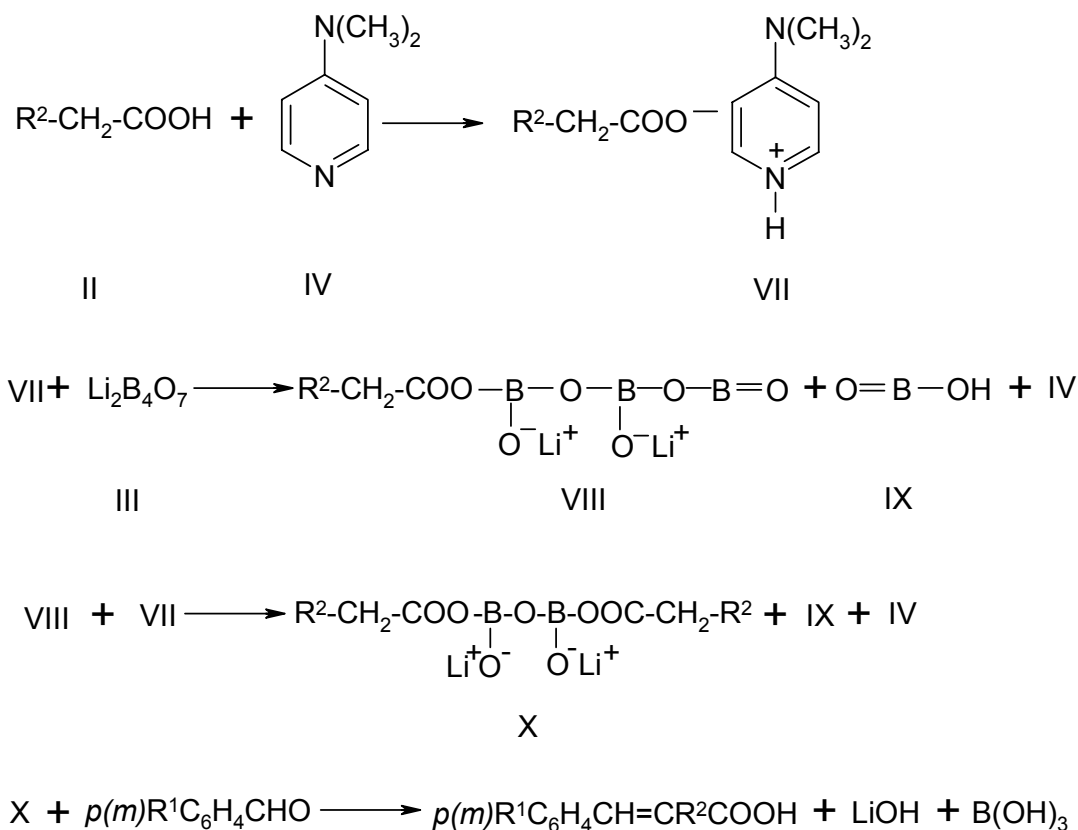


Scheme 1 – Direct synthesis of cinnamic acids in the presence of lithium tetraborate.

In order to identify the suitable solvent/mixture of solvents, several solvents, such as DMSO, DMF, NMP, HMPTA (hexamethylphosphortriamide), etc., were tested under these synthesis conditions. Finally, we selected NMP due to its favorable behavior towards all reagents involved in the reaction and high boiling point (202°C). The synthesis requires high temperatures (reflux at 180-190°C), for 8-12 hours (Table 1). At lower temperatures, the yields decreased. For example, the

yield for product VI_f decreased to 41-43%, when the reaction was performed at 140-150°C; similarly, when the synthesis was conducted at reflux for a smaller time interval (5-6h), the yield decreased to 42-43%.

A very important aspect in this one-pot synthetic procedure is the order of adding each reagent into the reaction system. This enables the emergence of the desired reactive species, as outlined in Scheme 2.



Scheme 2 – Mechanism of activation in the presence of lithium tetraborate and DMAP.

As shown, the carboxylic acid (II) reacts with DMAP (IV), resulting in a carboxylate anion (VII), which is a stronger nucleophile reagent than the corresponding acid, intermediate able to undergo

further reaction with lithium tetraborate (III). Similarly to many other cases,¹¹ for the compound (VII) two resonance structures can be ascribed:

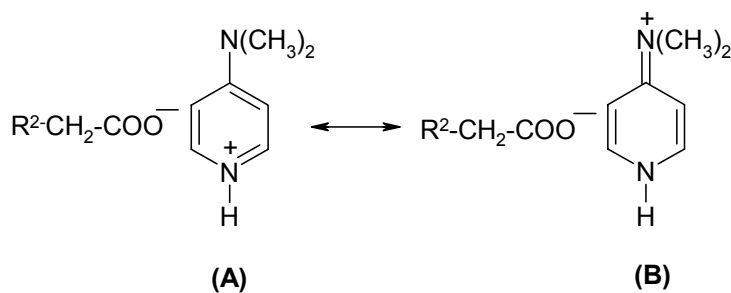


Table 1

Cinnamic acids obtained by direct synthesis in the presence of sodium tetraborate-lithium chloride

Cinnamic acid ^a	Yield ^b	Reaction time (h)	m.p. ^c (°C)	Literature m.p. (°C)
VIa	83	10	248-250	249-250 ¹³
VIb	85	10	285-286	284-286 ¹⁴
VIc	80	9	176-177	175-177 ¹⁵
VI d	82	8	195-197	196-197 ¹⁶
VIe	78	11	131-132	132-133 ¹⁵
VI f	64	12	173-175	173-175 ¹⁵
VI g	76	12	105-107	106-107 ¹⁴
VI h	77	12	196-197	196-197 ¹⁴

^a Cinnamic acids were identified by comparison of their m.p., and ¹H NMR and FTIR spectra with authentic samples.

^b Yields were calculated based on the aromatic aldehydes I employed.

^c After recrystallization.

Among them, the structure (B) is considered to be preponderant because it has a “*p*-quinoide” structure, which is more stable than structure (A), in concordance with an interesting theory in this field, the “*p*-quinoide theory”.¹²

When R² is alkyl (methyl, ethyl, etc.), intermediates (VIII) and (X) show enriched reactivity due to the presence of boron atoms in their structures; in fact, these intermediates are reagents with methylene activated groups, able to undergo a subsequent direct condensation reaction with aromatic aldehydes (I), resulting in cinnamic acids (VI). The detailed mechanism of this reaction will be discussed in a separate communication.

As can be seen in Table 1, cinnamic acids were obtained in yields ranging from 64 to 85%, depending on the reaction conditions and structure of aromatic aldehydes.

The cinnamic acid VI_f was obtained with the lowest yield. Cinnamic acids with electron-withdrawing groups were obtained in good yields.

EXPERIMENTAL

General procedure for the direct synthesis of cinnamic acids: In a 100 mL three-necked Claisen flask 5 mmol (1.9 g) Na₂B₄O₇ · 10H₂O was heated at 160-180°C in an oven under vacuum for 3-4h, until the final product became anhydrous (water loss was measured by periodic weighting). Then, 10 mmol (0.43 g) anhydrous lithium chloride, 5 mmol (0.61 g) DMAP, 20 mmol (1.61 mL) pyridine and 3 mL NMP as solvent were added. This mixture was heated at reflux, under stirring for 2-2.5 h, when lithium tetraborate results. At this point, 20 mmol aliphatic carboxylic acid (II) was introduced under continuous stirring. To this solution, at 70-90°C, 20 mmol aldehyde (I) was added. The obtained solution was heated under reflux at 185-190°C for 8-12h (see Table 1). A condenser was used to remove the unreacted acid (II) by distillation. The final solution was then treated with 50-70 mL water and NaOH solution 20% up to pH=9-10. From this solution, the unreacted aromatic aldehyde (I) was distilled with water, until the distillate was no longer cloudy. The final solution was filtered. The filtrate was treated with HCl solution 15-20% to pH=1-2, when then cinnamic acid precipitated. After 2-3 h of stirring under cooling with ice, the final product VI obtained was filtered, washed with 15-20 mL cold water and dried. Yields ranged from 64 to 85% (Table 1).

The presence of the new generated C=C double bond in the resulted compounds was evidenced in their FTIR and ¹H NMR spectra. As expected, all FTIR spectra presented absorption bands located between 1625 and 1635 cm⁻¹, and between 977 and 988 cm⁻¹ assigned to vinylene C=C stretching vibration and *trans*-vinylene CH deformation, respectively.¹⁷ Concomitantly, in the ¹H NMR spectra, two doublet signals ap-

peared between 6.40 and 6.75 ppm (ascribed to =CH-COO proton), and between 7.55 and 7.80 ppm (attributed to Ar-CH= proton) with a coupling constant of about 16 Hz,¹⁷ suggesting that *trans* cinnamoyl group was successfully generated during the reaction from aromatic aldehydes and aliphatic carboxylic acids in the presence of sodium tetraborate and lithium chloride.

IR spectra were recorded on a Bruker Vertex 79 FTIR spectrophotometer, using the KBr pellet technique. Melting points were determined with a Gallenkamp hot-block point apparatus. ¹H-NMR spectra were recorded on a Bruker Avance DRX 400 device. All solvents and reagents were purchased from Fluka and were used, when necessary, after purification.

CONCLUSION

In conclusion, we have shown that, in the presence of the lithium tetraborate generated *in situ*, the reaction between aromatic aldehydes and aliphatic carboxylic acids yielding in cinnamic acids is possible under certain conditions (solvent, base, temperature, reaction time, structure of reagents), through a new direct one-pot synthesis. This novel approach allows the preparation of various cinnamic acids in good to high yields (up to 85%). The use of acids instead of the corresponding anhydrides for this direct condensation is the main advantage of our method. The acquired high reactivity of the intermediate (X), generated by the activating system made of the boron-containing reagent, DMAP and Py, enables this synthesis to take place. Without this boron compound the reaction cannot be performed. Therefore, this approach can be considered as an effective alternative to the classic Perkin synthesis.

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