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Separation and determination of cresol isomers (Ortho, Meta, Para)

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Abstract
Alkylation of phenol has attracted attention of scientists since the beginning of synthetic era. While testing some catalysts for improving selectivity of phenol alkylation we came across a hurdle of analyzing mixture of cresol isomers. Gas chromatographic methods available for separation of cresol isomers are very sensitive and require costly specific chromatographic columns which are considerably unstable. UV method available in literature; works well for analyzing pure isomeric mixture but fails when it's a matter of analyzing reaction mass. Few HPLC methods are also available in literature, in lieu of developing alternate, simpler, fast, economic HPLC method, we developed the method being discussed.
In this work we introduce a simple, fast, economic and isocratic reverse phase HPLC Method. The total run time was less than 40 min. Most of the HPLC methods use Acetonitrile as eluent. An acute shortage of Acetonitrile has lead to increased demand and thus hiked price. In an effort to practice green chemistry this study was planned so as to substitute Acetonitrile with a dilute, safer and less toxic eluent (Methanol).

Keywords: Ortho Cresol, Para cresol, meta Cresol, HPLC, Gas cromatograph

Introduction
Separation and characterization of mixture of cresol isomers is a big hurdle for the scientists working on phenol alkylation. Phenol being highly susceptible for aromatic electrophilic substitution, the reaction of phenol with methanol gives a mixture of cresol isomers as well as o-alkylation leads to formation of anisole to some extent. Analytical methods for separation and quantification of cresol isomers works well for pure isomeric mixtures but it was observed that these methods doesn't give good separation while analyzing the reaction mass. Initially we analyzed pure isomeric mixture on gas chromatograph using methods [1, 2] available in literature and got a fair separation but later on when reaction mass was injected, the chromatogram was too messy to interpret. While doing literature search; we came across methods [3, 4, 5] depicting use of UV spectrophotometer. The absorption maxima of individual isomers as well as mixture were recorded. O-cresols gave absorption maxima at 280nm where as m- and p- cresol gave absorption maxima at 272 and 278 nm respectively.
Again there was no clear separation between o- and p- cresol when reaction mass was analyzed.
There are many HPLC methods available in literature. Some of the HPLC methods use α, β-cyclodextrins in mobile phase to get better resolution [6, 7]. It quest of developing a new, simpler, fast and economic HPLC method; method development work was undertaken.
Initially trials were conducted on cresols but later on looking at low resolution of cresol isomers in the chromatogram we thought of derivatizing cresols using acetyl chloride and analyzing it on HPLC. Rigorous work was conducted for developing analytical method. Detailed developed method is as below.

Material & Method
Equipment
Chromatographic separation was performed on Shimadzu system consist of Model – Prominence I LC-2030 having PDA detector and auto injector with 20 µl volume. Shimadzu Lab Solutia software applied for data collecting & processing.

Reagent & Chemicals
Methanol and water of HPLC grade procure form Fischer Scientific Mumbai. Formic acid AR grade was purchased from E-Merck chemicals Mumbai, India.
For standard, O-Cresol, M-cresol & P-Cresol (Synthesis grade) was purchased from Loba Chemie Mumbai & Acetyl Chloride 99% was used from Excel Ind. Ltd.

HPLC condition
Detailed HPLC conditions using which a high performance liquid chromatogram was recorded are as mentioned below,
A Hypersil BDS C-18 column (250X 4.6 mm, 5 µ) was used as stationary phase. A mixture of water and Methanol (65: 35 v/v) premixed with 0.1% Formic acid was used as mobile phase. It was Filtered through 0.45 µ filter & degassed. The Mobile phase was pumped at 1 ml / min. by isocratic method. The eluent was monitored at 260 nm. The Injection volume of sample and standard was 20 µl. The column temp. was 27 ºC. Diluent - Methanol: Water (50:50)

Standard Solution
Synthesis of cresyl acetate: The synthetic steps leading to acylated isomeric mixture of cresols are as mentioned below,
Take 5.0 gm O-cresol, M-cresol, P-cresol in separate 100 ml round bottom flask. Add 1: 1.2 Mole acylating agent very slowly and start heating the reaction mass to 50C. Maintain the reaction mass at 50 °C for 2 Hr. Cool the reaction mass and wash with water for a couple of times & distill out the organic layer.

Standard solution preparation: Weigh accurately about 100 mg of standard O-cresyl acetate, M-cresyl acetate, P-cresyl acetate each into a separate 25 ml volumetric flask. Add about 4-5 ml of diluents (Methanol: Water 50:50) and sonicate to dissolve. Make up to the mark with diluent, mix well and sonicate to degas

Test solution preparation: Weigh accurately about 100 mg of test sample in to a 25 ml volumetric flask. Add about 4-5 ml of diluent, sonicate to dissolve. Make up to the mark with diluent, mix well and sonicate. (0.25 mg/ml)

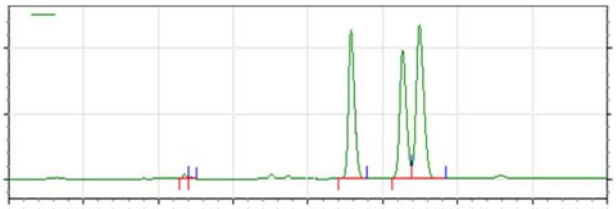
Procedure: After equilibrating the column, inject diluent as blank, standard solution and test solution into the liquid chromatograms. Disregard peaks due to the blank. Calculate the impurities by area normalization method.

- Inject 20 µl of blank (diluent) into the chromatograph and record the chromatogram.
- Inject 20 µl of reference solution into the chromatograph and record the chromatogram.
- Inject 20 µl of sample solution into the chromatograph and record the chromatogram.
- Examine the blank chromatogram for any peak due to diluents and disregard corresponding peaks observed in the chromatogram of sample solution.

Calculation: By Area % method

Results and discussion
Separation and resolution of cresol isomers was not adequate by GC using polyethylene glycol stationery phase.
By UV-spectrophotometer standard sample gave desired results. The absorption maxima of individual isomers as well as mixture were recorded. O-cresols gave absorption maxima at 280nm where as m- and p- cresol gave absorption maxima at 272 and 278 nm respectively, but there was no clear separation between o- and p- cresol when reaction mass was analyzed.

Area % Report
Sample: Mix O/M/P Cresyl Acetate
Wavelength: 260 nm



VWD: Signal A, 260 nm Results Peak Number 1 2 3 4 5

Peak	RT	Area	Area%	Name
01	11.750	934291	0.54	
02	12.207	247974	0.14	
03	22.877	53278301	30.17	O-cresyl acetate
04	26.333	50627586	29.17	M-cresyl acetate
05	27.453	68457810	39.45	P-cresyl acetate

Acyl derivatives of cresol isomers show a clear cut separation on isocratic reverse phase high pressure liquid chromatographic method.

Conclusion: An efficient isocratic reversed phase high performance liquid chromatographic method has been developed and optimized. Resolution and quality of the peaks were simultaneously optimized.

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