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Selective alkylation of *m*-cresol with isopropyl alcohol under solvent-free conditions

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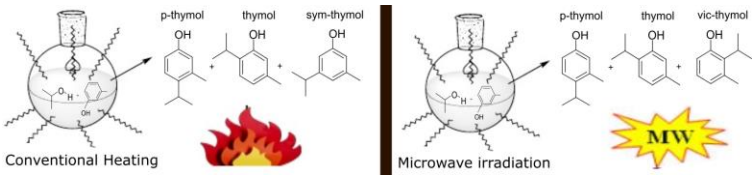
Abstract

The outcome of the solvent free alkylation of *m*-cresol with isopropyl alcohol over strong acid resin catalyst has been investigated under microwave irradiation as well as conventional heating. The various reaction parameters like catalyst amount, mole ratio of reactants, temperature and reaction time were found to be the main factors controlling the reactivity and selectivity. Also, the chemoselectivity O- *versus* C-alkylation can be fine-tuned by choosing the appropriate reaction conditions.



Keywords: Solvent free alkylation; Microwave irradiation; Strong acid resin catalyst; Overheating

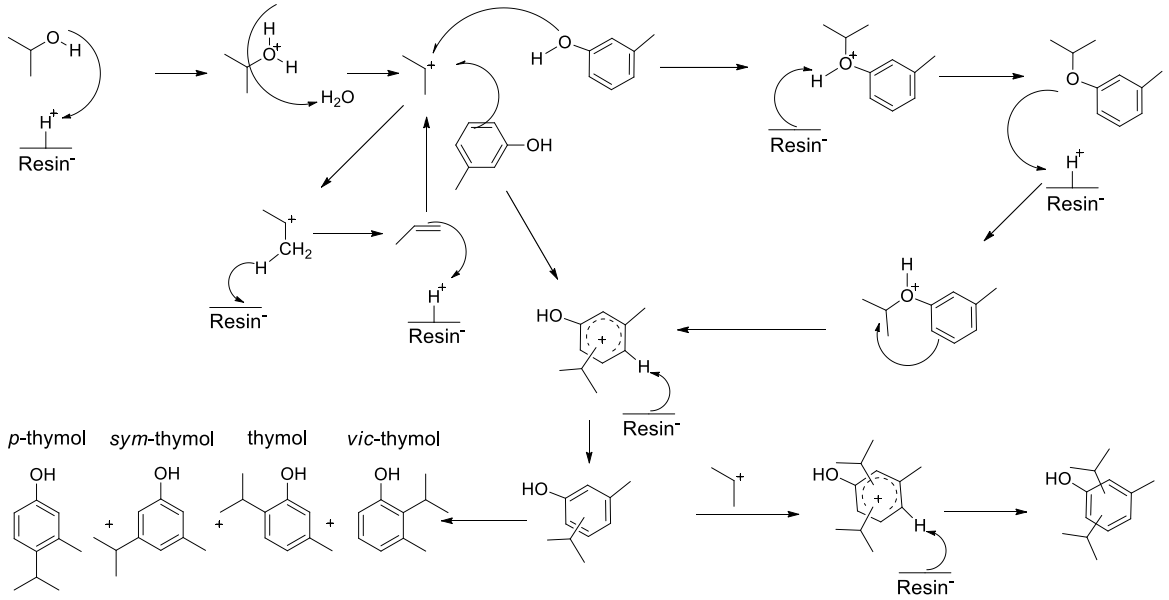
Introduction

Alkylphenols are a class of privileged compounds, they have found numerous applications in the industrial area (bulk chemicals, fine chemicals, pharmaceutical and perfumery products and other chemicals).[1,2] Because of the wide variety of applications, alkylphenols synthesis is a continuous goal in chemistry. Friedel-Crafts alkylation is the most used synthesis route, various alkylating agents (propylene, isopropyl alcohol (IPA), isopropylbromide, etc.) and different catalytic systems (homogenous[3,4] and heterogeneous[5-8]) being used in order to optimize the reaction yield and the efficiency of the process. The major drawback of the process is the need of high temperature and pressure. Due to his environmental benefits the heterogeneous catalysis seems to be favored. Moreover, the coupling of heterogeneous catalysis with non-conventional synthetic strategies like ultrasound,[9] supercritical fluids[10,11] and microwave irradiation[12-15] improve the efficiency of the Friedel-Crafts alkylation process, with shorter reaction time[16-18] and solvent free reactions.

Based on this state of the art, the main objective of the present work is to study the alkylation of *m*-cresol with isopropyl alcohol (IPA) in heterogeneous acid catalysis without using any solvent, both under microwave and conventional heating in order to prepare alkylphenols, especially mono-alkylphenols, because of their wide applications and importance. Thus, conditions have to be controlled precisely to minimize the formation of poly-alkylated by-products.

Results and Discussion

Our results are consistent with the reaction mechanism depicted in Scheme 1 which was previously proposed by Shekara and Ramesh in the case of *p*-cresol.[13,14,19] In the first step, abstraction of a proton from the acid sites of the catalyst produce an isopropyl cation which depending either on the attack to the oxygen atom or the aromatic ring leads to formation of an O- *versus* C-alkylated compound. In time, the O-alkylated product, due to low thermal stability can be converted into C-alkylated products. The catalyst anion is then protonated in a second step to yield the corresponding alkylated compounds and to conclude the catalytic cycle with regeneration of the acid sites of the catalyst. Obtaining di-alkylated products it is also possible by an attack of the isopropyl cation to the aromatic ring of the mono-alkylated products.



Scheme 1. Reaction route of alkylation of *m*-cresol with isopropyl alcohol.

This mechanism obviously points out the main role played by the acid sites of the catalyst on the reactivity, therefore, for this study strongly acidic polymer resins were selected and their characteristics (specific surface area, pore volume, functional group and temperature limit of H^+ form) are presented in Table 1.

Table 1. Characteristics of Catalysts

Catalyst	Specific Surface Area (m^2/g)	Pore Volume (ml/g)	Functional Group	Temp Limit H^+ Form (K)
CT-151 DR Resin	15-25	0.15 - 0.30	Sulfonic acid	453
Nafion NR-50	0.02	non-porous	Fluorosufonic acid	553

Effect of molar ratio of reactants

The effect of mole ratio of reactants on conversion and selectivity was studied by varying the mole ratio of *m*-cresol to IPA from 1:1 to 3:1 and 5:1 by keeping all other conditions constant. By conventional heating, as the mole ratio of *m*-cresol to IPA was increased up to 5:1, the trend of results obtained in the case of CT-151 DR Resin is similar to those described in the literature in the case of acid catalysts,[19] there was an increase in selectivity for the C-alkylated products. The results obtained under microwave irradiation establish also that the 5:1 molar ratio is the optimum to obtain the best selectivity in C-alkylated products, yielding up to 92.8% of the mono-alkylated products versus 7.2% di-alkylated. Further, for a stoechiometric value, even if the reaction time was 60 min, despite its low thermal stability the product formed mainly was the O-alkylated product as shown in Table 2.

Table 2. Selectivity of alkylated products as a function of the molar ratio of reactants

m-cresol :IPA	Selectivity (%)[a]		
	mono-alkylated	di-alkylated	O-alkylated
5:1	92.8	7.2	0
3:1	88.2	11.8	0
1:1	59.8	0.7	39.5

[a]Reaction conditions: microwave irradiation 300 W, reaction time 60 min, temperature 453 K, CT-151 DR concentration 0.05 g cm^{-3} on the basis of total volume of the reaction mixture.

A mole ratio of *m*-cresol to IPA 5:1 was maintained for the following experiments to avoid the formation the secondary products and to reduce the effect of the water formed by dehydration of IPA *in situ*.

Effect of temperature

Temperature has a significant effect on the alkylation catalyzed by acids, the influence on the conversion and products distribution being studied under otherwise similar conditions in previous literature.[20-22] A lower temperature favours O-alkylation whereas at temperature beyond 423 K C-alkylation dominates. The maximum value is also set by the thermal resistance of the catalyst. Considering the above findings, 453 K was chosen as suitable reaction temperature for further experiments.

The effect of reaction time

For comparison, effect of reaction time on the alkylation of *m*-cresol by IPA was studied under conventional heating and microwave irradiation over acid resin catalyst by varying the reaction time from minutes to hours. Final conversion under conventional heating was obtained in about 60 min but continuing the heating up to 240 min a different distribution between C-alkylated products was observed (Table 3). The resultant product distributions converged toward mostly thymol and *p*-thymol, some *sym*-thymol and a small amount of *vic*-thymol. These results can be attributed to the mesomeric effect, by which the lone electron pairs of the oxygen atom of the *m*-cresol are delocalised into the aromatic nucleus *via* π orbitals, thus activating *m*-cresol in the *para*- and *ortho* positions (kinetically favoured) for electrophilic attack by a carbenium ion.[23] The small amount of *vic*-thymol and the improvement in rate of *sym*-thymol can be explained by the thermal stability of the mono-alkylated cresol in the presence of acid catalyst, the order being as follows: *sym*-thymol > thymol > *p*-thymol > *vic*-thymol.[24] S*ym*-thymol is the thermodynamically favoured isomer as it has higher stability compared to the other isomers. This increased stability arises from the fact that the inductive effect of the propyl and methyl groups in the *meta*-positions does not prevent delocalisation of the lone pair electrons on the hydroxyl group into the aromatic system to the same extent as would be the case for these substituents in the *para* and *ortho*-positions. It has also noticed that the amount of the C-di-alkylated products decrease with the increase of the reaction time and the O-alkylated compound was not found among the components of the final reaction mixture.

Table 3. C-alkylated products as a function of the reaction time under conventional heating

Time (min)	Selectivity (%)[a]				
	mono-alkylated				di-alkylated
	thymol	*sym*-thymol	*p*-thymol	*vic*-thymol	
60	59.8	5.2	28.0	1.1	5.9
120	59.9	9.8	24.4	1.2	4.7
180	60.0	10.8	23.4	1.1	4.7
240	57.8	14.1	23.0	1.1	3.6

[a]Reaction conditions: conventional heating, *m*-cresol:IPA 5:1, CT-151 DR concentration 0.05 g cm^{-3} on the basis of total volume of the reaction mixture, temperature 453 K.

In the case of microwave assisted process was observed that the minimum time for the formation of alkylated products is a few minutes, at 10 min mark about 87% of C-alkylated products being already formed. With further increase in the reaction time, selectivity towards C-alkylated products increased with concomitant decrease in selectivity towards O-alkylated compound as shown in Figure 1, at least 30 min being required to complete conversion to C-alkylated products.

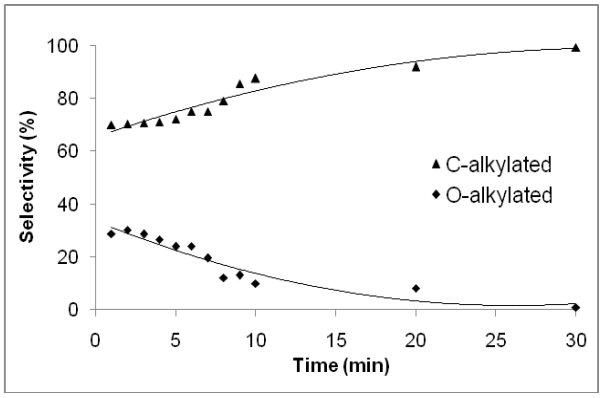


Figure 1. The chemoselectivity O- *versus* C-alkylation of *m*-cresol with IPA
Reaction conditions: 300 W, temperature 453 K, *m*-cresol:IPA 5:1, 0.05 g cm^{-3} CT-151 DR on the basis of total volume of the reaction mixture.

The distribution of C-alkylated products obtained for the microwave assisted process is different from that obtained by conventional heating, *vic*-thymol being obtained despite of *sym*-thymol (Table 4). Even if *vic*-thymol is thermally unstable, with longer exposure to microwave radiation it is still obtained. These results may be explained by the overheating microwave effect of polar liquids, avoiding thus the decomposition of thermally unstable compounds.[25-27] Overheating has a greater impact in closed systems, as in our case, maintaining *vic*-thymol as a product even for a 60 min reaction time.

Table 4. Alkylated products as a function of the reaction time under microwave irradiation

Time (min)	Selectivity (%)[a]					
	mono-alkylated				di-alkylated	O-alkylated
	thymol	*sym*-thymol	*p*-thymol	*vic*-thymol		
1	28.5	0.1	15.7	21.0	4.3	30.4
5	28.8	0.3	18.5	22.0	4.7	25.7
10	31.3	0.8	23.2	22.9	5.9	15.9
20	34.3	0.9	23.7	26.2	6.8	8.1
30	34.4	1.1	26.8	26.3	10.6	0.8
60	34.6	1.3	27.0	26.6	10.2	0.3

[a]Reaction conditions: microwave irradiation 300 W, *m*-cresol:IPA 5:1, CT-151 DR concentration 0.05 g cm^{-3} on the basis of total volume of the reaction mixture.

Effect of catalyst amount

The catalyst loading was varied over a range of 0.05-0.2 g cm^{-3} on the basis of total volume of the reaction mixture and no conversion was observed in the control experiments (absence of catalyst). With isopropyl alcohol as alkylating agent, conversion increased with an increase in the catalyst amount which is apparently due to the proportional increase in the number of active sites. However, beyond a catalyst loading of 0.05 g cm^{-3}, there was no significant increase in the conversion, but the distribution of the products changes with catalyst loading.

Under conventional heating regardless of the amount of the catalyst the *vic*-thymol is almost absent. As the catalyst amount was increased, there was an increase in selectivity for *sym*-thymol from 14.1% to 25.2% while the selectivity of *p*-thymol decrease from 23% to 14.7% (Table 5). The results are consistent with those obtained in study of reaction time influence and are attributed to the thermal stability of the mono-alkylated cresol in the presence of acid catalyst, *p*-thymol turns into the more stable isomer *sym*-thymol (thermodynamically favoured isomer). The acidity of the reaction mixture increased with an increase in catalyst loading, which was due to the proportional increase in the number of active sites. Moreover, the amount of the C-di-alkylated products decreases with the increase of the number of active sites of catalyst, as observed also with the increase of the reaction time.

In order to support our assumption that the distribution of C-alkylated products changes with the acidity, Nafion NR-50, a catalyst with higher acidity and a lower surface area compared with CT-151-DR, was examined under the same reaction conditions. There was almost no effect of catalyst amount on distribution of the alkylated products.

Table 5. C-alkylated products as a function of the catalyst amount under conventional heating

Catalyst	Cat. loading (g cm^{-3})	Selectivity (%)[a]				
		mono-alkylated				di-alkylated
		thymol	*sym*-thymol	*p*-thymol	*vic*-thymol	
CT-151-DR	0.05	57.8	14.1	23.0	1.1	3.6
	0.1	59.3	19.2	17.2	1.3	3.2
	0.2	56.9	25.2	14.7	1.2	2.1
Nafion NR-50	0.05	59.7	8.9	20.8	0.9	9.8
	0.2	58.1	9.6	21.1	0.9	10.4

[a]Reaction conditions: conventional heating, *m*-cresol:IPA 5:1, reaction time 240 min, temperature 453 K.

Under microwave irradiation, the strong effect of overheating still controls the reaction outcome, so the catalyst amount did not have a big impact on the products, only minor changes being achieved (Table 6). Thymol selectivity slightly increases while *vic*-thymol and di-alkylated products selectivities decreases due to the increase in the number of active sites.

Table 6. C-alkylated products as a function of the catalyst amount under microwave irradiation

Catalyst	Cat. loading (g cm^{-3})	Selectivity (%)[a]				
		mono-alkylated				di-alkylated
		thymol	*sym*-thymol	*p*-thymol	*vic*-thymol	
CT-151-DR	0.05	34.4	1.1	26.8	26.3	10.6
	0.2	41.3	0.9	27.1	23.0	7.3

[a]Reaction conditions: microwave irradiation 300 W, *m*-cresol:IPA 5:1, reaction time 30 min.

Conclusions

Liquid phase Friedel-Crafts alkylation of *m*-cresol with isopropyl alcohol was studied for a variety of reaction conditions to establish how to control the end-products of the process. A temperature of 453 K, a 5:1 molar ratio between *m*-cresol and isopropyl alcohol with a catalyst loading of 0.05 g cm^{-3} ensure high selectivity for mono-alkylated products regardless the two modes of heating.

Under conventional heating, the time of the reaction and the catalyst loading can influence the selectivity of the end-products, obtaining thymol, *p*-thymol and *sym*-thymol as main products. Furthermore, increasing either the time of the reaction or the catalyst loading or both increases the selectivity in *sym*-thymol while the selectivity of *p*-thymol decreases without decreasing the rate of thymol.

Through microwave assisted synthesis a shorter reaction time and different products distribution are achieved, obtaining thymol, *p*-thymol and *vic*-thymol as main products. If the time is too short O-alkylated compound can be obtained in significant quantities. The time needed for the O-alkylated product to completely convert into C-alkylated compounds is about 30 min.

The comparison between conventional *versus* microwave heating provides a practical example on the effect of the overheating phenomenon encountered in the microwave processes. Instead of *sym*-thymol (thermodynamically favored isomer) *vic*-thymol (the least stable compound) was obtained, proving that overheating through microwave irradiation can avoid the decomposition of thermally unstable compounds in the presence of acid catalyst.

The reaction seems to be significantly influenced by reaction parameters, being possible to obtain a higher selectivity in thymol and by modifying certain parameters to control the outcome of the other end-products of the process.

Experimental Section

General. Isopropyl alcohol (IPA), *m*-cresol and Nafion NR-50 were procured from Sigma-Aldrich Ltd. CT-151 DR Resin was procured from Purolite Ltd. All chemicals were of analytical reagent grade and were used as received without any further purification.

Microwave heated reactions were conducted in a microwave lab station START-S (Milestone Inc. Company, USA) having software that enables the on-line control of temperature of the reaction mixture. All the reactions were stirred with the help of built-in automatic magnetic stirrer using teflon stirring bar and were carried out in a 30 mL closed glass vessel under autogenous pressure. The reaction under conventional heating was carried out in stainless steel autoclave equipped with a magnetic stirrer and plunged in an oil bath. The analysis of samples was carried out by Agilent GC-MS 6890N equipped with Agilent HP-5ms capillary column (0.25 mm x 30 m x 0.25 µm). A standard calibration method with synthetic mixtures was used for quantification of data.

Procedure. In a typical experiment, 33 mmol of *m*-cresol and 6.6 mmol of IPA (5:1 mole ratio of *m*-cresol to IPA) were charged in the reaction vessel with a catalyst loading over a range of 0.05-0.2 g cm^{-3} of total volume of liquid phase. The mixture was heated under stirring up to the desired temperature (453 K) under autogenous pressure, up to 4 hours. The reaction was carried out without any solvents, having a total volume of 4 mL.

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