The increase in the amount of 2-hydroxy-3-methoxyphenacyl chloride in the reaction is also attributed to the elevated reaction temperature and the enhanced stability of this isomer at higher temperatures, which arises from the formation of a hydrogen bond in the C-acylated product.

ASEC 2025 Conference

The 6th International Electronic Conference on Applied Sciences

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Selective Chloroacetylation of Methoxyphenol Isomers in the Presence of Various Catalysts: Product Distribution and Mechanistic Insights

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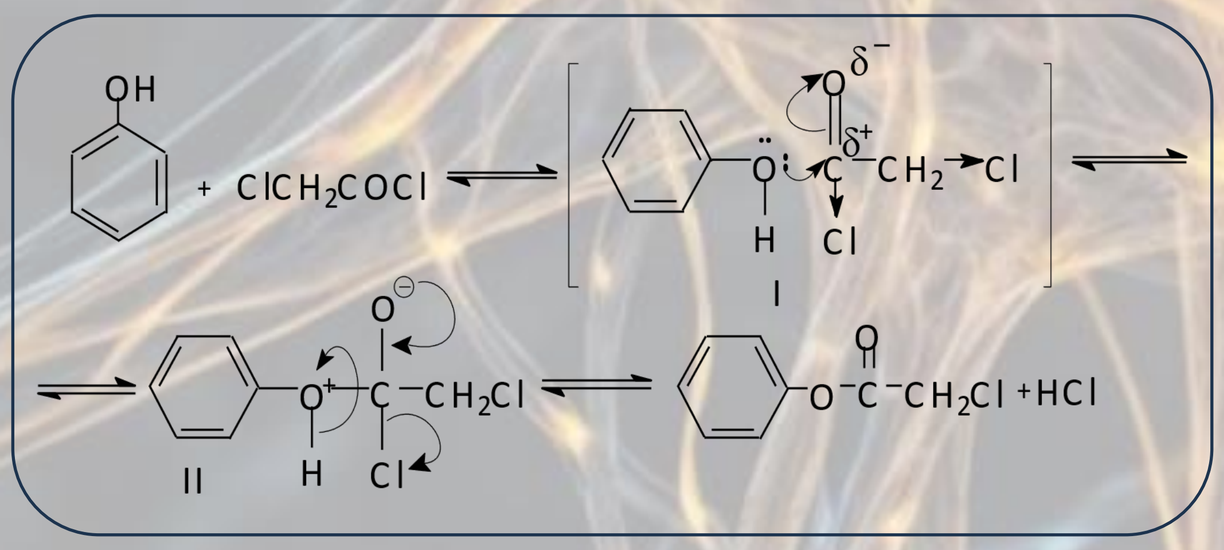
INTRODUCTION & AIM

Catalysts, particularly Lewis acids, play a crucial role in regulating the selectivity and reactivity of substrates in organic synthesis. Phenolic derivatives constitute an important class of organic compounds with widespread applications in the pharmaceutical, agrochemical, and polymer industries. Their structural diversity and high reactivity make them suitable starting materials for the preparation of bioactive molecules, functionalized monomers, and advanced materials. Within this family, methoxyphenols are of particular significance due to the dual activating effects of hydroxyl and methoxy substituents, which render the aromatic ring highly reactive toward electrophilic substitution. These compounds occur naturally in lignin-derived materials and essential oils, while also serving as versatile intermediates in medicinal chemistry. Consequently, the development of selective functionalization strategies for methoxyphenols continues to attract growing research interest.

The influence of catalyst type, catalyst loading, reaction temperature, and reaction time was systematically examined, and the resulting product distributions were analyzed using spectroscopic techniques (IR, UV, and NMR). The results provide valuable mechanistic insights into the competition between O-acylation and C-acylation pathways, offering practical guidance for the targeted synthesis of phenolic intermediates.

METHOD

Thin layer chromatography (TLC) was used on Silufol - 254 plates to determine the composition of the reaction products. TLC was used to examine the reaction's progression and the purity of the chemical compounds created throughout the procedure in the mobile phase system of petroleum ether and ethyl ether of acetic acid (7:3). For the TLC stationary phase, silica gel coated aluminum plates (silica gel 60 F254) bought from MERCK, India were utilized. The distribution of chemicals on TLC plates is seen using UV light. The reaction mixture was cleaned using column chromatography, and the yield of the chemical reaction that followed isolation was calculated. The reaction mixture was verified by TLC using petroleum ether and ethyl acetate (7:3) as the mobile phase after separation by column chromatography. The liquid was then dumped into ice cold water when the reaction was finished. The precipitated solid substance was filtered and dried. Petroleum ether and ethyl ester of acetic acid were used in column chromatography to clean the crude product. Using the KBr pellet technique, the products' FT-IR spectra were acquired on a Specord IR-71 spectrophotometer. TMS was used as the internal standard for the 1H NMR recordings, and chemical shift values were expressed in ppm scale using a Bruker 400 MHz NMR apparatus. The uncorrected melting points of the synthesized compounds were measured using the open capillary technique and the Mvtec melting point apparatus.



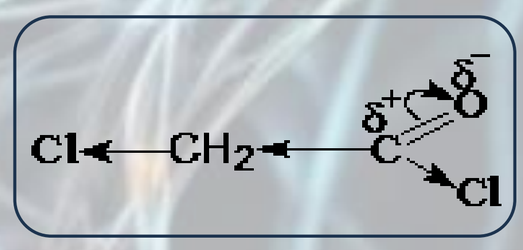
During the reaction of phenol with chloroacetyl chloride, the electron density in the chloroacetyl chloride molecule is shifted toward the electronegative oxygen, giving the oxygen a partial negative charge. As a result of the influence of the electronegative chlorine and oxygen atoms, the carbon atom acquires a partial positive charge and interacts with the lone pair of electrons of the hydroxyl group in the phenol molecule, forming Complex I. In the course of the reaction, a covalent bond is formed between the oxygen and carbon atoms, producing Complex II, from which hydrogen chloride is released along with the reaction product.

The proposed O-acylation scheme for this reaction is also applicable to the reactions of isomeric methoxyphenols with chloroacetyl chloride in absolute benzene, where the O-acylation likewise proceeds according to the same mechanism.

RESULTS & DISCUSSION

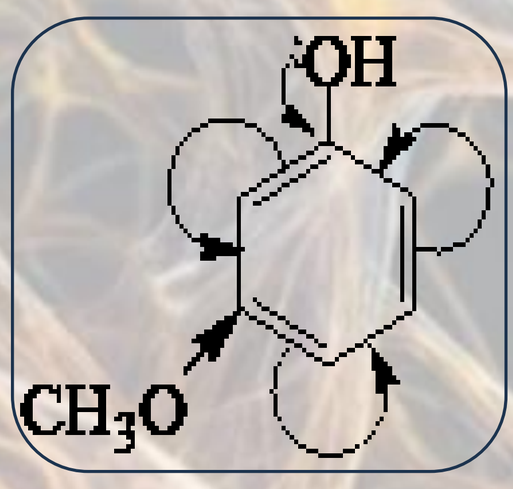
The course of the chloroacetylation reactions of phenols in the presence of small amounts of catalysts depends on the nature, number, and position of the substituents in the aromatic ring. In addition, the reaction pathway is significantly influenced by the type and amount of catalyst employed, as well as the temperature and duration of the process.

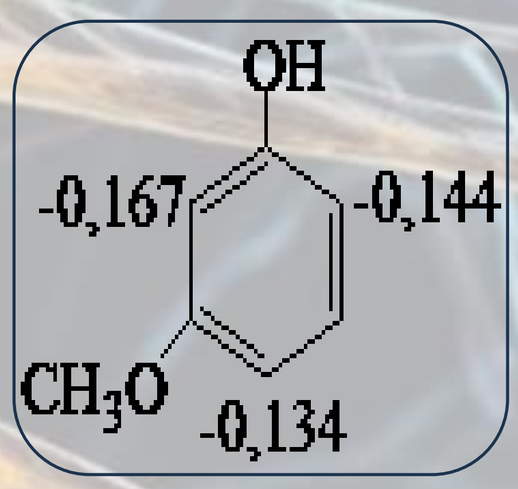
In the study of the chloroacetylation reaction, monochloroacetic acid chloride was used as the acylating agent. This choice was motivated by two main factors: first, many compounds containing the chloroacetyl group are known to exhibit significant biological activity; second, chloroacetyl chloride is recognized as a strong acylating agent. The latter can be explained by the inductive effect of the halogen atom, which causes a redistribution of the electron density within the carbonyl group, thereby imparting an additional positive charge to the carbon atom. As a result, the progress of the electrophilic substitution reaction is facilitated.



Chloroacetylation reactions of *m*-methoxyphenol, like those of *o*-methoxyphenol, are scarcely reported in the literature; therefore, investigating the regiochemical course of the chloroacetylation of *m*-methoxyphenol in the presence of small amounts of catalysts, and the effects of reagent ratio, reaction temperature, and catalyst type on the reaction pathway, is of both theoretical and practical significance.

In *m*-methoxyphenol, due to the +I effect of the methoxy group and the strong +M effect of the hydroxyl group, the electron density in the benzene ring is higher at the *ortho*- and *para*-positions relative to the hydroxyl group. Therefore, electrophilic substitution reactions readily occur at these positions.





The chloroacetylation reactions of *m*-methoxyphenol were carried out in the presence of catalytic amounts of $FeCl_3$, $MoCl_5$, WCl_6, $ZnCl_2$, $SnCl_4$, VCl_3, $FeCl_3 \cdot 6H_2O$, $Fe_2(SO_4)_3$, TAA, and TSA catalysts, and in all cases, the reaction products consisted of the compounds indicated above (I, II, III) [79; p. 86].

CONCLUSION

The selective chloroacetylation of *o*-, *m*-, and *p*-methoxyphenol was systematically investigated using different Lewis acid catalysts. The study revealed that product yields and regioselectivity strongly depend on catalyst type, loading, reaction temperature, and reagent ratios.

o-Methoxyphenol afforded three products, with 2-hydroxy-3-methoxyphenacyl chloride prevailing over the 4-hydroxy isomer. *m*-Methoxyphenol produced two C-acylated regioisomers along with the O-acylated ester, while *p*-methoxyphenol displayed higher selectivity, mainly giving *p*-methoxyphenyl chloroacetate. $FeCl_3$ provided the highest yields and favored O-acylation, whereas stronger Lewis acids such as $SnCl_4$ and $MoCl_5$ promoted C-acylation.

FUTURE WORK / REFERENCES

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