Proceeding Paper

One Pot Synthesis of the Knoevenagel Condensation Products Using Boric Acid as a Catalyst †

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Abstract: In present study, we investigated a catalytic power of Boric acid for the synthesis of 2-alkylidene/arylidene derivatives resulted from active methylene compounds and 4-chlorobenzaldehyde in the presence of 10 mol% of boric acid in ethanol under conventional conditions. We achieved good to excellent yields of synthesized products and furthermore, characterized using conventional spectroscopic techniques.

Keywords: green synthesis; boric acid; malononitrile; SAR study; Knoevenagel condensation

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1. Introduction

The Knoevenagel condensation, which involves the reaction of aldehydes with active methylene compounds, is a highly significant chemical conversion with broad applications in organic synthesis [1]. It serves as a fundamental method for creating carbon-carbon bonds, playing a crucial role in the production of pharmaceutically and biologically active compounds [2,3]. In various organic transformations, boric acid has proven to be an effective catalyst (Figure 1) [4–10]. Its catalytic properties have been exploited in numerous reactions, including decarboxylation, bromination, amidation, esterification, trans-esterification, β-acetamido ketone synthesis, condensation reactions, ipso-hydroxylation, Mannich reactions, aza-Michael addition, and Biginelli reactions, among others. The versatility of boric acid as a catalyst underscores its importance in facilitating diverse synthetic processes [4–10].

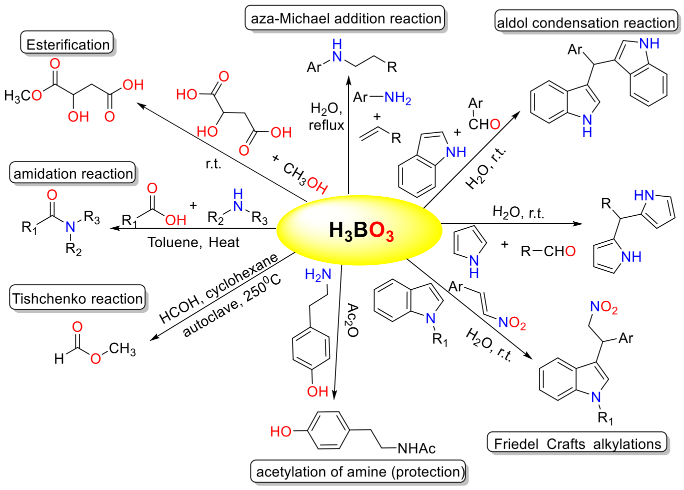


Figure 1. Different chemical conversion catalyzed by boric acid.

Multiple mechanisms involving Bronsted acid catalysis have been proposed for the Knoevenagel condensation (Figure 2) [4]. The commonly utilized active methylene compounds include acyclic 1,3-dicarbonyls, as well as analogous compounds such as malononitrile, acetonitrile, acetyl acetone, acetoacetates, malonates, and others. Various cyclic compounds such as oxazepanediones, Meldrum's acid, etc. were also found to be employed. In certain instances, isolating the Knoevenagel product becomes challenging due to rapid Michael addition of the adduct with a second molecule of the active methylene compound. β, γ-unsaturated products were often observed as a part of isomerization of α, β-unsaturated products. Various catalysts have been reported, including, PTCs (phase transfer catalysts), KF, Bronsted acids, Lewis's acids, amines and their corresponding ammonium salts, among others. Further, we did not notice any utilization of metal salts of such methylene compounds. Consequently, numerous mechanisms have been proposed to explain the reaction (Figure 2). In addition, our lab has recently explored some biologically active compounds with the ease of various catalysts and theoretical methods [11–17].

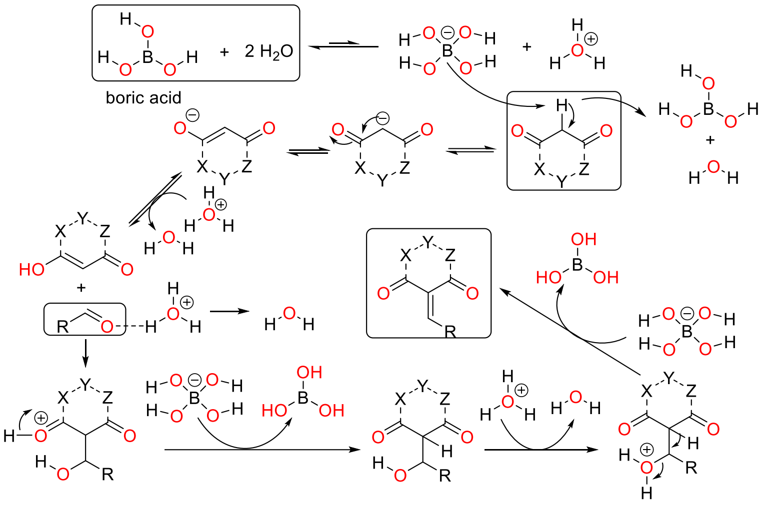
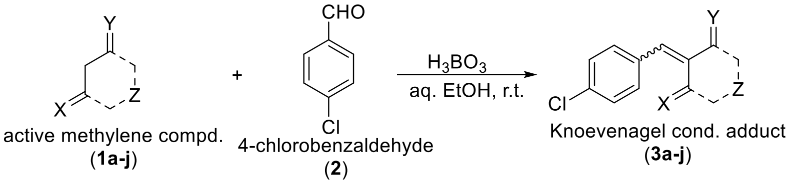


Figure 2. Possible mechanism of Knoevenagel condensation in presence of boric acid catalyst in ethanol.

The ethanol used to contain small amount of water get reacted with boric acid forming $B(OH)_4^-$ with release of H^+ in the solution. Based on this, the possible mechanism was proposed shown in Figure 2. Initially, enolate of activated methylene compound was added with carbonyl group of aldehydes which initially activated by H^+ leads to formation of tetrahedral intermediate. It was further undergoing acid catalyzed dehydration to condensed unsaturated product. The reaction was carried in limited amount of water otherwise at aqueous condition, starting material or product get dissolved in water or in absence of water, boric acid does not act as catalyst. Considering the potential of boric acid as a catalyst, we have developed a new methodology for the synthesis of Knoevenagel condensation products (**3a–j**) (Scheme 1**)**. This methodology utilizes boric acid as a catalyst and involves the condensation of active methylene compounds (**1a–j**) with 4-chlorobenzaldehyde (**2**) in aqueous ethanol at room temperature.



Scheme 1. Synthesis of Knoevenagel condensation adduct (**3a–j**) from active methylene compounds (**1a–j**) and 4-chlorobenzaldehyde (**2**).

2. Materials and Methods

The synthesis experiments were conducted using commercially available p-Chlorobenzaldehyde, active methylene compounds, and solvents obtained from commercial chemical sources. These chemicals were utilized in their as-purchased state without undergoing any purification procedures. The reactions took place in a reaction vessel equipped with a condenser under atmospheric pressure and magnetic stirring. Melting points reported herein were uncorrected and checked using traditional method. All synthesized compounds were tested for their ^{1}H-NMR spectra with $CDCl_3$ as a solvent on Bruker NMR machine. A Shimatzu GCMS was used for analyzing molecular masses of synthesized compounds. A Bruker Tensor 2 model was used to record FTIR (Fourier-transform infrared spectroscopy) of compounds.

Synthesis

To perform the synthesis, dissolve 1 mmol of p-chlorobenzaldehyde and 1 mmol of active methylene compounds in 5 mL of aqueous ethanol at room temperature. Add 10 mol% of boric acid catalyst and stir the solution on a magnetic stirrer until the reaction is complete (reaction time recorded in the following table). The completion of the reaction was monitored by performing TLC in a mixture of 10 parts ethyl acetate and 1 part hexane. After the reaction is complete, cool the contents in an ice bath, filter the solid product, and wash it with cold ethanol or extract the product in ethyl acetate. Record the yield, melting point, and characterize the product by performing spectral analysis.

3. Results and Discussion

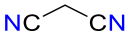
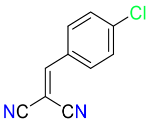
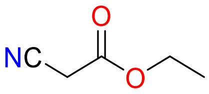
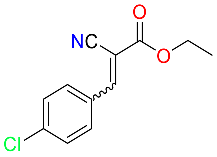
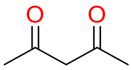
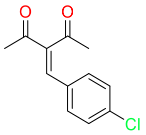
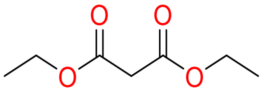
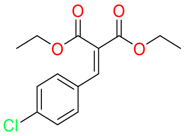
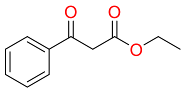
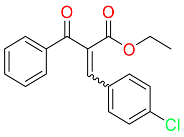
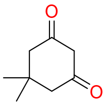
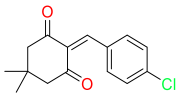
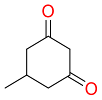
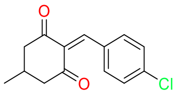
For the synthesis of various heterocyclic compounds from active methylene compounds, the Knoevenagel condensation product was obtained as an intermediate or it was one of the major impurities formed during the reaction due to a slight excess of reagents [4–10]. Therefore, synthesizing such an intermediate is crucial. To identify a suitable catalyst for the Knoevenagel condensation between 4-chlorobenzaldehyde and malononitrile in aqueous ethanol at room temperature, we conducted the reaction in the presence of various organic compounds and salts, including diethylamine, morpholine, ammonium chloride, sodium bicarbonate, copper sulfate, ferric chloride, nickel chloride, nanomaterials, sodium bicarbonate, boric acid, L-proline, etc.

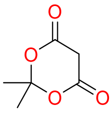
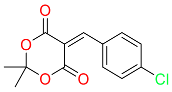
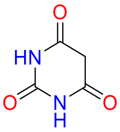
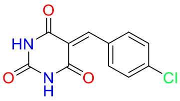
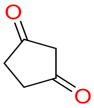
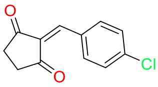
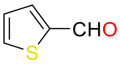
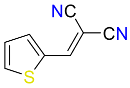
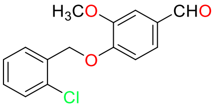
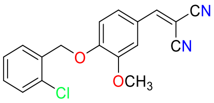
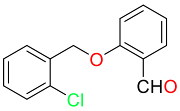
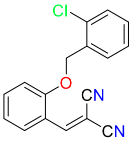
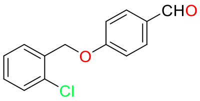
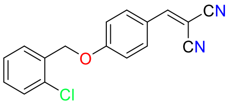
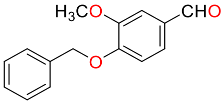
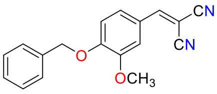
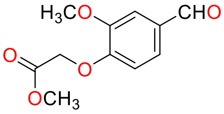
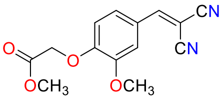
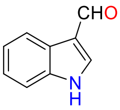
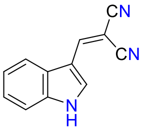
Our research unveiled boric acid as a highly efficient catalyst, demonstrating remarkable catalytic activity, high product yield, and facile purification through cold ethanol washing. To enhance the scope of boric acid's catalytic applications, we conducted Knoevenagel condensation reactions between 4-chlorobenzaldehyde and various acyclic and cyclic active methylene compounds. The results unequivocally established boric acid as a potent Bronsted acid catalyst for this reaction. In the characterization of unknown compounds, infrared spectroscopy emerged as a valuable tool, particularly for identifying functional groups. However, extracting comprehensive structural information solely from an infrared spectrum can be challenging due to the presence of multiple absorption bands.

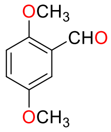
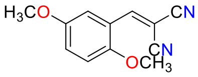
Notably, the carbonyl group, indicative of a carbon-oxygen double bond, manifested distinct and localized vibrations in numerous interacting compounds. Within esters and ketones, the absorption range for the carbonyl group was observed between 1753–1674 cm^{-1}. Furthermore, the C-O stretching vibrations of esters and ethers were evident within the 1300–1100 cm^{-1} region. Characterization of aromatic compounds frequently revealed strong bands below 1000 cm^{-1}. Regarding the aromatic ring's C=C bonds, absorption bands were observed in the range of 1600–1500 cm^{-1}. Moreover, the cyanide group of compounds 3a-b exhibited prominent stretching vibrations at 2222–2225 cm^{-1}, while the newly formed olefinic bond was characterized by stretching vibrations in the range of 1564–1609

cm^{-1}. The formed olefinic bond showed a strong absorption band around 1485 cm^{-1} in 3i-3r. The product formation was confirmed by recording the GC-MS of the molecules. In the mass spectra of (3a) and (3f), two peaks (M and M + 2) were observed with an intensity ratio of 3:1. The yield of the product depends on the reactivity and stability of the active methylene group, rather than the electronic nature of the group attached to the aldehydes (Table 1) (*Please refer Supplementary Material for spectral data*).

Table 1. Reaction time, yield, color, physical constant and IR stretching wavenumbers of Knoevenagel condensation adduct (3a-j).

Active Methylene Compounds	Product	Color	Yield (%)	Reaction Time (min)	m.p. (°C)
 **1a**	 **3a**	Colorless solid	87	50	161.0–163.0
 **1b**	 **3b**	Buff	79	60	88–90
 **1c**	 **3c**	White solid	76	60	167–169
 **1d**	 **3d**	Light Yellow oil	79	75	--
 **1e**	 **3e**	Buff white solid	72	75	155–157
 **1f**	 **3f**	Light yellow	94	60	126–128
 **1g**	 **3g**	Light yellow	90	60	182–184

 **1h**	 **3h**	Colorless solid	91	60	154–156
 **1i**	 **3i**	Yellow	88	65	270.0–272.0
 **1j**	 **3j**	White	86	80	222–223
 **(2b)**	 **3k**	Buff white	87	65	78–80
 **(2c)**	 **3l**	Light yellow	88	60	141–143
 **(2d)**	 **3m**	Light yellow	92	60	133–135
 **(2e)**	 **3n**	Light brown	93	60	135–137
 **(2f)**	 **3o**	Light yellow	95	65	158–160
 **(2g)**	 **3p**	Yellow	89	65	142–144
 **(2h)**	 **3q**	Dark brown	78	75	220–222

 (**2i**)	 **3r**	Yellow solid	91	65	98–100

4. Conclusions

In conclusion, the synthesis of heterocyclic compounds through the Knoevenagel condensation reaction involving active methylene compounds is a valuable method in organic chemistry. The Knoevenagel condensation product serves as an intermediate or a major impurity in the reaction due to the excess use of reagents, highlighting the importance of synthesizing and understanding such intermediates. Through extensive experimentation, boric acid has been identified as an effective catalyst for the Knoevenagel condensation, exhibiting good catalytic activity, high yields, and facilitating easy purification of the products. The reaction between 4-chlorobenzaldehyde and various acyclic and cyclic active methylene compounds has demonstrated the versatility and efficiency of boric acid as a Bronsted acid catalyst. The characterization of the synthesized compounds through spectral analysis, including proton Magnetic Resonance (PMR) spectroscopy, mass spectrometry (GC-MS), and infrared spectroscopy (FTIR), has provided insights into the structural features and functional groups present in the products. Overall, the findings of this study contribute to expanding the understanding and application of boric acid as a catalyst in the synthesis of heterocyclic compounds through the Knoevenagel condensation reaction.

Supplementary Materials:

Author Contributions: Conceptualization, S.N.M., B.R.T. and S.D.T.; methodology, D.M., B.R.T.; software, S.N.M.; writing—review and editing, S.N.M. and B.R.T.; visualization, S.N.M. and B.R.T.; supervision, B.R.T. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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