Master Thesis Report

For the master thesis on

**Nucleophilic aromatic substitutions using ethyl 3-mercaptopropionate as nucleophile**

**Scope and limitations**

Biomolecular Chemistry 160p
Södertörns Högskola

Rositha Antonsson
rositha01.antonsson@student.sh.se

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Examiner:

Prof. Elke Schweda
Professor of Analytical Chemistry, PhD.
Södertörns Högskola and Karolinska Institute
Clinical Research Center, NOVUM, Huddinge
elke.schweda@kfc.ki.se

Supervisors:

Dr. Kristin Hammer
Medicinal Chemistry, Pre-Clinical Development
Biovitrum AB, Solna
kristin.hammer@biovitrum.com

Dr. Tomasz Janosik
Institute of Biosciences & Nutrition
Unit of Heterocyclic Organic Chemistry
Karolinska Institute, NOVUM, Huddinge
tomasz.janosik@cnt.ki
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Abstract

The scope and limitations of nucleophilic substitutions of aryl halides have been studied using ethyl 3-mercaptopropionate as nucleophile and microwave heating. A diversity of aromatic compounds have been investigated according to different types of leaving groups, regio isomers and substituents. Experimental design has been used as a tool to optimize the reaction. An electron-withdrawing group in ortho or para position of the leaving group proved to be necessary for a positive outcome of the reaction. Fluorine was, without competition, the best leaving group. Some examples of how the synthesized aryl sulfanyl propionates can be used as starting material for producing aryl thio ethers, sulfoxides and unique benzothiophenes are described.
1 Introduction

Both nucleophilic and electrophilic pathways are known in the synthesis of aryl sulfonyl propionates\(^1,2\). Depending on the electron-withdrawing group and the leaving group, rather harsh conditions have been used for the nucleophilic substitution\(^3\).

The ethyl propionate chain serves as a valuable thiol protection group which is stable under acidic and mild basic conditions. The corresponding thiol can easily be released by using a strong base, Scheme 1.

The purpose of this diploma work was to study the scope and limitations of nucleophilic substitutions of aryl halides using ethyl 3-mercaptopropionate as nucleophile and a microwave reactor for heating. A diverse set of aromatic compounds should be investigated according to leaving group, regio isomers and different substituents. Some of the aryl sulfonyl propionates should be used as starting materials for producing small unique drug-like compounds of aryl thio ethers, sulfoxides and sulfones. Some aryl sulfonyl propionates should also be used as starting material for synthesis of unique benzothiophenes.

Questions that were asked were: Can the \(\sigma\)-value of an aromatic compound be used to predict the outcome of the reaction? Is the type of leaving group of importance? Will different regio isomers have different impact on the outcome?

2 Experimental design

Experimental design was used as a tool to optimize the substitution, Scheme 2. Pre-investigations with 4-fluorobenzaldehyde had indicated that using \(\text{K}_2\text{CO}_3\) or \(\text{Cs}_2\text{CO}_3\) (especially) as a base seemed to give a better yield than using triethylamine (TEA). Performing the reaction under inert atmosphere with acetonitrile (MeCN) as the solvent did not seem to significantly increase the yield. Both MeCN, and dimethyl formamide (DMF) seemed to be suitable solvents and concentrations of 0.2 M seemed to work. Some reactions even occurred after only 5 min at 60 \(^\circ\)C.

Questions that were asked were: Can the \(\sigma\)-value of an aromatic compound be used to predict the outcome of the reaction? Is the type of leaving group of importance? Will different regio isomers have different impact on the outcome?
MODDE 8.0, which is a computerized program for experimental design and optimization\(^4\), was used to set up the design. Six factors were investigated in a screening-like procedure using D-optimal design in two levels. The different factors were: base (Cs\(_2\)CO\(_3\)/TEA), solvent (MeCN/DMF), concentration (0.2M/0.8M), time (5/30min), temperature (60/150˚C), and \(\sigma\)-value (0.50/0.66). For \(\sigma\)-values see Appendix 1. Base and solvent were qualitative factors and time, temperature and \(\sigma\)-value were quantitative.

D-optimal design was used since this design can handle a large amount of factors. In this design a computerized algorithm covers a space where all factors have been combined. The experimental set-up represents the datapoints at the outer limits of this space, Figure 1. For experimental set-up according to D-optimal design, see Appendix 2.

Based on the results from the D-optimal design, further investigations of three factors were done using a Full factorial analysis. The factors that were investigated were time (5/30 min), temperature (60/150 ˚C) and type of substituent in para position (\(p\)-aldehyde or \(p\)-nitrile). Time and temperature were quantitative factors and \(p\)-substituent was qualitative. A Full factorial analysis is achieved by combining high and low values of the factors so that all possible combinations are made. The design is in two levels, and if the number of factors are three the resulting experimental section is a cubic region, figure 2. For experimental set-up, see Appendix 3.

### 2.1 Analysis of experimental design

In the summary plot, the Q2 value tells you how well the model predicts new data, meaning that if one part of the data is left out, how well will the model predict this data by using all the other available data? In a perfect model, the value of Q2 is 1. \(R^2\) describes how well the model fits with the data. \(R^2\) should be close to 1. The coefficient plot shows which parameters that are significant for the result. The factors that are significant are the ones that do not have a confidence interval including the value zero. Model validity tells you about how well the model fits with the experimental data. When the value of the model validity is larger than 0.25 there is no lack of fit of the model, but when the model validity is less than 0.25 you have a significant lack of fit. Reproducability is a measurement of the control of experimental error. You will get a high reproducibility when you have a good control over experimental error.
3 The $S_{N}Ar$ mechanism

The $S_{N}Ar$ mechanism is an addition-elimination mechanism where the first step usually is rate determining\(^5\). The carbanion that is formed is called the Meisenheimer complex, Figure 3. The negative charge is spread over the five $sp^2$-hybridized carbons. The partial charge is higher in ortho and para positions, than in meta\(^6\). The Meisenheimer complex needs to be stabilized by an electron acceptor in para or ortho position\(^5\).

![Figure 3. Nucleophilic attack on aromatic compound, formation of the Meisenheimer complex](image)

As an example, a nitro group in para or ortho position can well stabilize the partial charge, Figure 4.

![Figure 4. $S_{N}Ar$ on an aromatic compound with a nitro group in para position](image)

Nucleophilic substitutions with electron-withdrawing groups in meta position have been reported\(^7\), Scheme 3.

**Scheme 3\(^a\).**

| Reactants and conditions: MeSNa, DMF, 20 °C, 4.5 days, 92 % |

Fluorine is the best leaving group among halogens, in most aromatic nucleophilic substitutions. This can be compared to the fact that it is the poorest leaving group among the halogens when it comes to $S_{N}1$ and $S_{N}2$ mechanisms\(^5\).

4 Microwave heating

Microwaves are electromagnetic waves with frequencies between 0.3 and 300 GHz. In the electromagnetic spectrum the microwave region is between infrared and radio frequencies. Microwave reactors used for chemical synthesis operates at a frequency of 2.45 GHz which corresponds to a wavelength of 12.2 cm. Microwave chemistry is based on the heating of materials by dielectric heating effects. In the microwave cavity,
the sample will be hit by a microwave that consists of one electrical and one magnetic component. The electrical component is responsible for the dielectric heating. There are two mechanisms that are important in dielectric heating: the dipolarisation mechanism and the conduction mechanism. A dipole moment is necessary for a substance to be able to generate heat when it is hit by a microwave. The dipole will be sensitive to an external electric field and will align itself with the oscillating field by rotation. In the microwave frequency the molecules do not rotate in the exact same phase as the field; just when the dipole has almost realigned to the field, then the direction of the field changes. This phase difference will cause collisions and frictions between molecules and energy will be converted into heat.

The conduction mechanism will occur if there are ions present in the solution. The ions will move by influence of the electric field, and when they collide with each other or with other molecules, the kinetic energy will be transformed into heat. This mechanism is more heat generating than the dipolarisation mechanism. An example of this is if you heat distilled water and tap water at a fixed microwave irradiation power under a fixed period of time, the final temperature will be higher in the tap water. A substance with a high dielectric constant will not automatically give a more rapid heating than a substance with a low. The important thing is the ability of a substance to convert the absorbed energy into heat. This ability is expressed by its loss factor, tan δ. The higher value of tan δ, the more rapid is the heating. Non-polar solvents are more or less microwave transparent. Polar additives such as ionic liquids can be added to increase the absorbance of microwave irradiation.

An advantage of microwave heating over conventional heating is that the temperature will be more uniform in the reaction vessel since it is the content in the vessel that is the heating source. Temperatures of 100-150 °C higher than the temperature of the bulk liquid have been registered in heterogeneous mixtures containing solids. This kind of superheating can be avoided using an appropriate magnetic stirrer. The presence of metals can create extreme hot spots since microwaves interacts strongly with metals. It has also been observed that the boiling point of liquids are higher when using microwave heating than their normal boiling points at atmospheric pressure.
5 Result

5.1 Experimental design

5.1.1 D-optimal design

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**Figure 6.** Coefficient plot for D-optimal design. Investigated factors: Base, solvent, temperature, time, concentration and \( \sigma \)-value

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**Figure 7.** Summary fit for D-optimal design. Investigated factors: Base, solvent, temperature, time, concentration and \( \sigma \)-value

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\(^1\text{AcN} = \text{Acetonitrile}\)
5.1.2 Full factorial analysis

**Figure 8. Coefficient plot for Full factorial analysis. Investigated factors: Temperature, time and p-substituent.**

**Figure 9. Summary fit for Full factorial analysis: Investigated factors: Temperature, time and p-substituent**
5.2 Modifications of starting materials

Electron-poor 5- and 6-fluorindole derivatives were prepared by sulfonation of the corresponding indoles, Scheme 4. The triflate derivative of 4-fluor-2-nitrophenol was synthesized according to Scheme 5.

Scheme 4

\[ \text{Reagents and conditions: } (a) \text{ } t\text{-BuOK, benzenesulfonyl chloride, THF, RT, 54 %, } (b) \text{ } t\text{-BuOK, benzenesulfonyl chloride, THF, RT, 25 %}. \]

Scheme 5

\[ \text{Reagents and conditions: } N\text{-Phenyltrifluoromethanesulfonamide, TEA, MeCN, RT, 30 %}. \]
5.3 Successful substitutions

Table 1. Successful substitutions using ethyl 3-mercaptopropionate as nucleophile*

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>No.</th>
<th>Yield (%)</th>
<th>Conditions</th>
<th>σ-value</th>
<th>Mp (°C) Recorded/reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>H F O S O</td>
<td>H F O S O</td>
<td>4</td>
<td>88</td>
<td>5 min, 80 °C</td>
<td>0.42</td>
<td>Oil</td>
</tr>
<tr>
<td>O N F</td>
<td>O N F</td>
<td>5</td>
<td>55</td>
<td>10 min, 90 °C</td>
<td>0.78</td>
<td>38.5-40/35-36</td>
</tr>
<tr>
<td>F F F</td>
<td>F F F</td>
<td>6</td>
<td>54</td>
<td>10 min, 70 °C</td>
<td>0.78</td>
<td>43-46/-</td>
</tr>
<tr>
<td>O N F</td>
<td>O N F</td>
<td>7</td>
<td>50d</td>
<td>10 min, 80 °C + 10 min, 90 °C</td>
<td>0.37</td>
<td>Oil</td>
</tr>
<tr>
<td>F O N O</td>
<td>F O N O</td>
<td>8</td>
<td>49e</td>
<td>10 min, 120 °C</td>
<td>0.80</td>
<td>54-57/-</td>
</tr>
<tr>
<td>O O O</td>
<td>O O O</td>
<td>9</td>
<td>45f</td>
<td>10 min, 90 °C</td>
<td>0.37 (F)</td>
<td>Oil</td>
</tr>
<tr>
<td>O O O</td>
<td>O O O</td>
<td>10</td>
<td>42g</td>
<td>5 min, 90 °C</td>
<td>0.42</td>
<td>Oil</td>
</tr>
<tr>
<td>O O F</td>
<td>O O F</td>
<td>11</td>
<td>32</td>
<td>10 min, 60 °C</td>
<td>0.42</td>
<td>Oil</td>
</tr>
<tr>
<td>N C F N C</td>
<td>N C F N C</td>
<td>12</td>
<td>28h</td>
<td>5 min, 60 °C</td>
<td>0.66</td>
<td>49-50/-</td>
</tr>
<tr>
<td>O O C l</td>
<td>O O O</td>
<td>13</td>
<td>27</td>
<td>10 min, 80 °C</td>
<td>0.42</td>
<td>Oil</td>
</tr>
<tr>
<td>O O F</td>
<td>O O F</td>
<td>14</td>
<td>23</td>
<td>10 min, 60 °C</td>
<td>-</td>
<td>Oil</td>
</tr>
<tr>
<td>O O B r</td>
<td>O O B r</td>
<td>15</td>
<td>11</td>
<td>10 min, 60 °C</td>
<td>0.42</td>
<td>Oil</td>
</tr>
<tr>
<td>O O F</td>
<td>O O F</td>
<td>16</td>
<td>10</td>
<td>5 min, 80 °C</td>
<td>0.50</td>
<td>65-66/-</td>
</tr>
<tr>
<td>O O C l</td>
<td>O O O</td>
<td>17</td>
<td>9</td>
<td>10 min, 60 °C</td>
<td>0.42</td>
<td>Oil</td>
</tr>
<tr>
<td>O N O C F O</td>
<td>O N O C F O</td>
<td>18</td>
<td>~10i</td>
<td>10 min, 80 °C</td>
<td>0.78</td>
<td>Semi solid</td>
</tr>
</tbody>
</table>

*One pre-run was done for each successful experiment to try to find out at which temperature the best yield would be obtained. This was done by running the sample for 10 min at 60°C, draw a sample for analysis by LC-MS and occasionally by GC-MS, then heat the sample again for 10 min at 70°C and so on up to 140 °C, by stepwise increasing the temperature by ten degrees. Finally the sample was run for 10 min at 160 °C.
Footnotes, table 1 continued

a. Isolated yield.
b. All heating was done by a microwave reactor.
c. Values are only available for substituents in meta and para positions of the leaving group, see Appendix 1. Values from > 1 substituent are added to each other.
d. 1.5 eq nucleophile gave a major substitution of flouro but also some disubstitution (~ 5 % according to LC-MS UV$_{180-305\text{nm}}$) and a small amount of substitution of chloro (~ 5 % according to LC-MS UV$_{180-305\text{nm}}$).
   1 eq of nucleophile gave a small amount of dissubstitution (<5%) but no monosubstitution of chlorine.
e. A test-run using 2.5 eq of base instead of 1.5 eq was done but it did not seem to give a better yield than using 15 eq. The isolated yield is checked using 1.5 eq base.
f. 1.5 eq and 1.3 eq nucleophile gave a small amount of monosubstitution of chlorine (< 5 %). No disubstitution.
g. A test run using 2 eq of nucleophile and 2 eq of base was also done.
h. The synthesis was also performed using K$_2$CO$_3$, 15 min, 120 °C (19).
i. The isolated product was not pure. Yield reported is the yield according to NMR and GC-MS.

5.3.1 Tables: σ-values versus yields

![Figure 10. σ-values versus yield. All starting materials in Table 1.](image)

![Figure 11. σ-values versus yield. Starting materials with substituents only in para position of the leaving group (-F), Table 1.](image)
5.4 Non-successful substitutions

Table 2. Non-successful substitutions using ethyl 3-mercaptopropionate as nucleophile*

<table>
<thead>
<tr>
<th>Aromatic compound</th>
<th>Conditions</th>
<th>σ-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Fluorobenzaldehyde</td>
<td>10 min, 60-160 °C</td>
<td>0.35</td>
</tr>
</tbody>
</table>
| 1-Bromo-4-fluorobenzene                       | 10 min, 60-160 °C | Substitution of F: 0.23
|                                               |            | Substitution of Br: 0.06 |
| 4-Fluorobenzoic acid                          | 10 min, 60-160 °C | 0.45    |
| 1-Fluoro-3-nitrobenzene                       | 10 min, 60-160 °C | 0.71    |
| 6-Fluorindole                                 | 10 min, 60-160 °C | Not available |
| 6-Fluoro-1-(phenylsulfonyl)-1H-indole         | 10 min, 60-160 °C | Not available |
| 3-Fluoro-5-(trifluoromethyl)benzene           | 10 min, 60-160 °C | 0.55    |
| 5-Fluorindole                                 | 10 min, 60-160 °C | Not available |
| 5-Fluoro-1-(phenylsulfonyl)-1H-indole         | 10 min, 60-160 °C | Not available |
| 4-Bromo-3-fluoroacetanilide                   | 10 min, 60-160 °C | Substitution of Br: 0
|                                               |            | Substitution of F: 0.21 |
| 4-Fluorobenzene- sulphonamide                 | 10 min, 60-140 °C | 0.57    |
| N-(4-Fluorobenzoyl)piperidine                 | 10 min, 60-160 °C | Not available |
| 1-Fluoro-3-(trifluoromethyl)benzene           | 10 min, 60-140 °C | 0.43    |
| 1-Fluoro-2-(trifluoromethyl)benzene           | 10 min, 60-160 °C | -       |
| (1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl-methanol | 10 min, 60-160 °C | Not available |
| 5-Fluoroisatin                                | 10 min, 60-70 °C | Not available |

* Not successful = 0 area-% according to LC-MS, UV 180-305 nm and molecular ion not found in GC/MS-EI. General experimental procedure: The aromatic compound, ethyl 3-mercaptopropionate (1.5 eq), and cesium carbonate (1.5 eq otherwise noted in table 2.) were dissolved in MeCN (2 ml) in a microwave
tube (2 ml). A magnetic stirrer was added, the tube was sealed with a septum and heated in a microwave reactor. The sample was run for 10 min at 60 °C, a sample was drawn for analysis by LC-MS or by GC-MS if there were peaks in the UV-spectrum that did not give a good signal in TIC (total ion count). Then the sample was heated for 10 min at 70 °C and so on up to 140 °C by stepwise increasing the temperature by ten degrees. Finally the sample was run for 10 min at 160 °C.

a. All heating was done by a microwave reactor.
b. $\sigma$-values are only available for substituents in meta and para position of the leaving group, see Appendix 1. If there are more than one substituent, the $\sigma$-values are added to each other.
c. The experiment was also performed under the given conditions using DMF/acetonitrile as a solvent and potassium tert-butoxide as a base. Neither experiment was successful.
d. 2 eq of base was used.
e. Experiments were done using both 1.5 and 2.5 eq base.
f. 2.5 eq of base was used.
g. The reaction mixture was only heated up to 140 °C since the pressure inside the vial was too high at 160 °C, and the heating process was stopped by the microwave reactor.
h. The experiment was stopped at 140 °C since there were only starting material and lots of by-products present.
i. The $\sigma$-value for $N$-(4-fluorobenzoyl)piperidine is not known but the $\sigma$-value for a secondary amine $C=O(NHMe)$, in para position is $\sigma$ 0.36.
j. The experiment was stopped at 140 °C since there were lots of starting material and some by-products.
k. 2 eq of base was used. The experiment was stopped since lots of byproducts were present already at 60 °C.

5.5 Substitutions in gram-scales

Compounds (4) and (11) were also synthesized in gram-scale, according to a procedure reported by Liu$^2$, Scheme 6:

Scheme 6$^a$

![Scheme 6](image)

$^a$ Reagents and conditions: (a), (b) Ethyl 3-mercaptopropionate (1.1 eq), $K_2CO_3$ (1.5 eq), DMF, 60 °C.

(a) 87 % (b) 85 %
5.6 Aryl sulfanyl propionates as starting materials

5.6.1 Syntheses of aryl thio ethers and a sulfoxide

Aryl sulfanyl propionates can be used as starting material in syntheses of aryl thio ethers and sulfoxides, Scheme 7.

Scheme 7

![Scheme 7](image)

- a. Reductive amination
- b. One-pot-alkylation via β-elimination
- c. Selective oxidation
- d. One-pot-alkylation via β-elimination

(a) NaBH(OAc)$_3$, morpholine, AcOH (cat), DCE, RT, 76 % (b) NaOEt (RT), 3-methoxy-benzylbromide (RT + 40 °C), MeCN, 18 % (c) Oxone, Al$_2$O$_3$, DCM, reflux, 17 % (d) NaOEt, (RT) bromoacetaldehyde dimethyl acetal, 130 °C (microwave reactor), MeCN, 28 %

5.6.2 Synthesis of a unique benzothiophene

Compound 20 was used in a novel synthesis of 7-Bromo-1-benzothiophene-5-carbaldehyde (27), Scheme 8:

Scheme 8

![Scheme 8](image)

(a) t-BuOK (RT), bromoacetaldehyde dimethyl acetal (reflux), MeCN, 18 %, (b) PPA, PhCl, reflux, 10 %
6 Discussion

The results from the D-optimal design showed that the only significant factor for the yield was the type of base, Figure 6. Cs$_2$CO$_3$ had a significant positive effect while TEA had a significant negative effect. The results from the Full factorial analysis shows that both temperature and time had a significant negative effect on the yield, Figure 8. The summary of fit for both designs, Figure 7 and 9, shows that the model validity was less than zero. This was interpreted as if the models did not fit with the experimental data. Therefore, the experimental set-up for the investigation of different aromatic compounds could not completely rely on the results from the experimental design. Preinvestigations and in-house-experience of a successful substitution of a bromobenzene with an oxazole derivate in para position using ethyl 3-mercaptopropionate as a nucleophile, under heating by a microwave reactor for 10 min at 130 °C, also needed to be taken under consideration. It should be mentioned that when setting up the D-optimal design, 4-bromo-1-fluorobenzene (σ 0.23), was initially used for the first six runs, Appendix 2. Since the yield turned out to be 0 % in all these runs, another aromatic compound, acetophenone (σ 0.50) was used instead.

Using 4-fluorobenzaldehyde as starting material gave a yield of 42 % (10) while 4-bromo-benzaldehyde and 4-chlorobenzaldehyde gave yields around 10 % (15 and 17), Table 3. 4-chloro-2-fluorobenzaldehyde yielded almost only monosubstitution of fluorine (using 1.5 eq nucleophile gave < 5 % monosubstitution of chlorine and < 5 % dissubstitution, using 1 eq of nucleophile gave < 5 % dissubstitution and no monosubstitution of chlorine) (7). 2-chloro-6-fluorobenzalehyde yielded also almost only monosubstitution av fluorine (1.3 eq of nucleophile gave < 5 % monosubstitution of chlorine, and no dissubstitution) (9). That no dissubstitution took place in this case probably is due to steric effects.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>No.</th>
<th>Yield (% isolated)</th>
<th>Conditions *&lt;sup&gt;b&lt;/sup&gt; Microwave heating</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.jpg" alt="Reactant" /></td>
<td><img src="image2.jpg" alt="Product" /></td>
<td>10</td>
<td>42</td>
<td>5 min, 90 °C</td>
</tr>
<tr>
<td><img src="image3.jpg" alt="Reactant" /></td>
<td><img src="image4.jpg" alt="Product" /></td>
<td>15</td>
<td>11</td>
<td>10 min, 60 °C</td>
</tr>
<tr>
<td><img src="image5.jpg" alt="Reactant" /></td>
<td><img src="image6.jpg" alt="Product" /></td>
<td>17</td>
<td>9</td>
<td>10 min, 60 °C</td>
</tr>
<tr>
<td><img src="image7.jpg" alt="Reactant" /></td>
<td><img src="image8.jpg" alt="Product" /></td>
<td>7</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 min, 80 °C + 10 min, 90 °C</td>
</tr>
<tr>
<td><img src="image9.jpg" alt="Reactant" /></td>
<td><img src="image10.jpg" alt="Product" /></td>
<td>9</td>
<td>45&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 min, 90 °C</td>
</tr>
<tr>
<td><img src="image11.jpg" alt="Reactant" /></td>
<td><img src="image12.jpg" alt="Product" /></td>
<td>5</td>
<td>55</td>
<td>10 min, 90 °C</td>
</tr>
<tr>
<td><img src="image13.jpg" alt="Reactant" /></td>
<td><img src="image14.jpg" alt="Product" /></td>
<td>18</td>
<td>~10</td>
<td>10 min, 80 °C</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1.5 eq nucleophile gave < 5 % chlorine and < 5 % dissubstitution, 1 eq of nucleophile gave < 5 % dissubstitution and no monosubstitution of chlorine.

<sup>b</sup> 1.3 eq of nucleophile gave < 5 % monosubstitution of chlorine, and no dissubstitution.
4-fluoro-2-nitrophenol gave a yield of 55 % (5), while its triflate derivate (3), Scheme 5, gave a yield of ~ 10 % (18), Table 3. The reason for this low yield using the triflate derivate was that a large amount of a by-product was formed. All starting material, 4-fluoro-2-nitrophenol, was consumed after heating by a microwave reactor for 10 min at 60 °C. Present was a large amount of a by-product, m/z 266 (GC-MS), and a small amount of the desired product, (18). The by-product had a high absorbance in UV$_{254nm}$, which shows presence of an aromatic group, otherwise for possible identities of m/z 266 (GC-MS), see Figure 12. It has been reported that when aryl triflates react with various nucleophiles the nucleophilic attack appears to be limited to an attack at sulfonyl sulfur and, for strongly basic and hindered nucleophiles, generation of benzene$^{10}$. The comparisons between different leaving groups, Table 3, shows that fluorine is the best leaving group.

![Figure 12. Possible main products in synthesis of compound 18.](image)

The para isomer of fluorobenzaldehyde gave a yield of 42 % (10) while the ortho isomer gave 23 % (14), Table 4. No substitution took place on the meta isomer. Not even a very strong electron-withdrawing group like –NO$_2$ in meta position resulted in a substitution. A nitro group in meta position has $\sigma$-value 0.71, and in para 0.78. Despite the fact that the $\sigma$-values for these regio isomers are almost the same, a substitution on the para isomer took place already at 60 °C and while there was no substitution on the meta isomer even when heated at 160 °C. In this reaction, regio selectivity is obviously more important than $\sigma$-value, and this is in good agreement with the theories presented under section 3, The S$_N$Ar mechanism.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>No.</th>
<th>Yield (%)</th>
<th>Conditions</th>
<th>$\sigma$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="diethyl 3,3'-disulfanediyldipropanoate" /></td>
<td>![ethyl 3-[(trifluoromethyl)sulfonyl]sulfonyl]propanoate](image)</td>
<td>10</td>
<td>42</td>
<td>5 min, 90 °C</td>
<td>0.42</td>
</tr>
<tr>
<td><img src="image" alt="diethyl 3,3'-disulfanediyldipropanoate" /></td>
<td>![ethyl 3-[(trifluoromethyl)sulfonyl]sulfonyl]propanoate](image)</td>
<td>14</td>
<td>23</td>
<td>10 min, 60 °C</td>
<td>-</td>
</tr>
<tr>
<td><img src="image" alt="diethyl 3,3'-disulfanediyldipropanoate" /></td>
<td>![ethyl 3-[(trifluoromethyl)sulfonyl]sulfonyl]propanoate](image)</td>
<td>-</td>
<td>0</td>
<td>10 min, 60-160 °C</td>
<td>0.35</td>
</tr>
<tr>
<td><img src="image" alt="diethyl 3,3'-disulfanediyldipropanoate" /></td>
<td>![ethyl 3-[(trifluoromethyl)sulfonyl]sulfonyl]propanoate](image)</td>
<td>5</td>
<td>55</td>
<td>10 min, 90 °C</td>
<td>0.78</td>
</tr>
<tr>
<td><img src="image" alt="diethyl 3,3'-disulfanediyldipropanoate" /></td>
<td>![ethyl 3-[(trifluoromethyl)sulfonyl]sulfonyl]propanoate](image)</td>
<td>-</td>
<td>0</td>
<td>10 min, 60-160 °C</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Table 4. Comparison of regio isomers, data from Table 1 and 2

To select an aromatic compound for this substitution reaction only by looking at its $\sigma$-value is not a good approach, see Figure 10, where yield is plotted as a function of $\sigma$-
value for all successful substitutions, Table 1. A plot of σ-values versus yield for starting materials with substituents only in para position of the leaving group (-F), Figure 11, gave a R² value of 0.2, which means that the correlation between between σ-value and yield was very weak.

Substitution with 2-fluoro-4-nitro-1-(trifluoromethyl)benzene worked well,(6), while substitution of its derivative 1-fluoro-2-(trifluoromethyl)benzene did not, Table 5. This indicates that, in this case, electronic effects were more important than steric effects.

Table 5. Comparison of yields using 2-fluoro-4-nitro-1-(trifluoromethyl)benzene or 1-fluoro-2-(trifluoromethyl)-benzene as starting materials, data from Table 1 and 2

<table>
<thead>
<tr>
<th>Reactant Product</th>
<th>No.</th>
<th>Yield (% isolated)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF₃NO₂</td>
<td>6</td>
<td>54</td>
<td>10 min, 70 °C</td>
</tr>
<tr>
<td>F</td>
<td>-</td>
<td>0</td>
<td>10 min, 60-160 °C</td>
</tr>
</tbody>
</table>

Using an aromatic compound with an electron-withdrawing substituent in para position and an electron donating substituent in meta position, 5-fluoro-2-nitrophenol, also worked, Table 6. A hydroxy group in meta position will give a partial negative charge especially in ortho and para position of this group. Since the leaving group in this case, was situated in meta position of the electron donating group, the negative impact of the hydroxy group on the substitution was small. This can be seen by comparing the yield using 5-fluoro-2-nitrophenol as starting material, 49 % (8), with the yield using 1-fluoro-4-nitrobenzene; 55 % (5).

Table 6. Comparison of yields using 5-fluoro-nitrobenzene or 1-fluoro-4-nitrobenzene, data from Table 1

<table>
<thead>
<tr>
<th>Reactant Product</th>
<th>No.</th>
<th>Yield (%)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNO₂</td>
<td>8</td>
<td>49</td>
<td>10 min, 120 °C</td>
</tr>
<tr>
<td>F</td>
<td>5</td>
<td>55</td>
<td>10 min, 90 °C</td>
</tr>
</tbody>
</table>

The reason why an electron donating group in para positions of the leaving group did not work, can be explained by looking at the resonance structures which shows that the resonance forms gives partial negative charges in ortho and para positions, Figure 13.

Figure 13. Resonance forms of (1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl-methanol

The low to moderate yields can be explained by the fact that one or more by-products usually were formed, sometimes already at 60 °C, for example when 4-chlorobenzaldehyde and 4-bromobenzaldehyde was used. The starting material was generally not consumed, instead, a mixture of starting material, one or more by-
products and the product was often seen (LC-MS, UV$_{180-305\text{nm}}$). The amount of by-products increased with temperature. The only reactions where the yield could be checked when all starting material was gone and no by-products were present were 3,4-difluorobenzaldehyde and 3,4-dibromobenzaldehyde. It is strange that the yield using 3,4-dibromobenzaldehyde was not higher than 32 % (11) compared to the yield using 3,4-difluorobenzaldehyde; 88 % (4). The formation of by-products might have been caused by local temperature maxima which is known to be a problem in heterogeneous mixtures. When removing the sample from the microwave reactor, there was always some Cs$_2$CO$_3$ “glued” to the walls at the bottom of the vessel and even if the sample always is cooled before removal from the microwave chamber, the bottom of the vessel was usually still hot. All the successful substitutions could be seen already when heated at 60 °C for 10 min.

Scaling up the syntheses of 4 and 11 to gram-scales (20 and 21) according to a procedure described by Liu$^2$, Scheme 6, was successful, Table 7. It gave no side reactions, was easy to work-up and gave high yields. Scaling up 4 from 100 mg to 500 mg by using microwave chemistry was not that successful. After heating for 5 min at 80 °C (reaction conditions that gave a yield of 88 % in 100 mg scale), lots of starting material remained and by-products were formed. The reason for this may have been insufficient stirring. Locally elevated temperatures can cause side reactions and may cause degradation.

![Image of molecules 4 and 11]

Table 7. Syntheses in gram-scales by conventional heating versus syntheses in mg-scales by microwave heating, Scheme 6

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conventional heating gram-scale (2 h, 60 °C)</td>
<td>Microwave heating mg-scale (5 min, 80 °C)</td>
</tr>
<tr>
<td>HOC(O)CO</td>
<td>HOC(O)CO</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>OCO</td>
<td>OCO</td>
<td>87</td>
<td>32</td>
</tr>
</tbody>
</table>

Direct reductive amination of 4 to yield 22, Scheme 9, was done according to a procedure described by Abdel-Magid and Mehrman$^{11}$. The choice of reducing agent was very important. A reducing agent that selectively reduces imines or iminium ions over aldehydes or ketons was needed. Sodium triacetoxy borohydride, NaBH(OAc)$_3$, fulfills this criterion. The authors recommended 1.1 eq of the amine, but 1.4 eq was used according to in-house-experience. The authors wrote that “when performing reductive amination on aldehydes, usually no acid catalyst is necessary to speed up the reaction”. Two test-runs were done, one run where 1 drop of acetic acid was added and one run without. After stirring for 21 h in RT starting material was still present in both experiments but in the acid-catalyzed reaction much more product had been formed (LC-MS, UV$_{180-305\text{nm}}$).
Scheme 9\textsuperscript{a} (part of Scheme 7), reductive amination

\[
\begin{array}{c}
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{N} & \text{O} & \text{S} & \text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{N} & \text{O} & \text{S} & \text{O}
\end{array}
\]

\textsuperscript{a} Reagents and conditions: (a) NaBH(OAc)\textsubscript{3}, morpholine, AcOH (cat), DCE, RT, 76 \%

The one-pot-alkylation of 20, to yield 26, Scheme 10, worked well when the synthesis was done in a 50 mg scale but when these conditions were scaled up to 1 g, a large amount of a by-product was formed almost immediately. The identity of the by-product is not known. It had a m/z 296/298 (M+H)\textsuperscript{+} while compound 26 has a m/z 305/307 (M+H)\textsuperscript{+}. The by-product was not the corresponding disulfide which has been reported by Becht\textsuperscript{1} as a possible by-product in \(\beta\)-eliminations.

Scheme 10\textsuperscript{a} (part of Scheme 8), one-pot-alkylation

\[
\begin{array}{c}
\text{O} & \text{Br} & \text{S} & \text{O} \\
\text{O} & \text{Br} & \text{S} & \text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} & \text{Br} & \text{S} & \text{O} \\
\text{O} & \text{Br} & \text{S} & \text{O}
\end{array}
\]

\textsuperscript{a} Reagents and conditions: (a) KOBu-t, bromoacetaldehyde dimethyl acetal, MeCN, RT, 18 \%

Selective oxidation of 23 to yield 24, Scheme 11, was performed using a procedure for selective oxidation of sulfides to the corresponding sulfoxides and sulfones reported by Greenhalgh\textsuperscript{12}. According to the author, using 1 eq of Oxone should yield only the sulfoxide, 3 eq of Oxone should yield only sulfones. It turned out that sulfoxide was the major product in both procedures. After 6 h reflux, additional Oxone 3 eq (a total of 6 eq) was added. After additional 18 hours of reflux, the major product was still sulfoxide. Two small peaks, both containing the m/z of the sulfone were present in LC-MS, UV\textsubscript{180-305nm}. The reaction was run in such a small scale that these products could not be isolated and characterized. It is possible that one of the peaks contained the sulfone and that the other peak was the N-oxide plus sulfoxide. One drop of trifluoroacetic acid was added to the sulfide before the reaction to protonate the nitrogen and thereby protect it from being oxidized. The active component in Oxone is peroxomonosulphate\textsuperscript{13}. NMR-spectra of 23 and 24 are shown in Appendix 4. The evidence for the oxidation of the sulfur is that the signal from the two protons on the carbon next to the sulfur has changed from being a singlet at 4.03ppm (2H) to two duplets each integrated to 1H. The reason is that the protons no longer are magnetically equivalent since the sulfoxide is chiral. The synthesized sulfoxide is therefore a racemic mixture.

Scheme 11\textsuperscript{a} (part of Scheme 7), selective oxidation

\[
\begin{array}{c}
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{N} & \text{O} & \text{S} & \text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{O} & \text{S} & \text{O} & \text{F} \\
\text{N} & \text{O} & \text{S} & \text{O}
\end{array}
\]

\textsuperscript{a} Reagents and conditions: Oxone, Al\textsubscript{2}O\textsubscript{3}, DCM, reflux, 17 \%
A novel synthesis of 7-Bromo-1-benzothiophene-5-carbaldehyde (27), Scheme 12, was done once. The reaction progress was followed by GC-MS and LC-MS. The desired product started to form after 1 h reflux. Both after 2 h and 4.5 h reflux m/z 242 (M_w of 11) was the dominating peak in GC-MS. There were a few small other peaks present (none of the peaks contained the molecular ion of an intermediate that would be formed when the starting material, 26, loses -OCH_3). The reaction was stopped after 4.5 h even though a small amount of starting material was present. It could be well worth letting the reflux continue and follow the reaction by TLC. One explanation of the low yield, 10 %, is that some of the product or intermediates decomposed under the reaction conditions since LC-MS, UV_{180-305nm}, showed no other peaks than solvent (chlorobenzene) and the peak containing m/z 242/244 (M+H)^+. This method for preparation of heterocyclic compounds by cyclization of acetals has been reported in a patent\textsuperscript{14}, where phosphoric acid was used for cyclization, but the synthesized benzothiophene (27) is unique.

Scheme 12\textsuperscript{a} (part of Scheme 8), synthesis of a unique fused benzothiophene

\begin{center}
\begin{tikzpicture}
\node at (0,0) {26};
\node at (1.5,0) {27};
\draw [thick, ->] (0.75,0) -- (1.25,0);
\draw [thick, -] (0.5,0) -- (1.5,0);
\draw [thick, -] (0.75,0.25) -- (1.25,0.25);
\draw [thick, -] (0.75,-0.25) -- (1.25,-0.25);
\node at (2,0) {O};
\node at (2.5,0) {O}.
\end{tikzpicture}
\end{center}

\textsuperscript{a} Reagents and conditions: PPA, PhCl, reflux, 10 %

Finally, a separate experiment was done to compare microwave heating to conventional heating. Two identical prepared samples (containing 4-fluorobenzaldehyde, ethyl 3-mercaptopropionate, cesium carbonate, MeCN (2 ml) and a magnetic stirrer) were prepared. One sample was heated by a microwave reactor for 5 min at 60 °C, the other sample was heated for 5 min at 60 °C in a stemblock. Identical LC-MS methods were used for the analyses that were done after 5 min. The sample heated by the microwave reactor showed a yield of 78 % (area-% in LC-MS, UV_{180-305nm}), while the sample heated in the stemblock showed a yield of 3 %. After being heated in the stemblock at 60°C for 3 h, the yield had increased to 30 %.

7 Conclusions

The \sigma-value of an aromatic compound can not be used to predict the outcome of the substitution. An electron-withdrawing group in ortho or para position of the leaving group proved to be necessary. Fluorine was the best leaving group of –F, -Cl, -Br and –OSO\textsubscript{2}CF\textsubscript{3}.

Despite moderate yields, the presented method should be useful since a variety of protected aryl thiols can be synthesized in a fast and extremely simple way. The synthesized aryl sulfanyl propionates can be used as starting materials in syntheses of libraries of aryl thio ethers, sulfoxides and unique benzothiophenes.
8 Experimental

8.1 General

Analytical HPLC was performed using an Agilent 1100/1200 Series Liquid Chromatograph/Mass Selective Detector (MSD) (Singel quadropole) (1946A/1946C/1956C/6110) equipped with an electrospray interface. The columns that were used were ACE C8, 3µm (3.0x50 mm) and Xterra MS C18, 3.5µm (3.0x50mm). Acidic conditions (ACE column): Mobile phase water containing 0.1% TFA and acetonitrile at a flow rate of 1ml/min with gradient times of 3 min. Basic conditions (Xterra column): Mobile phase water containing 10mM NH₄HCO₃ (pH10) and acetonitrile at a flow rate of 1 ml/min with gradient times of 3 min.

Preparative HPLC/UV was performed on a Gilson system in accordance to the experimental details specified in the examples. Big column – basic conditions: Xbridge Prep C18, 5µm (30x75mm), mobile phase water containing 50 mM NH₄HCO₃ (pH 10) and acetonitrile at a flow rate of 45 ml/min with gradient times of 8.5 min. Small column – basic conditions: Xterra MS C18, 5µm (19x50 mm), mobile phase water containing 50 mM NH₄HCO₃ (pH 10) and acetonitrile at a flow rate of 25 ml/min with gradient times of 6 min. Small column – acidic conditions: ACE C8, 5 µm (21.2x50 mm), mobile phase water containing 0.1% TFA and acetonitrile at a flow rate of 25 ml/min with gradient times of 6 min.

¹H NMR and ¹³C NMR spectra were recorded on a Varian Inova 400 (at 400 Mz and 100 MHz). Chemical shifts are reported in parts per million (ppm) using residual CDCl₃ (7.27 ppm) and CDCl₃ (77.00 ppm) as references. Coupling constants (J) are reported in herz (Hz).

GC-MS was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a HP-5MS crosslinked 5% PhMe Siloxane column (30 m x 0.25mm x 0.25 µm film thickness) with a Hewlett-Packard 5971A mass selective detector using EI.

IR spectra were acquired on a Thermo Nicolet Avatar 330 FT-IR instrument. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected.

Microwave reactions were performed with a Smithcreator from Biotage, using Microwave Vial Kit 0.5-2 ml or 2-5 ml from Biotage, fitted with aluminium caps and septa. The heating time was recorded once the target temperature was reached.

Merck silica gel 60 (0.040-0.063 mm) was used for flash chromatography. Thin layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ (2.5x7.5 cm) from Merck.

A phase separator (Isolute SPE Accecories) was used for filtrations of reaction mixtures after run in a microwave reactor.

All reagents were purchased from commercial suppliers and used without further purifications.
8.2 Experimental procedures

5-Fluoro-1-(phenylsulfonyl)-1H-indole (1)

5-Fluoroindole (100.1 mg, 0.7407 mmol) was dissolved in THF (3 ml). Potassium tert-butoxide (207.6 mg, 1.845 mmol, 2.5 eq) and benzenesulfonyl chloride (0.2375 ml, 1.852 mmol, 2.5 eq) were added and stirred in RT over night (16 h). The reaction mixture was extracted in DCM/H$_2$O, the combined organic phases were washed with brine, dried over MgSO$_4$, filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH$_4$HCO$_3$ (pH 10) – CH$_3$CN), small column, to give the title compound as a yellow powder (111 mg, 54 %), mp 131-132°C (119-121ºC). MS m/z 276 (M+H)$^+$. IR (neat) 1477 (s), 1363 (s), 1172 (vs), 1116 (s) 634 (s) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.62 (dd, 1 H) 7.04 (td, $J$=9.0, 2.8 Hz, 1 H) 7.18 (dd, $J$=8.9, 2.3 Hz, 1 H) 7.42 – 7.48 (m, 2 H) 7.52 – 7.58 (m, 1 H) 7.60 (d, $J$=3.7 Hz, 1 H) 7.86 (dd, $J$=8.6, 1.2 Hz, 2 H) 7.94 (dd, $J$=9.0, 4.4 Hz, 1 H)

6-Fluoro-1-(phenylsulfonyl)-1H-indole (2)

6-Fluoroindole (57.5 mg, 0.426 mmol) was dissolved in THF (2 ml). Potassium tert-butoxide (71.5 mg, 0.637 mmol, 1.5 eq) and benzenesulfonyl chloride (0.0819 ml, 0.638 mmol, 1.5 eq) were added and the mixture was stirred in RT. After stirring for 3.5 h, there was still starting material left and additional potassium tert-butoxide (47.9 mg, 0.426 mmol, 1 eq) and benzenesulfonyl chloride (0.0548 ml, 0.426 mmol, 1 eq) were added. The reaction mixture was stirred in RT for another 20.5 h. The reaction was stopped even though it was not complete. The reaction mixture was extracted in DCM/H$_2$O, the combined organic phases were washed with brine, dried over MgSO$_4$, filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH$_4$HCO$_3$ (pH 10) – CH$_3$CN), small column, to give the title compound as a light-yellow powder (29 mg, 25 %), mp 105-106 ºC (101.3-101.4ºC). MS m/z 276 (M+H)$^+$. IR (neat) 1359 (s), 1203 (s), 1184 (s), 1171 (vs), 855 (s), 633 (s) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.61 (dd, $J$=3.7, 1.0 Hz, 1 H) 6.96 (td, $J$=9.0, 2.3 Hz, 1 H) 7.40 – 7.45 (m, 3 H) 7.51 – 7.55 (m, 2 H) 7.71 (dd, $J$=9.8, 2.4 Hz, 1 H) 7.85 (dd, $J$=8.4, 1.3 Hz, 2 H)

4-Nitrophenyl trifluoromethanesulfonate (3)

4-Nitrophenol (950.0 mg, 6.829 mmol) was dissolved in MeCN (20 ml). N-Phenyltrifluoromethanesulphonamide (2.927 g, 8.195 mmol, 1.2 eq), and triethylamine (1.9065 ml, 13.658 mmol, 2 eq) were added. The mixture was stirred in RT for 2 h, although it, according to LC-MS, would have been better to stop the reaction after 1 h. The reaction mixture was extracted in H$_2$O/DCM and the combined organic phases were dried over MgSO$_4$, filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH$_4$HCO$_3$ (pH 10) – CH$_3$CN), big column, to give the title compound as a light-brown powder (560 mg, 30 %), mp 56-58°C (52-56ºC). LC-MS m/z 272 (M+H)$^+$. GC-MS m/z 271. IR (neat) 1589 (s), 1485 (s), 1408 (s), 1250 (vs), 1174 (vs), 889 (vs), 740 (s), 639 (s) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.46 – 7.48 (m, 1 H) 7.49 – 7.51 (m, 1 H) 8.34 – 8.37 (m, 1 H) 8.37 – 8.39 (m, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 117.2, 122.7, 126.2, 147.3, 153.2
**Ethyl 3-[(4-formylphenyl)thio]propanoate (4)**

3,4-Difluorobenzaldehyde (110.8 mg, 0.7886 mmol), cesium carbonate (380.6 mg, 1.18 mmol, 1.5 eq), ethyl 3-mercaptopropionate (0,1528 ml, 1.18 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirring bar were placed in a microwave tube (2 ml) and heated in a microwave reactor for 5 min at 80°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a colourless oil (179 mg, 88 %). MS m/z 257 (M+H)⁺. IR (neat) 1727 (s), 1692 (s), 1227 (s), 1097 (s), 746 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (t, J=7.1 Hz, 3 H) 2.66 (t, J=7.3 Hz, 2 H) 3.25 (t, J=7.3 Hz, 2 H) 4.14 (q, J=7.1 Hz, 2 H) 7.42 (d, J=9.6 Hz, 1 H) 7.50 (dd, J=9.6, 1.6 Hz, 1 H) 7.59 (dd, J=7.1 Hz, 1 H) 9.89 (d, 1 H).  

**Ethyl 3-[(4-nitrophenyl)thio]propanoate (5)**

1-Fluoro-4-nitrobenzene (102.9 mg, 0.7293 mmol), ethyl 3-mercaptopropionate (0.1413 ml, 1.094 mmol, 1.5 eq), cesium carbonate (358.4 mg, 1.100 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 90°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by flash chromatography (DCM/Petroleum spirit 40-60°C 60:40). The purification gave the title compound as a yellow-brown oily crust (102 mg, 55 %), mp 38.5-40°C. MS m/z 256 (M+H)⁺. IR (neat) 1724 (s), 1591 (s), 1499 (s), 1328 (vs), 1175 (s), 787 (s), 581 (m), 540 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.26 (t, J=7.1 Hz, 3 H) 2.70 (t, J=7.5 Hz, 2 H) 3.29 (t, J=7.5 Hz, 2 H) 4.17 (q, J=7.1 Hz, 2 H) 7.32 – 7.37 (m, 2 H) 8.12 (d, J=9.0 Hz, 2 H).  

**Ethyl 3-[(4-nitro-2-(trifluoromethyl)phenyl)thio]propanoate (6)**

2-fluoro-4-nitro-1-(trifluoromethyl)benzene (106.3 mg, 0.5108 mmol), ethyl 3-mercaptopropionate (0.0985 ml, 0.7626 mmol, 1.5 eq), cesium carbonate (249.3 mg, 0.7651 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 70°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by flash chromatography (DCM/Petroleum Spirit 40-65°C 60:40). The purification gave the title compound as yellow oily needles (94 mg, 54 %), mp 43-46°C. MS m/z 324 (M+H)⁺. IR (neat) 1727 (s), 1578 (m) 1521 (s), 1280 (s), 787 (s), 581 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (t, J=7.2 Hz, 3 H) 2.70 (t, J=7.3 Hz, 2 H) 3.29 (t, J=7.3 Hz, 2 H) 4.15 (q, J=7.1 Hz, 2 H) 7.32 – 7.37 (m, 2 H) 8.45 (d, J=2.4 Hz, 1 H).  

**Ethyl 3-[(5-chloro-2-formylphenyl)thio]propanoate (7)**

4-Chloro-2-fluorobenzaldehyde (99.1 mg, 0.625 mmol), ethyl 3-mercaptopropionate (0.0807 ml, 0.625 mmol, 1 eq), cesium carbonate (245.1 mg, 0.7523 mmol, 1.2 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 90°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a yellow oil (84 mg, 50 %). MS m/z 273 (M+H)⁺. IR (neat) 1728 (s), 1686 (s), 1576 (s), 1192 (s), 875 (s), 746 (m), 572 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.23 (t,
Nucleophilic aromatic substitutions using ethyl 3-mercaptopropionate as nucleophile. Scope and limitations.
Rositha Antonsson 2008-01-28

Ethyl 3-[(3-hydroxy-4-nitrophenyl)thio]propanoate (8)

5-Fluoro-2-nitrophenol (96.9 mg, 0.617 mmol), ethyl 3-mercaptopropionate (0.1248 ml, 0.9663 mmol, 1.5 eq), cesium carbonate (315.1 mg, 0.9671 mmol, 1.6 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 120°C. The reaction mixture was extracted with DCM/HCl (1M), the combined organic phases were dried over MgSO₄, filtrated and evaporated in vacuo. The crude product was purified by flash chromatography (Petroleum spirit 40-60°C/DCM 50:50). The purification gave the title compound as yellow-brown needles (82 mg, 49 %), mp 54-57°C. MS m/z 272 (M+H). IR (neat) 1719 (s), 1570 (s), 1358 (s), 1252 (s), 1183 (s), 664 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.27 (t, J=7.2 Hz, 3 H) 2.72 (t, J=7.2 Hz, 2 H) 3.27 (t, J=7.3 Hz, 2 H) 4.18 (q, J=7.2 Hz, 2 H) 6.79 (dd, J=9.0, 2.0 Hz, 1 H) 6.91 (d, J=2.0 Hz, 1 H) 7.96 (d, J=9.0 Hz, 1 H) 10.79 (s, 1 H)

Ethyl 3-[(3-chloro-2-formylphenyl)thio]propanoate (9)

2-Chloro-fluorobenzaldehyde (104.3 mg, 0.6597 mmol), ethyl 3-mercaptopropionate (0.1105 ml, 0.8576 mmol, 1.3 eq), cesium carbonate (279.5 mg, 0.8578 mmol, 1.3 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 80°C and for 10 min at 90°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by flash chromatography (DCM/Petroleum spirit 40-60°C 70:30). The purification gave the title compound as a yellow oil (87 mg, 45 %). MS m/z 273 (M+H). IR (neat) 1728 (s), 1683 (s), 1184 (s), 772 (s), 664 (m) cm⁻¹. LC-MS showed ≤5 % of m/z 257 (M+H), which could be substitution of chlorine instead of fluorine. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.25 (t, J=7.2 Hz, 3 H) 2.68 (t, J=7.6 Hz, 2 H) 3.18 (t, J=7.6 Hz, 2 H) 4.15 (q, J=7.2 Hz, 2 H) 7.20 (dd, J=7.9, 1.10 Hz, 1 H) 7.26 (d, J=8.1 Hz, 1 H) 7.38 (t, J=8.1 Hz, 1 H) 10.56 (s, 1 H)

Ethyl 3-[(4-formylphenyl)thio]propanoate (10)

4-Fluorobenzaldehyde (0.0864 ml, 0.806 mmol), ethyl 3-mercaptopropionate (0.1561 ml, 1.209 mmol, 1.5 eq), cesium carbonate (393.9 mg, 1.209 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirring bar were placed in a microwave tube (5 ml) and heated in a microwave reactor for 5 min at 90°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by flash chromatography (DCM/Petroleum spirit 40-60°C 70:30). The purification gave the title compound as a colourless oil (81 mg, 42 %). MS m/z 239 (M+H). IR (neat) 1728 (s), 1588 (s), 1212 (s), 1087 (s), 812 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.21 (t, J=7.1 Hz, 3 H) 2.65 (t, J=7.3 Hz, 2 H) 3.12 (t, J=7.3 Hz, 2 H) 4.12 (q, J=7.2 Hz, 2 H) 7.34 (d, J=8.1 Hz, 2 H) 7.73 (q, J=3.9 Hz, 1 H) 9.88 (s, 1 H)

Ethyl 3-[(2-bromo-4-formylphenyl)thio]propanoate (11)

3-Bromo-4-fluorobenzaldehyde (111.7 mg, 0.5502 mmol), cesium carbonate (270.4 mg, 0.8299 mmol, 1.5 eq), ethyl 3-mercaptopropionate (0.1066 ml, 0.8253 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml)
and heated in a microwave reactor for 10 min at 60°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a light yellow oil, (57 mg, 32 %). MS m/z 317/319 (M+H)⁺. IR (neat) 1730 (s), 1692 (m), 1371 (m), 1184 (s), 1101 (s), 1051 (s), 811 (m), 664 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 (t, J=7.2 Hz, 3 H) 2.75 (t, J=7.5 Hz, 2 H) 3.29 (t, J=7.6 Hz, 2 H) 4.19 (q, J=7.1 Hz, 2 H) 7.32 (d, J=8.1 Hz, 1 H) 7.77 (dd, J=8.1, 1.7 Hz, 1 H) 8.01 (d, J=1.7 Hz, 1 H) 9.88 (s, 1 H)

**Ethyl 3-[(4-cyanophenyl)thio]propanoate (12)**

4-Fluorobenzonitrile (100.4 mg, 0.8289 mmol), cesium carbonate (405.7 mg, 1.245 mmol, 1.5 eq), ethyl 3-mercaptopropionate (0.1606 ml, 1.243 mmol, 1.5 eq), MeCN (2ml) and a magnetic stirrer were placed in a microwave tube (2 ml). The mixture was heated in a microwave reactor for 5 min at 60°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN) to give the title compound as a white powder (54 mg, 28 %), mp 49-50°C. MS m/z 236 (M+H)⁺. IR (neat) 2216 (s), 1726 (s), 1605 (s), 1316 (s), 1244 (s, br), 1110 (s), 843 (s), 545 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.23 (t, J=7.1 Hz, 3 H) 2.64 (t, J=7.3 Hz, 2 H) 3.22 (t, J=7.3 Hz, 2 H) 4.13 (q, J=7.1 Hz, 2 H) 7.27 – 7.32 (m, 2 H) 7.49 – 7.53 (m, 2 H)

**Ethyl 3-[(2-fluoro-4-formylphenyl)thio]propanoate (13)**

4-Chloro-3-fluorobenzaldehyde (100.2 mg, 0.6319 mmol), ethyl 3-mercaptopropionate (0.1224 ml, 0.9479 mmol, 1.5 eq), cesium carbonate (311.2 mg, 0.9551 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 80°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a colourless oil (44 mg, 27 %). MS m/z 257 (M+H)⁺. IR (neat) 1727 (s), 1688 (vs), 1598 (s), 1227 (s), 1060 (s), 747 (s), 570 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.26 (t, J=7.2 Hz, 3 H) 2.68 (t, J=7.5 Hz, 2 H) 3.27 (t, J=7.3 Hz, 2 H) 4.16 (q, J=7.1 Hz, 2 H) 7.44 (d, J=7.1 Hz, 1 H) 7.52 (dd, J=9.6, 1.6 Hz, 1 H) 7.61 (dd, J=8.1, 1.7 Hz, 1 H) 9.91 (d, J=2.0 Hz, 1 H)

**Ethyl 3-[(2-formylphenyl)thio]propanoate (14)**

2-Fluorobenzaldehyde (50.5 mg, 0.837 mmol), ethyl 3-mercaptopropionate (0.1622 ml, 1.256 mmol, 1.5 eq), cesium carbonate (206.9 mg, 0.6350 mmol, 1.5 eq), MeCN (2ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 60°C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a light-yellow oil (45 mg, 23 %). MS m/z 239 (M+H)⁺. IR (neat) 1728 (s), 1690 (s), 1192 (s), 751 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.22 (t, J=7.1 Hz, 3 H) 2.63 (t, J=7.5 Hz, 2 H) 3.19 (t, J=7.5 Hz, 2 H) 4.12 (q, J=7.1 Hz, 2 H) 7.31 (t, J=7.2 Hz, 1 H) 7.44 (d, J=0.98 Hz, 1 H) 7.49 (dd, J=7.2, 1.6 Hz, 1 H) 7.82 (dd, J=7.7, 1.6 Hz, 1 H) 10.35 (s, 1 H)
Ethyl 3-[(4-formylphenyl)thio]propanoate (15)

4-Bromobenzaldehyde (102.3 mg, 0.5529 mmol), ethyl 3-mercaptopropionate (0.1071 ml, 0.8292 mmol, 1.5 eq), cesium carbonate (271.1 mg, 0.8321 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 60˚C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column to give the title compound as a colourless oil (14 mg, 11 %). MS m/z 239 (M+H)⁺. IR (neat) 1728 (s), 1694 (s), 1589 (s), 1212 (s), 1169 (s), 1087 (s), 836 (s), 812 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.28 (t, J=7.1 Hz, 3 H) 2.71 (t, J=7.5 Hz, 2 H) 3.30 (t, J=7.3 Hz, 2 H) 4.16 (d, J=6.1 Hz, 2 H) 7.40 (d, J=8.3 Hz, 2 H) 7.79 (d, J=8.6 Hz, 2 H) 9.94 (s, 1 H)

Ethyl 3-[(4-acetylphenyl)thio]propanoate (16)

4-Fluoroacetophenone (107.5mg, 0.7782 mmol), cesium carbonate (380.8mg, 1.17 mmol, 1.5 eq), ethyl 3-mercaptopropionate (0.1508 ml, 1.17 mmol, 1.5 eq), MeCN (2 ml), and a magnetic stirrer were placed in a microwave tube (2 ml). The mixture was heated in a microwave reactor for 5 min at 80˚C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a grey-white powder (20 mg, 10 %), mp 65-66˚C. MS m/z 253 (M+H)⁺. IR (neat) 1727 (vs), 1667 (vs), 1588 (s), 1270 (s), 817 (s), 625 (s) cm⁻¹. ¹H NMR (400 MHz, DCl₃) δ ppm 1.23 (t, J=7.2 Hz, 3 H) 2.54 (s, 3 H) 2.65 (t, J=7.3 Hz, 2 H) 3.23 (t, J=7.5 Hz, 2 H) 4.13 (d, J=7.3 Hz, 2 H) 7.30 (d, J=8.8 Hz, 2 H) 7.84 (d, J=8.6 Hz, 2 H)

Ethyl 3-[(4-formylphenyl)thio]propanoate (17)

4-Chlorobenzaldehyde (105.3 mg, 0.7491 mmol), ethyl 3-mercaptopropionate (0.1451 ml, 1.124 mmol, 1.5 eq), cesium carbonate (365.1 mg, 1.121 mmol, 1.5 eq), MeCN (2ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 60˚C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a colourless oil (17 mg, 9 %). MS m/z 239 (M+H)⁺. IR (neat) 1728 (s), 1693 (s), 1212 (s), 1087 (s), 812 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (t, J=7.1 Hz, 3 H) 2.67 (t, J=7.5 Hz, 2 H) 3.26 (t, J=7.3 Hz, 2 H) 4.14 (q, J=7.1 Hz, 2 H) 7.34 – 7.39 (m, 2 H) 7.72 – 7.78 (m, 2 H) 9.91 (s, 1 H)

Ethyl 3-[(4-nitrophenyl)thio]propanoate (18)

4-Nitrophenyl trifluoromethanesulfonate (3) (101.7 mg, 0.3750 mmol), ethyl 3-mercaptopropionate (0.0727 ml, 0.563 mmol, 1.5 eq), cesium carbonate (184.0mg, 0.5640 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 80˚C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a colourless oil (17 mg, 9 %). MS m/z 239 (M+H)⁺. IR (neat) 1728 (s), 1693 (s), 1212 (s), 1087 (m), 812 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (t, J=7.1 Hz, 3 H) 2.67 (t, J=7.5 Hz, 2 H) 3.26 (t, J=7.3 Hz, 2 H) 4.14 (q, J=7.1 Hz, 2 H) 7.34 – 7.39 (m, 2 H) 7.72 – 7.78 (m, 2 H) 9.91 (s, 1 H)

Ethyl 3-[(4-nitrophenyl)thio]propanoate (18)

4-Nitrophenyl trifluoromethanesulfonate (3) (101.7 mg, 0.3750 mmol), ethyl 3-mercaptopropionate (0.0727 ml, 0.563 mmol, 1.5 eq), cesium carbonate (184.0mg, 0.5640 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirrer were placed in a microwave tube (2 ml) and heated in a microwave reactor for 10 min at 80˚C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a colourless oil (17 mg, 9 %). MS m/z 239 (M+H)⁺. IR (neat) 1728 (s), 1693 (s), 1212 (s), 1087 (m), 812 (s), 697 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (t, J=7.1 Hz, 3 H) 2.67 (t, J=7.5 Hz, 2 H) 3.26 (t, J=7.3 Hz, 2 H) 4.14 (q, J=7.1 Hz, 2 H) 7.34 – 7.39 (m, 2 H) 7.72 – 7.78 (m, 2 H) 9.91 (s, 1 H)
to GC-MS the major product was m/z 266 while there was only 12.5% of m/z 255. According to $^1$H NMR, the product contained ~ 10% of ethyl 3-[(4-nitrophenyl)thio]propanoate if the major product was diethyl 3,3'-disulfanediyl-dipropanoate ($M_w$ 266). If the major product was ethyl 3-[(trifluoromethyl)sulfonyl]sulfanyl] propanoate ($M_w$ 266), then the yield of ethyl 3-[(4-nitrophenyl)thio]propanoate was ~ 12%. See appendix 4 for chemical structures.

**Ethyl 3-[(4-formylphenyl)thio]propanoate (19)**

4-Fluorobenzaldehyde (0.0864 ml, 0.806 mmol), ethyl 3-mercaptopropionate (0.1561 ml, 1.209 mmol, 1.5 eq), potassium carbonate (167.2 mg, 1.21 mmol, 1.5 eq), MeCN (2 ml) and a magnetic stirring bar were placed in a microwave tube (5 ml) and heated in a microwave reactor for 15 min at 120˚C. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (ACE C8, 0.1%TFA – CH3CN), small column, to give the title compound as a colourless oil (73 mg, 38%). MS m/z 239 (M+H)$^+$. IR (neat) 1728 (s), 1693 (s), 1588 (s), 1560 (s), 1213 (s), 1086 (s), 811 (s), 696 (m) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.24 (t, $J$=7.1 Hz, 3 H) 2.67 (t, $J$=7.5 Hz, 2 H) 3.24 (t, $J$=7.6 Hz, 2 H) 4.15 (q, $J$=7.2 Hz, 2 H) 7.27 (d, $J$=8.3 Hz, 1 H) 7.73 (dd, $J$=8.2, 1.8 Hz, 1 H) 9.79 (d, $J$=1.7 Hz, 1 H) 9.84 (s, 1 H)

**Ethyl 3-[(2-bromo-4-formylphenyl)thio]propanoate (20)**

3-Bromo-4-fluorobenzaldehyde (3.3785 g, 16.641 mmol) was dissolved in DMF (25 ml), and K$_2$CO$_3$ (3.4365 g, 24.962 mmol, 1.5 eq) was added. Ethyl 3-mercaptopropionate (2.3644 ml, 18.3053 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred for 2 h at 60˚C under N$_2$. The reaction mixture was cooled to RT and extracted in diethylether/H$_2$O, and the combined organic phases were washed with brine, dried over MgSO$_4$, filtered and evaporated in vacuo. The work-up gave the title compound as a white solid (4.618 g, 87%), mp 83-85 °C. MS m/z 318 (M+H)$^+$. IR (neat) 1731 (s), 1683 (s), 1375 (s), 1278 (s), 889 (s), 790 (s), 553 (s) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.24 (t, $J$=7.1 Hz, 3 H) 2.67 (t, $J$=7.3 Hz, 2 H) 3.26 (t, $J$=7.3 Hz, 2 H) 4.14 (q, $J$=7.1 Hz, 2 H) 7.36 (m, 2 H) 7.75 (m, 2 H) 9.91 (s, 1 H)

**Ethyl 3-[(2-fluoro-4-formylphenyl)thio]propanoate (21)**

3,4-Difluorobenzaldehyde (3.0032 g, 21.133 mmol) was dissolved in DMF (25 ml) and potassium carbonate (4.3835 g, 31.716 mmol, 1.5 eq) was added. Ethyl 3-mercaptopropionate (3.0025 ml, 23.246 mmol, 1.1 eq) was added dropwise to the reaction mixture and the solution was stirred for 2 h at 60˚C under N$_2$. The mixture was extracted in diethylether/H$_2$O and the combined organic phases were washed with brine, dried over MgSO$_4$, filtered and evaporated in vacuo. The work-up gave the title compound as a colourless oil (4.59 g, 85%). MS m/z 257 (M+H)$^+$. IR (neat) 1727 (s), 1689 (s), 1226 (s), 1060 (s), 814 (s), 745 (s), 570 (s) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.25 (t, 3 H) 2.68 (t, $J$=7.3 Hz, 2 H) 3.27 (t, $J$=7.3 Hz, 2 H) 4.16 (q,
J=7.1 Hz, 2 H) 7.44 (d, J=6.8 Hz, 1 H) 7.52 (dd, J=9.6, 1.6 Hz, 1 H) 7.61 (dd, J=7.8, 1.7 Hz, 1 H) 9.91 (d, J=2.0 Hz, 1 H)

**Ethyl 3-[[2-fluoro-4-(morpholin-4-ylmethyl)phenyl]thio]propanoate (22)**

Ethyl 3-[[2-fluoro-4-formylphenyl]thio]propanoate (4) (959.3 mg, 4.043 mmol) was dissolved in dichloroethane (DCE) (25 ml) and morpholine (495.2 mg, 5.684 mmol, 1.4 eq) and 1 drop of AcOH were added. The mixture was stirred in RT for 1 h. Sodium triacetoxyborohydride (1198.2 mg, 5.652 mmol, 1.4 eq) was added and the mixture was stirred in RT for 17 h. The reaction mixture was extracted in DCM /Na₂CO₃ (1 M, pH 10) and the combined organic phases are washed with brine, dried over MgSO₄, filtered and evaporated in vacuo. The crude product was dissolved in EtOH and evaporated in vacuo (x 2). The work-up gave the title compound as a light-yellow oil (1.1959 g, 76%). MS m/z 328 (M+H)+. GC-MS m/z 327. IR (neat) 1730 (vs), 1114 (s), 1008 (s), 863 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.16 (td, 3 H) 2.35 (d, J=2.7 Hz, 4 H) 2.50 (td, J=7.4, 3.1 Hz, 2 H) 3.04 (td, J=7.5, 3.2 Hz, 2 H) 3.37 (d, J=2.7 Hz, 2 H) 3.61 (d, J=3.9 Hz, 4 H) 4.04 (qd, J=7.1, 3.5 Hz, 2 H) 6.94 – 7.05 (m, 2 H) 7.25 (td, J=7.7, 2.9 Hz, 1 H)

**4-{3-Fluoro-4-[(3-methoxybenzyl)thio]benzyl}morpholine (23)**

Ethyl 3-[[2-fluoro-4-(morpholin-4-ylmethyl)phenyl]thio]propanoate (22) (168.7 mg, 0.5162 mmol), was dissolved in MeCN (3 ml), and sodium etoxide (70.1 mg, 1.031 mmol, 2 eq) was added. The mixture was stirred in RT for 0.5 h. 3-methoxybenzylbromide (207.20 mg, 1.0305 mmol, 2 eq) was added and the mixture was stirred at 40˚C for 3 h. The reaction mixture was extracted with DCM/H₂O and the combined organic phases were washed with brine, dried under MgSO₄, filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), big column, to give the title compound as a colourless oil (63 mg, 34 %). MS m/z 348 (M+H)+. IR (neat) 1296 (s), 1150 (vs), 1062 (m), 908 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.39 (t, J=4.6 Hz, 4 H) 3.41 (s, 2 H) 3.68 (t, J=9.3 Hz, 4 H) 3.72 (s, 3 H) 4.03 (s, 2 H) 6.74 (dd, J=1.0 Hz, 1 H) 6.82 (d, J=7.6 Hz, 1 H) 6.94 (dd, J=7.9, 1.59 Hz, 1 H) 7.05 (dd, J=10.4, 1.6 Hz, 1 H) 7.16 (dt, J=19.8, 7.8 Hz, 2 H)

**4-{3-Fluoro-4-[(3-methoxybenzyl)sulfinyl]benzyl}morpholine (24)**

4-{3-Fluoro-4-[(3-methoxybenzyl)thio]benzyl}morpholine (23) (44.80 mg, 0.1289 mmol) was dissolved in DCM (1 ml) and 1 drop of TFA was added. The solution was evaporated in vacuo so that a TFA-salt was formed, which was then added to a vigorously stirred mixture of Oxone (80.0 mg, 0.1289 mmol, 1 eq) and wet alumina 128.9 mg in DCM (2 ml). The wet alumina was prepared by adding H₂O (200 ml) to Al₂O₃ (1.00 g) in a Falcon tube (10 ml) and the mixture was shaken until a free flowing homogeneous powder was formed. The mixture was refluxed for 22.5 h, although it in hindsight looked like nothing had happened between 7 and 22.5 h, and a small amount of starting material was still left after 22.5 h reflux. The reaction was stopped and the reaction mixture was extracted in DCM/Na₂CO₃ (1 M, pH 10), and the combined organic phases were washed with brine, dried over MgSO₄, filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give the title compound as a yellow oil
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(8 mg, 17 %). MS m/z 364 (M+H). IR (neat) 1296 (s), 1152 (vs), 1065 (vs, br), 908 (s).

1H NMR (400 MHz, CDCl₃) δ ppm 2.43 (br. S., 4 H) 3.51 (br. S., 2 H) 3.67 – 3.77 (m, 7 H) 3.97 – 4.03 (d, 1 H) 4.18 – 4.23 (d, 1 H) 6.59 (s, 1 H) 6.68 (d, J=7.6 Hz, 1 H) 6.81 (dd, J=7.9, 2.3 Hz, 1 H) 7.11 – 7.24 (m, 3 H) 7.43 – 7.49 (m, 1 H)

4-[(2,2-Dimethoxyethyl)thio]-3-fluorobenzaldehyde (25)

Ethyl 3-[(2-fluoro-4-formylphenyl)thio]propanoate (4) (70.1 mg, 0.449 mmol, 1 eq) was dissolved in MeCN (2 ml) in a microwave tube (5 ml) and sodium etoxide (42.2 ml, 0.538 mmol, 1.2 eq) was added. The mixture was stirred in RT for 30 min. An orange-yellow precipitate appeared almost immediately. After 30 min, 50 % of the starting material still remained and additional sodium etoxide (0.0422 ml, 0.538 mmol, 1.2 eq) was added. After stirring additional 10 min at RT the reaction was complete. Bromoacetaldehyde dimethyl acetal (0.0636 ml, 0.538 mmol, 1.2 eq) was added and the mixture was heated in a microwave reactor for 5 min at 80˚C, for 5 min at 90˚C and so on up to 130˚C, by stepwise increasing the temperature with 10 degrees. After heating for 5 min at 130˚C no starting material remained. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₃CN), small column, to give a white snowflake-like oily semi solid (37 mg, 28 %). MS m/z 245 (M+H). IR (neat) 1690 (s), 1114 (vs), 1056 (vs) cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ ppm 3.20 (d, J=5.6 Hz, 2 H) 3.40 (s, 6 H) 4.59 (s, 1 H) 7.46 – 7.55 (m, 2 H) 7.58 – 7.64 (m, 1 H) 9.92 (d, J=2.0 Hz, 1 H)

3-Bromo-4-[(2,2-dimethoxyethyl)thio]benzaldehyde (26)

Ethyl 3-[(2-bromo-4-formylphenyl)thio]propanoate (20) (1.016 g, 3.2030 mmol) was dissolved in MeCN (40 ml) and potassium tert-butoxide (0.7189 g, 6.406 mmol, 2 eq) was added. The mixture was stirred in RT for 1.5 h. Bromoacetaldehyde dimethyl acetal (0.6496 g, 3.844 mmol, 1.2 eq) was added and the mixture was refluxed for 1 h. The reaction mixture was filtered and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₂CN), big column to give the title compound as a yellow solid (187 mg, 18 %). MS m/z 305/307 (M+H). IR (neat) 1630 (m), 1584 (s), 1188 (m), 1109 (s), 1056 (s), 829 (m), 701 (m) cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ ppm 3.20 (d, J=5.4 Hz, 2 H) 3.41 (s, 6 H) 4.63 (t, J=5.5 Hz, 1 H) 7.36 (d, J=8.3 Hz, 1 H) 7.74 (dd, J=8.3, 1.7 Hz, 1 H) 7.99 (d, J=1.7 Hz, 1 H) 9.87 (s, 1 H)

7-Bromo-1-benzothiophene-5-carbaldehyde (27)

3-Bromo-4-[(2,2-dimethoxyethyl)thio]benzaldehyde (26) (187.0 mg, 0.6127 mmol) was dissolved in PhCl (15 ml), and one teaspoon of polyphosphorous acid (PPA) was added. The mixture was refluxed for 4.5 h under vigorously stirring. The reaction mixture was extracted in DCM/Na₂CO₃ (1 M, pH 10) since a lot of product remained in the water phase when extracting with DCM/H₂O. The combined organic phases were washed with brine, and evaporated in vacuo. The crude product was purified by preparative HPLC (Xterra C18, 50 mM NH₄HCO₃ (pH 10) – CH₂CN), small column, to give the title compound as a light-yellow powder (15 mg, 10 %), mp 99-100˚C. MS m/z 341/343 (M+H). IR (neat) 1676 (vs), 1323 (s), 1243 (s), 1106 (s) 871 (s), 689 (vs) cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ ppm 7.56 – 7.67 (m, 2 H) 8.02 (s, 1 H) 8.25 (d, J=1.2 Hz, 1 H) 10.05 (s, 1 H)
References


4. www.umetrics.com


14. H. Matsuda; M. Torihara; Y. Tamai, Preparation of heterocyclic compounds by cyclization of aldehydes or acetals, WO 2002100850


10 Appendices

Appendix 1.

\( \sigma \)-value = The acid constant, \( K_a \), of benzoic acid with a substituent, \( R \), in meta or para position. There are no \( \sigma \)-values for ortho substituents since there is also a steric factor involved in that case. If there are more than one substituents the \( \sigma \)-values of the individual substituents are added.

\[
\begin{align*}
\text{O} & \quad \text{O}^- \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{O}
\end{align*}
\]

\( \sigma \)-values or meta and para substituents\(^\text{19} \)

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a. Dimethylformamide (DMF), acetonitrile (AcN)

b. Area-% LC-MS, UV₁₈₀-₃₀₅nm
Appendix 3.

Exp No 1-4, 9-11

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In all experiments MeCN was used as a solvent, the concentration was 0.2M and Cs₂CO₃ was used as base.

Area-% LC-MS, UV₁₈₀-₃₀₅nm

Exp No 5-8

σ = 0.42

σ = 0.66

Experimental set-up, Full factorial analysis, factors: time, temp and *p*-substituent*. 

---

*In all experiments MeCN was used as a solvent, the concentration was 0.2M and Cs₂CO₃ was used as base.

a Area-% LC-MS, UV₁₈₀-₃₀₅nm
Appendix 4.

$^1$H NMR, zoomed area 2.9-4.3 ppm, 4-{3-fluoro-4-[(3-ethoxybenzyl)thio]benzyl}morpholine (23)

$^1$H NMR, zoomed area 2.9-4.3 ppm, 4-{3-fluoro-4-[(3-ethoxybenzyl)sulfinyl]benzyl}morpholine (24)