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**p-Cymenesulphonyl Chloride: A Bio-Based Activating Group and Protecting Group for Greener Organic Synthesis**

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A bio-derived protecting/activating group has been synthesized by introducing a sulphonyl chloride group to the aromatic ring of p-cymene derived from citrus peel waste. The resulting p-cymenesulphonyl chloride was evaluated as an activating group by reacting with 1-octanol, 2-octanol, phenol and piperidine, and further reactions of the activated alcohols. The comparison to tosyl chloride demonstrates that the bio-based alternative can be effectively utilized as a direct replacement for the current fossil derived equivalent.

**Keywords:** citrus waste, p-cymene, sulphonyl chloride, activating group, protecting group

**Introduction**

An essential part of synthetic chemistry, activating groups and protecting groups are often used in more than one molar equivalent to the substrate, thus accounting for a significant share of the total amount of reagents used. Tosyl chloride is an example of such reagent. It is widely used as a protecting group1 or an activating group2 for alcohols and amines in the synthesis of complex molecules. Within the 12 principles of green chemistry it is explicitly stated that “unnecessary derivatization should be minimized or avoided if possible, because such steps require additional reagents and can generate waste” (principle 8).3 However progress in achieving this goal has been slow and limited to specific examples,4 due to the need for protecting and activating groups in some areas of synthetic organic chemistry. It would be considerable benefit, if just an intermediate step towards the eventual elimination of activating and protecting groups, to obtain these chemicals from a renewable source instead of petroleum (coinciding with principle 7).

Under the encouragement of the Brazilian government, 5 the European Comission 6 and other nations, the share of bio-based products in the global chemical market is projected to grow. 7 Consumer pressure 8 and some government procurement strategies, 9 are also helping to accelerate the development of greener and renewable products. Greater demand means that biomass utilization will have to be increasingly directed towards valorizing waste streams instead of using food crops.

Citrus waste is a good example of a food waste with huge potential as a renewable chemical feedstock. 10 Citrus fruit juice production leaves behind approximately half of the fruit mass, estimated to amount to 15 million tons of citrus peel waste per year. 11 The waste is usually dried and incorporated into cattle feed. Because the energy cost of the drying process is high and the value of animal feed is low, the profit in the current process is not satisfying. 12,13 As a means of getting more value from the citrus peel waste, the essential oil can be extracted by a variety of methods.14 Extraction of essential oil from citrus peel waste has been demonstrated to be economically feasible in a large scale bio-refinery by using explosive pressure reduction (flashing) methods.13,15 Taking into account the yields of essential oil extraction from citrus waste, and the high limonene content in the essential oil (> 90%), it can be estimated that the capacity for limonene production in Brazil is 82,500 tons per year.16

To produce a replacement for tosyl chloride (TsCl), limonene can be converted into p-cymene (1-isopropyl-4-methyl-benzene, I) using the high yielding protocols published by Martin-Luengo et al. 17 then following the
methodology described by Cremlyn,18 a sulphonyl chloride functional group can be added onto the aromatic ring. The resulting p-cymenesulphonyl chloride abbreviated to CymCl (2), has been applied in this work as an activating group for alcohols and amines, and its reactivity compared to that of TsCl.

**Experimental**

Synthesis of p-cymenesulphonyl chloride

The synthesis of p-cymenesulphonyl chloride (CymCl) was carried out following the procedure described by Brown et al.19 Cold p-cymene (6.95 g, 52 mmol) was added drop-wise to 5 equivalents of chlorosulphonic acid (17 mL, 260 mmol) in an ice bath, under magnetic stirring. After 90 minutes the reaction mixture was poured onto crushed ice. A purple oily layer formed which was washed several times with distilled water until the purple color disappeared. The resulting light brown oil (9.64 g, 81%) was isolated in a separation funnel, and the product stored at −18 °C. The reaction of 1-octanol, 2-octanol, phenol and

\[ \text{p-Cymene-\(\alpha\)-sulphonyl chloride} \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\) \delta 1.26 (d, 6H, J 6.95 Hz, CH\(_3\)) \]

\[ 2.73 \text{ (s, 3H, Ar–CH\(_3\)) , 2.97 (m, 1H, J 6.95 Hz, Ar–CH)} \]

\[ 7.32 \text{ (d, 1H, J 8.05 Hz, Ar–H), 7.46 (dd, 1H, J 1.80 Hz, J 7.69, Ar–H), 7.89 (d, 1H, J 1.80 Hz, Ar–H);} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3\) \delta 19.9, 23.8, 33.8, 126.6, 128.6, 133.5, 135.4, 142.9, 148.1; MS (EI +) m/z 232 [M]+.} \]

\[ \text{p-Cymene-\(\beta\)-sulphonyl chloride} \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\) \delta 1.32 (d, 6H, CH\(_3\)) \]

\[ 2.40 \text{ (s, 3H, Ar–CH\(_3\)) , 3.98 (m, 1H, Ar–CH), 7.23 (d, 1H, Ar–H), 7.46 (dd, 1H, Ar–H), 7.83 (d, 1H, Ar–H).} \]

Activation of reagents

The reaction of 1-octanol, 2-octanol, phenol and piperidine was performed according to the method described by Yoshida et al.20 The activating agent, TsCl or CymCl, was present in 1.50 molar equivalents and dissolved in 1 mL of the chosen solvent. The solution was added drop-wise to a reagent mixture composed of 1.00 mmol of the chosen nucleophile, 1 molar equivalent of Me\(_3\)N.HCl in 2.5 molar equivalents of Et\(_3\)N, all dissolved in 1 mL of the chosen solvent in ice bath under magnetic stirring. The solvent was toluene, p-cymene or acetonitrile. After one hour, the reaction mixture was quenched with water, extracted with ethyl acetate, then washed with brine, dried with MgSO\(_4\) and concentrated in vacuo to give the crude arylsulphonyl derivative of the substrate that was analyzed by GC-FID, GC-MS, NMR spectroscopy and IR spectroscopy as appropriate. The conversion was calculated using GC-FID of the crude mixture against a calibration curve.

Reactions of the activated octanol

The methodology for the reactions of the protected alcohols with sodium methoxide was based on the work of Hiroya et al.21 and Sarmah et al.22 In the first instance sodium metal (5 molar equivalents) was added slowly to excess methanol, and to the resulting sodium methoxide solution was added protected alcohol and stirred overnight at reflux. After 15 hours, the methanol was evaporated in vacuo, and the resulting residue dissolved in chloroform. After washing successively with water and brine, the organic phase was dried with MgSO\(_4\) and concentrated in vacuo to give the product.

For the alternative reaction of the activated alcohols with morpholine, based on the protocol of Hamrick and Hauser,23 an excess of morpholine (5 mL) was added to the protected alcohols (0.33 mmol) and stirred for 4 hours at 100 °C, then left to stand overnight at room temperature. The remaining morpholine was then removed by evaporation, and the resulting residue extracted with ether, washed with distilled water, and the organic phase separated, dried with MgSO\(_4\) and concentrated in vacuo to give the alkylated amine.

**Results and Discussion**

Synthesis of p-cymenesulphonyl chloride

The synthesis of p-cymenesulphonyl chloride (2) from p-cymene (1) and chlorosulphonic acid, Figure 1, yielded the two regioisomers in a proportion of approximately 5:1 when an overnight reaction was employed. When the reaction was carried out for 90 minutes, a 4:1 (i.e., 80% to 20%) ratio of isomers was more typical, as observed by NMR spectroscopy and GC-FID analysis. In both cases the major isomer is the \(\alpha\)-sulphonyl chloride (2a), meaning ortho to the methyl group. The minor isomer is the \(\beta\)-sulphonyl chloride (2b), meaning meta to the methyl group. The reaction also resulted in a small quantity of the diaryl sulphone, which was typically present in a proportion of around 1:30 relative to the major isomer of CymCl.
Of the reaction conditions attempted, the highest yield of CymCl was achieved when 5 molar equivalents of chlorosulphonic acid was employed. Table 1 shows the yields of CymCl, obtained from duplicate experiments, and an e-factor (environmental factor) for each set of reaction conditions. The e-factor analysis justifies the larger excess of chlorosulphonic acid to some extent because the improvement in yield results in less reactant waste, almost cancelling out the impact of the additional mass of chlorosulphonic acid used.

Table 1. Yield in the p-cymenesulphonyl chloride synthesis

<table>
<thead>
<tr>
<th>Molar equivalent of HOSO₂Cl²</th>
<th>Reaction time / h</th>
<th>Yield / %</th>
<th>E-factor³</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.5</td>
<td>81</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>35</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>49</td>
<td>2.2</td>
</tr>
</tbody>
</table>

²HOSO₂Cl = chlorosulphonic acid;³yield accounting for all isomers (combined α and β); e-factor, calculated from mass ratio of waste to product, excluding water.

The use of p-cymenesulphonyl chloride as an activating group

The functionalization of piperidine, phenol, 1-octanol (3a) and 2-octanol (3b) by TsCl and CymCl was performed according to literature precedent. The protected nucleophile was the only product observed, which was present as isomers in the case of reactions with CymCl. A representative reaction is shown in Scheme 1.

The conversion rates of each substrate under different reaction conditions are shown in Table 2. p-Cymenesulphonyl chloride (CymCl) met expectations as an activating group, meaning generally high yields and no significant side reactions. The conversions achieved were comparable to those obtained with TsCl for both primary and secondary alcohols. The functionalization of phenol is hindered by its low nucleophilicity but piperidine was successfully reacted with CymCl. The two isomers of CymCl are both reactive, with the regioselectivity of the sulphonylation reasonably preserved, as shown in Table 3 for all four substrates for reactions in acetonitrile. The CymCl isomers for these reactions had a starting ratio by GC of 80.0% major (α) to 20.0% minor (β), Figure 2.

Table 2. Activation of 1-octanol (3a) and 2-octanol (3b)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Protecting group</th>
<th>Solvent</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>2 p-cymene</td>
<td>toluene</td>
<td>90</td>
</tr>
<tr>
<td>3b</td>
<td>2 p-cymene</td>
<td>toluene</td>
<td>50</td>
</tr>
<tr>
<td>3a</td>
<td>TsCl toluene</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>2 toluene</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>TsCl toluene</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>2 toluene</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>TsCl acetonitrile</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>2 acetonitrile</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>TsCl acetonitrile</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>2 acetonitrile</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Phenol</td>
<td>2 acetonitrile</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Piperidine</td>
<td>2 acetonitrile</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

*Determined by GC.

Scheme 1. Esterification of 1-octanol with arylsulphonyl chlorides.
Therefore sulphonylation of the substrates showed a very slight preference for the major, less sterically hindered, α isomer to react. The piperidine substrate showed the highest shift in selectivity between the isomers, with a drop in the more sterically hindered β isomer from 20.0% to 14.5%. This more pronounced drop is logical as piperidine possesses the greatest steric bulk in the location of the reaction center of all the different nucleophiles investigated.

Often TsCl is used in conjunction with its parent molecule, toluene, a common solvent despite possessing a flash point below room temperature and possible chronic human toxicity. From a health, safety, and environmental perspective, it was fitting to assess the potential of p-cymene to replace toluene as the solvent. Although 1-octyl p-cymenesulphonate (4a) was obtained in good yield, the conversion to 2-octyl p-cymenesulphonate (4c) when attempted in p-cymene was too low to have practical use. The lower dipolarity of p-cymene compared to toluene might have resulted in insufficient stabilization of the more sterically hindered activated complex. Another factor to consider is substrate solubility. Acetonitrile was the only solvent investigated for experiments with phenol and piperidine for this reason.

Reactions of activated octanol

The reaction of 1-octyl p-cymenesulphonate (4a) and 2-octyl p-cymenesulphonate (4c) with sodium methoxide led to the formation of the desired methyl octyl ethers (Scheme 2), as evidenced by NMR spectroscopy and GC-MS (Supplementary Information). The yields of methyl 1-octyl ether (5a) and for optimal conditions methyl 2-octyl ether (5b) are presented in Table 4, and are comparable to those established in the literature on similar substrates. When the activated alcohols were reacted with excess morpholine, the p-cymenesulphonate esters underwent the anticipated substitution reaction, with yields of 68% (N-1-octyl morpholine, 6a) and 82% (N-2-octyl morpholine, 6b) achieved (Scheme 3).

![Figure 2](image_url)

*Figure 2. Example reaction of nucleophiles once protected with CymCl by reactions in acetonitrile.*

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conversion&lt;sup&gt;a&lt;/sup&gt; / %</th>
<th>Major isomer&lt;sup&gt;b&lt;/sup&gt; / %</th>
<th>Minor isomer&lt;sup&gt;b&lt;/sup&gt; / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a (1-octanol)</td>
<td>92</td>
<td>82.5 (4a')</td>
<td>17.5 (4a'')</td>
</tr>
<tr>
<td>2-octanol</td>
<td>93</td>
<td>82.3</td>
<td>17.7</td>
</tr>
<tr>
<td>Phenol</td>
<td>50</td>
<td>83.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Piperidine</td>
<td>91</td>
<td>85.5</td>
<td>14.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conversion determined by GC-FID via a calibration curve; <sup>b</sup>the percentage of the major and minor isomers were determined by taking the ratio of major and minor isomer peaks and assuming that each had the same relative response factor.

![Scheme 2](image_url)

*Schematic representation of the alkylation of sodium methoxide using an activated 1-octanol.*

Table 3. Relative ratios of major and minor isomers of nucleophiles once protected with CymCl by reactions in acetonitrile.
Conclusions

The synthesis of p-cymenesulphonyl chloride (CymCl) by reaction of p-cymene and chlorosulphonic acid was successful, with the two regioisomers able to form activating groups on alcohols and amines. The activated alcohols could then be reacted with sodium methoxide or morpholine to give the desired substitution products. Further optimization and scale-up of the production of CymCl would result in a practical renewable auxiliary for organic chemistry, complementing a growing catalogue of functional chemicals and materials derived from Brazilian sourced citrus waste.\textsuperscript{10,16,28}

Supplementary Information

Supplementary information (including spectra of compounds) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

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References


Table 4. Yields of methyl octyl ethers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Product yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 equivalents of sodium (room temperature)</td>
<td>15 (5a)</td>
</tr>
<tr>
<td>5 equivalents of sodium (reflux)</td>
<td>62 (5a); 88 (5b)</td>
</tr>
<tr>
<td>1.4 equivalents of sodium (reflux)</td>
<td>25 (5a)</td>
</tr>
</tbody>
</table>

Scheme 3. Nucleophilic substitution reaction of morpholine on 1-octyl p-cymenesulphonate (4a).


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