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Dedicated to Professor Alexandru T. Balaban on the occasion of his 80th anniversary

SODIUM TETRABORATE-DIBENZO-18-CROWN ETHER-6 COMPLEX AS REAGENT IN THE SYNTHESIS OF CINNAMIC ACIDS FROM AROMATIC ALDEHYDES AND ALIPHATIC CARBOXYLIC ACIDS

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Cinnamic acids have been prepared in 74-81% yields by a new synthesis from aromatic aldehydes and aliphatic carboxylic acids in the presence of anhydrous sodium tetraborate-dibenzo-18-crown ether-6 complex as reagent, 4-dimethylaminopyridine as activating agent, pyridine as base, and *N*-methyl-2-pyrolidinone as solvent, at reflux (180-190ºC) for 10-12 hours.

INTRODUCTION

A wide range of reactions aiming at cinnamic acids synthesis is now available, the most important being the Perkin reaction, Claisen condensation, Knoevenagel-Doebner condensation and Heck reaction.[1] Despite the great variety of well known and applied methods, the development of new general synthetic protocols for cinnamic acids is still an active field. On this line, we have some recent contributions,[2,3] especially in boron-mediated synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids.[4-6]

Continuing our research focused on alternate synthetic routes to obtain cinnamic acid and some of its derivatives, a novel boron-based activation system for the aliphatic carboxylic acids has been developed using the principles of crown ether chemistry.

Crown ethers possess numerous remarkable attributes and have been exhaustively studied in the last 30 years. These macrocyclic ligands are well known for their selectivity towards metal ions,[7-9] and their most important property is the ability to complex cations.[10] These complexes have an increased solubility in organic solvents and an increased reactivity. In addition, ammonium–crown ether recognition and an intramolecular stacking of moieties have been evidenced, resulting in very stable complexes as shown by ES-MS studies.[11] Dibenzo-18-crown ether-6 (DB18C6) was also employed in intramolecular long-distance energy transfer in bi-chromophoric compounds, as bridge moieties, when an efficient energy transfer (by a through-bond exchange mechanism) from the triplet state of the donor (*i.e.* benzophenonyl group) to the acceptor (i.e. naphtyl group) was proven by experimental data.[12]

Sodium tetraborate, well known for its large-scale application incites chemists interest due to the presence of boron atoms with both tetrahedral and trigonal planar stereochemistry in its structure. It shows a peculiar chemical behavior, allowing unique reactions and interesting complex formation. As source of boron, sodium tetraborate has been used to take advantage of the *co*-complexing ability of borate to form complex ions with various reagents in water.

The present paper deals with the one-pot synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids using sodium tetraborate-dibenzo-18-crown ether-6 complex as reagent and bases, namely pyridine

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(Py) and 4-dimethylaminopyridine (DMAP). Due to their unique properties, it is expected that DB18C6 would generate a complex with sodium from anhydrous sodium tetraborate, complex that is stable under the reaction conditions and have enhanced solubility in selected organic solvents.

RESULTS AND DISCUSSION

In a typical Perkin reaction, cinnamic acids are prepared from aromatic aldehydes and aliphatic carboxylic anhydrides in the presence of bases, particularly sodium or potassium salts of the carboxylic acids corresponding to the anhydrides used in reactions as reagents. Thus, potassium acetate was used in the reaction between acetic anhydride and benzaldehyde and afforded cinnamic acid in 70-72% yield. Using sodium acetate instead of potassium acetate, the yields are lower under identical conditions. It was also demonstrated that this reaction could not be performed when aliphatic aldehydes are employed. [1]

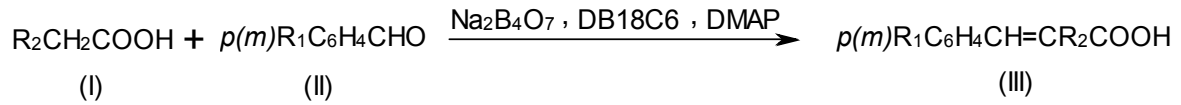
The premise of this research work is based on our experimental results, as well as on theoretical considerations, as follows. Our investigations were first focused on using aliphatic carboxylic acids instead of aliphatic carboxylic anhydrides, in order to offer an alternative to classic methods. Unfortunately, the conclusion was negative; the synthesis does not take place without the auxiliary activation of the acid. DMAP is one of the most well known reagents, famous for its ability to promote/initiate direct condensation (*i.e.*, aromatic esters or amides synthesis) by acid activation. Using DMAP as activating agent for the considered aliphatic acids, the condensation reaction with the selected aromatic aldehyde does not occur, proving that the activation of –COOH group induced by DMAP is not enough and a supplementary activation of the $–CH_2–$ group adjacent to –COOH is required. Further experiments investigating the possibility of using boron-mediated systems with sodium tetraborate as boron source in order to promote the activation of the methylene group yielded in inconclusive results, because tetraborate is insoluble in the organic reaction medium. Sodium tetraborate complexation with DB18C6 was regarded as a possible solution to this issue.

Based on the specific properties of sodium tetraborate and DB18C6, we have assumed that the reaction evolves through an *in situ* generated stable complex intermediate, which still contains boron-centered reactive sites. The stereochemistry of the anion $[B_4O_5(OH)_4]^{2-}$ from borax, preserved in the complex generated by the reaction with DB18C6, favors the bounding of the aliphatic carboxylic acid due to its activation through the formation of a reactive methylene group.

The experimental results have proved that aliphatic carboxylic acids (I) reacted with aromatic aldehydes (II) in the presence of sodium tetraborate, DB18C6 and DMAP resulting in cinnamic acids (III) as presented in Scheme 1.

As established by our previous experiments,[6] DMAP is required for acid activation, an indispensable stage for this synthesis. Its specific structure and activity was proven in many other reactions.[13]

Among various solvents tested (DMSO, DMF, NMP, HMPA), we selected NMP because it is a good solvent for reagents and reaction products and is stable under reaction conditions (it has a high boiling point). The synthesis requires high temperatures (reflux at 180-190ºC) for 10-12 h (Table 1). At lower temperatures, the yields decrease.

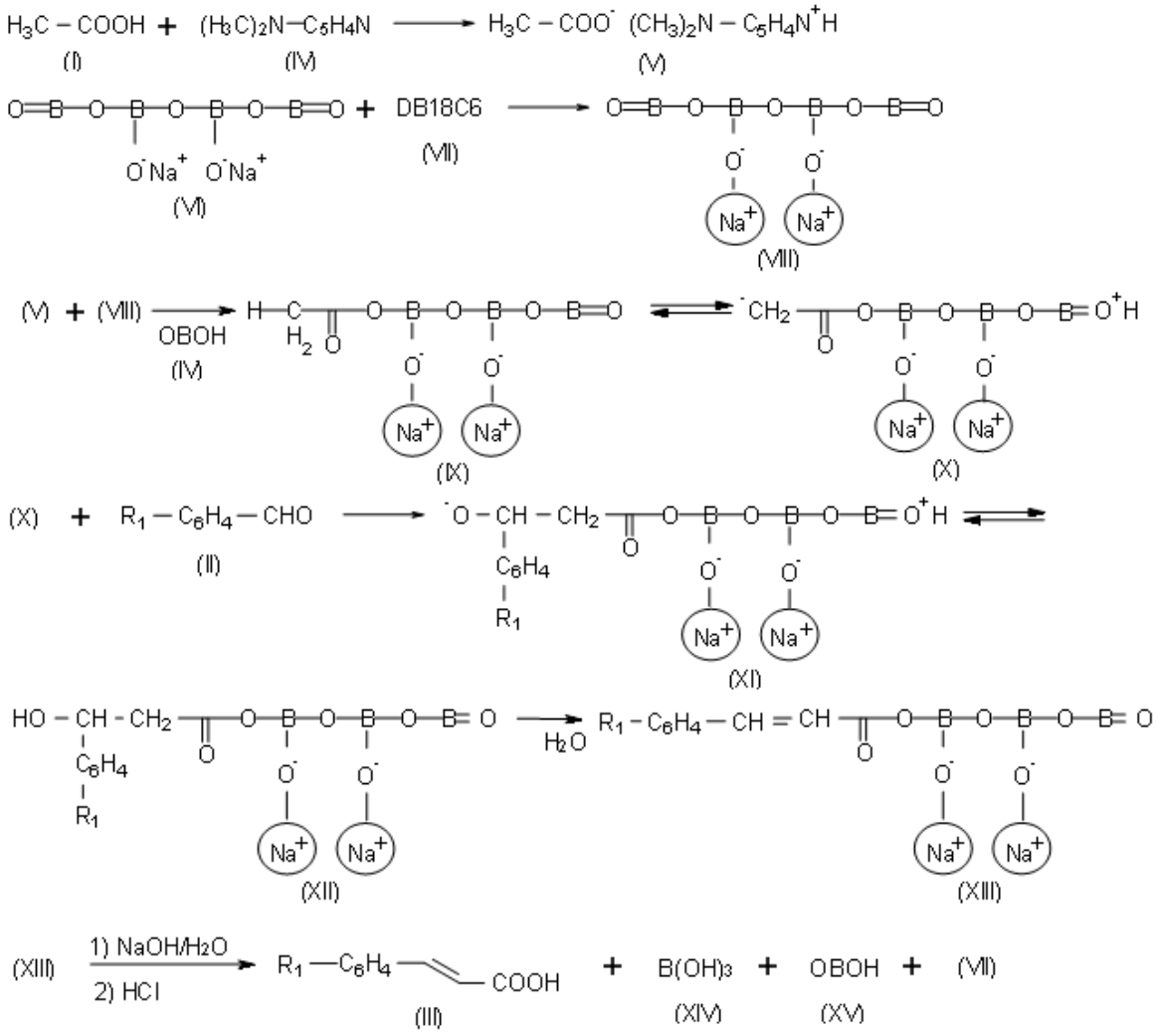


(III)	a	b	c	d	e	f	g
R_1	*p*-NO_2	*p*-Cl	*m*-Cl	*m*-NO_2	H	*m*-NO_2	*m*-Cl
R_2	H	H	H	H	H	CH_3	CH_3

Scheme 1 – Synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids in the presence of sodium tetraborate-dibenzo-18-crown ether-6 as reagent.

As a possible mechanism (Scheme 2), we have suggested that the organic salt (V), resulted from the interaction between carboxylic acid (I) and DMAP (IV), reacts with sodium tetraborate-dibenzo-18 crown ether-6 complex (VIII) resulted from the complexation reaction between sodium tetraborate (VI) and DB18C6 (VII). The resulted complex (X), which has an active methylene group, reacts with aromatic aldehydes (II) resulting in (XI) identical with (XII). By elimination of water from (XII) results (XIII), which by treatment with NaOH and water and then with HCl results in cinnamic acids (III), and boric acid $B(OH)_3$ (XIV) and metaboric acid OBOH (XV) as secondary products. The complexation reaction between sodium tetraborate and DB18C6 renders disodium tetraborate soluble in the Py/NMP mixture. As can be seen, carboxylic acid is activated in (V) and (X). The latter makes possible the reaction with aldehyde (II) and is based on activation of the methylene goup from aliphatic carboxylic acid structure. [1,3,6]

Intermediate compounds (IX) and (X) are activated by boron atoms due to their deficiency in electrons and, in consequence, the methylene activated group reacts with aromatic aldehydes (II), resulting in cinnamic acids (III). Sodium tetraborate-dibenzo-18-crown ether-6 complex (VIII) is a reactive boron compound having an anhydride structure. This *in situ* generated intermediate complex is soluble in the reaction medium and allows boron-centered reactive sites to undergo the activation through the anion $[B_4O_5(OH)_4]^{2-}$ that favors the bounding of the aliphatic carboxylic acid and its activation by the formation of a reactive methylene group.



Scheme 2 – The mechanism proposed for the synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids in the presence of sodium tetraborate-dibenzo-18-crown ether-6 as reagent.

The mechanism proposed in Scheme 2 is also supported by the fact that the organic salt (V) does not react with the aromatic aldehyde (II) in the absence of sodium tetraborate and DB18C6 and under the same reaction conditions (reflux for 12h). This proves the essential role of sodium tetraborate-dibenzo-18-crown ether-6 complex (VIII) as boron source, which generates a methylene reactive group in the structure of the carboxylic acid through the reaction of (VIII) with organic salt (V). As presented in Table 1, cinnamic acids (III) were obtained in yields ranging from 74 to 81%, depending on the reaction time and aldehyde structure.

The structure of cinnamic acid and its derivatives **III(a-g)** was confirmed by the FTIR (Table 2) and ^{1}H-NMR (Table 3) spectroscopy and elemental analysis. Elemental analysis data are in good agreement with the calculated values.

Table 1

Cinnamic acids obtained by the synthesis in the presence of sodium tetraborate-DB18C6 as a reagent

Cinnamic acid[a]	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg
Yield[b]	81	78	74	80	77	75	78
Reaction time (h)	10	12	11	10	12	12	10

[a] Cinnamic acids were identified by comparison of their m.p., and ^{1}H and ^{13}C NMR and FTIR spectra with authentic samples. [b] Yields were calculated based on the aromatic aldehydes (II) employed.

Table 2

The FTIR data of compounds **III(a-g)** (wavenumbers, cm^{-1})

Sample	C=O	O-H	C=C	asym -NO_2[a]	sym -NO_2[b]	-NO_2[c]	C-N	C-Cl	C-CH_3
IIIa	1694	2983	1632, 988	1522	1304	714	870		
IIIb	1701	2991	1626, 985					1492	
IIIc	1694	2972	1633, 982					1461	
IIId	1699	3092	1635, 977	1538	1307	715	850		
IIIe	1686	3027	1630, 981						
IIIf	1682	2978	1627, 980	1526	1306	710	872		2938, 1439
IIIg	1689	2970	1628, 978					1454	2932, 1444

[a] asymmetric – NO_2 stretching vibration; [b] symmetric – NO_2 stretching vibration; [c] – NO_2 out of plane bending vibration.

EXPERIMENTAL

General procedure: In a 100 mL three-necked Claisen flask, 5 mmol (1.9 g) $Na_2B_4O_7 \cdot 10H_2O$ was heated at 160-180ºC in an oven under vacuum for 3-4 h, until the final product became anhydrous (water loss was measured by periodic weighting). Then, 5 mmol (0.61 g) DMAP, 5 mmol (2.81 g) *p*-chlorobenzaldehyde, 5 mmol (1.8 g) DB18C6, 8.7 mmol (5 mL) acetic acid, 1.6 mL pyridine and 2 mL NMP were added. An air-cooled reflux condenser was fitted and the excess of acetic acid was removed by distillation, until the temperature in the flask increased up to 185-187°C. The obtained solution was heated under reflux at 185-187ºC, for 12 h. At the end of the reaction, the final solution was treated with 70 mL water and then with NaOH solution 20% until pH=9-10. From this solution, the unreacted aromatic aldehyde (II) was removed by azeotropic distillation, until the distillate was no longer cloudy. The final solution was filtered. The filtrate was treated with HCl solution 15-20% until pH=1-2, when cinnamic acid precipitated. After 2-3 h of stirring under cooling with ice, the final product was filtered, washed with 15-20 mL cold water and dried; yield 78%.

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. ^{1}H 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.

Table 3

The ^{1}H-NMR data of compounds **III(a-g)**

Sample	The ^{1}H-NMR chemical shifts (δ, ppm) and assignments
IIIa	8.24 (d, 2H, aromatic protons), 7.80 (d, 2H, aromatic protons), 7.70 (d, 1H, Ar-C*H*=, *J* = 16.0 Hz), 6.75 (d, 1H, =CH-COO, *J* = 16.0 Hz)
IIIb	7.74 (s, 1H, aromatic proton), 7.62 (m, 1H,=C*H*-Ar, *J* = 16.0 Hz and 1H, aromatic proton), 7.49 (m, 2H, aromatic protons), 6.60 (d, 1H, =CH-COO, *J* = 16.0 Hz)

Table 3 (continued)

IIIc	7.82 (s, 1H, aromatic proton), 7.68 (s, 1H, aromatic proton), 7.60 (d, 1H, Ar-C*H*=, *J* =16.0 Hz), 7.45 (d, 2H, aromatic protons), 6.65 (d, 1H, =CH-COO, *J* = 16.0 Hz)
IIId	8.52 (s, 1H, aromatic proton), 8.25 (d, 1H, aromatic proton), 8.19 (d, 1H, aromatic proton), 7.73 (m, 1H, Ar-C*H*=, *J* = 16.0 Hz and 1H, aromatic proton), 6.75 (d, 1H, =CH-COO, *J* = 16.0 Hz)
IIIe	7.80 (d, 1H, Ar-C*H*=, *J* = 16.0 Hz), 7.56 (s, 2H, aromatic protons), 7.40 (d, 3H, aromatic protons), 6.46 (d, 1H, =CH-COO, *J* = 16.0 Hz)
IIIf	8.56 (d, 1H, aromatic proton), 7.92 (d, 1H, aromatic proton), 7.68 (d, 1H, aromatic proton), 7.45 (d, 1H, aromatic proton), 7.30 (d, 1H, Ar -C*H*=, *J* = 16.0 Hz), 1.96 (d, 3H, CH_3)
IIIg	7.47 (d, 1H, aromatic proton), 7.39 (d, 1H, aromatic proton), 7.20-7.25 (m, 2H, aromatic protons and 1H, Ar -C*H*=, *J* = 16.0 Hz), 1.96 (d, 3H, CH_3)

CONCLUSION

A new alternative to the classic Perkin synthesis of cinnamic acids is introduced. The reaction between aromatic aldehydes and aliphatic carboxylic acids takes place in the presence of DMAP and a complex generated *in situ* by the reaction between sodium tetraborate and DB18C6. This complex has an increased solubility in organic solvents and an enhanced reactivity, and acts as an interesting boron activating reagent, which allows the activation of the aliphatic carboxylic acid, by generating a reactive methylene group prior to its reaction with the aromatic aldehyde and the formation of the cinnamic acid. We have also proved that sodium tetraborate, despite its chemical reactionlessness, can be used as valuable reagent in certain conditions reaction for cinnamic acid synthesis.

This condensation reaction allows chemists to obtain cinnamic acids derivatives with aliphatic substituents at the double bond and various chemical functions (Cl, NO_2) at the aromatic ring.

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