Uncommon reaction in 4-formyl phenols – substitution of the formyl group

Eleana Lopušanskaja, Anne Paju and Margus Lopp*

Department of Chemistry and Biotechnology, School of Science, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia

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Abstract. 4-formyl phenols with electron donating groups in ortho-position react with active alkyl halides in three directions: Williamson reaction up to 48%, aromatic substitution of the formyl group up to 36%, and addition to the ortho-position with dearomatization of the ring up to 10%. The ratio of the products depends on the substituents in the benzene ring and the used alkali and additives.

Keywords: alkylation, phenolates, electrophilic substitution of formyl group, electrophilic addition to arenes, dearomatization.

INTRODUCTION

Chemistry of aromatic substitution is one of the most fundamental topics in organic chemistry, well documented on the basic textbook level and not even needing references. However, there are still some less studied, uncommon substitution pathways that need attention. Already at the beginning of the last century, substitution not only of hydrogen but also of the carboxylic and formyl groups in allyl phenol ethers was observed. The reaction is known to proceed according to the Claisen rearrangement mechanism at higher temperatures [1,2] (Scheme 1).

The present article is devoted to the direct aromatic substitution of the formyl group in p-formyl phenols substituted with donating groups in the reaction with active alkyl bromides at room temperature (RT).

Scheme 1. Claisen rearrangement of substituted allyl phenol ethers with carboxyl and formyl group substitution.

* Corresponding author, margus.lopp@taltech.ee
MATERIALS AND METHODS

**General procedure:** Phenol 1 (1 mmol) was added to the aqueous solution of alkali (1 mL) and the mixture was stirred for 15 min at 0 °C. Alkyl bromide 2 (1.2 mmol) was added, the reaction mixture was allowed to warm up to RT, and it was stirred for 3.5 h for bromide 2a and 24 h for bromide 2b. Water (5 mL) was added, pH was adjusted to ~7, and the mixture was extracted with EtOAc [3]. The combined organic layers were washed with brine and dried with drying filter or on MgSO₄. The products were obtained after solvent evaporation and flash chromatography on silica gel using petroleum ether/acetone mixture. The products were analysed by nuclear magnetic resonance (NMR).

RESULTS AND DISCUSSION

When alkylating 2-methoxy-4-formyl phenol 1a with prenyl bromide 2a using basic conditions at RT, we observed formation of three types of products: formyl substitution product 3a as a main product in 17% yield, ortho-substitution product 4a in 15% yield, and ethers 5a’Prenyl and 5a”Prenyl in 9% and 3% yield, respectively (Scheme 2; the NMR spectra of the compounds in Note 1).

In order to elucidate whether this is a Claisen-type rearrangement process, the phenol ethers 5a’Prenyl and 5a”Prenyl were subjected at RT to alkali solution for 3.5 h. No reaction was observed (Scheme 3).

To elucidate the matter, we performed a series of experiments with ortho-di-methoxy-substituted 4-formyl phenol 1b in NaOH and KOH solution with prenyl bromide 2a. The results are presented in Table 1. The NMR spectra of the products are presented in Note 2.

The results in Table 1 show that both reactions – O-alkylation and C-alkylation occurred. The ratio of C-alkylation and O-alkylation was almost equal – both yields were about 20%. A considerable amount of 1b remained unreacted; a part of it was transformed to minor products. The best O-alkylation and C-alkylation yields were achieved in KOH with 1.2 eq. of pyridine additive, both with 23% (Table 1, No. 2). Without pyridine additive, the C-alkylation occurred in a slightly lower yield and with only a small amount of ester 6b forming.

In order to broaden the scope of the alkylation reaction, the substituted 4-formyl phenols 1b and 1c were alkylated with benzyl bromide 2b. Typical experimental conditions are included in Note 4. The results are presented in Table 2. The NMR spectra of the products are presented in Note 3.

According to the results in Table 2, the three reactions – substitution of formyl group by benzyl group, benzyl ether formation, and ortho-addition of the benzyl group with dearomatization proceeded in parallel. With donating OCH₃ groups in the ring (substrate 1b), the ether

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Scheme 2. Substitutions in 2-methoxy-4-formyl phenol 1a with prenyl bromide 2a at basic conditions.

Scheme 3. No Claisen rearrangement reaction of phenol ethers 5a at our alkylation conditions.
formation is dominating, with only moderate formyl substitution (14–17%) and with minor amount of dearomatization product formation (6–8%), not depending on the used alkali and its concentration (Table 2, Nos 1–3). The most valuable results were obtained with the substrate 1c, affording in LiOH solution mostly the formyl-substituted product 3cBn (36%) and the addition product 7c (10%), while the ether formation (product 5cBn) was observed only in 15% yield. This result may give a way to obtain quaternary substituted cyclohexanone derivatives.

In order to clarify the necessity of phenolate anion in the reaction, we checked separately the reaction of prenyl bromide 2a with substituted 4-formyl phenols 1 with benzyl bromide 2b

Table 1. Alkylation of 2,6-dimethoxy-4-formyl phenol 1b with prenyl bromide 2a in NaOH and KOH solution

<table>
<thead>
<tr>
<th>No.</th>
<th>Base 1N 1 eq.</th>
<th>Additive</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>O-alkylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5b*Preynl</td>
</tr>
<tr>
<td>1</td>
<td>NaOH</td>
<td>Py* 1,2 eq.</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>Py 1 eq.</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>KOH</td>
<td>– 1 eq.</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>NaOH</td>
<td>CaCO3 1 eq.</td>
<td>8</td>
</tr>
</tbody>
</table>

*Py – pyridine

Table 2. Alkylation of substituted 4-formyl phenols 1 with benzyl bromide 2b

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituted 4-formyl phenol; 1 R</th>
<th>Base; Equiv.</th>
<th>Additive</th>
<th>2b Equiv.</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1b; OCH3</td>
<td>1N NaOH; 1</td>
<td>NaHCO3 1.5</td>
<td>3bBn; 5bBn; 7b</td>
<td>15 37 6</td>
</tr>
<tr>
<td>2</td>
<td>1b; OCH3</td>
<td>1N LiOH; 1</td>
<td>– 1.2</td>
<td>3bBn; 5bBn; 7b</td>
<td>14 40 7</td>
</tr>
<tr>
<td>3</td>
<td>1b; OCH3</td>
<td>0.5N LiOH; 1</td>
<td>– 1.2</td>
<td>3bBn; 5bBn; 7b</td>
<td>17 48 8</td>
</tr>
<tr>
<td>4</td>
<td>1c; CH3</td>
<td>0.6N LiOH; 1.2</td>
<td>– 1.5</td>
<td>3cBn; 5cBn; 7c</td>
<td>36 15 10</td>
</tr>
</tbody>
</table>
bromide 2a with phenyl ether 8 and did not observe any reaction at ordinary reaction conditions (Scheme 4).

The chemistry of the process may be rationalized as outlined in Scheme 5. Path I is a usual phenolate reaction with alkyl halides known as the Williamson reaction, which does not need any comment.

Path II is the addition reaction with dearomatization, observed and discussed earlier by us, with substituted phenolates, naphtholates and resorcinolates [4,5,6].

Path III leading to substitution of the formyl group includes two steps: addition of the alkyl group to p-position, followed by elimination of formic acid. The formation of phenyl formate 6b in situ from substituted phenol 3bPrenyl and formic acid that was observed in the case of 2,6-dimethoxy-4-formyl phenol 1b also support the presented scheme.

**CONCLUSION**

4-formyl-2,6-disubstituted phenolates react with alkyl halides in three pathways: Path I – Williamson ether formation, Path II – substitution of the p-formyl group by the alkyl group, and Path III – addition to the ortho-position with dearomatization of the ring. Depending on the substrate and conditions, Path I or Path II predominate. In some cases, the reactions have a preparative value.

**NOTES**

1. NMR spectra of the compounds: 3a: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.84 (d, $J = 8.5$ Hz, 1H), 6.71–6.66 (m, 2H), 5.49 (s, 1H), 5.32 (tdq, $J = 7.3, 2.9, 1.4$ Hz, 1H), 3.88 (s, 3H),
2. NMR spectra of the compounds: 

bPrenyl: 1H NMR (400 MHz, CDCl₃) δ 6.40 (s, 2H), 5.36 (s, 1H), 5.30 (dd, J = 7.2, 5.7, 2.9, 1.4 Hz, 1H), 3.87 (s, 6H), 3.27 (d, J = 7.2 Hz, 2H), 1.76 (q, J = 1.4 Hz, 3H), 1.74–1.70 (m, 3H); 13C NMR (101 MHz, CDCl₃) δ 147.1, 133.0, 132.9, 132.6, 123.5, 104.9, 56.4, 25.9, 18.0. 

bPrenyl: 1H NMR (400 MHz, CDCl₃) δ 9.86 (s, 1H), 7.11 (s, 2H), 5.53 (td, J = 7.1, 2.8, 1.4 Hz, 1H), 4.60 (dt, J = 7.3, 0.8 Hz, 2H), 3.91 (s, 6H), 1.73 (d, J = 1.4 Hz, 3H), 1.66 (d, J = 1.3 Hz, 3H); 13C NMR (101 MHz, CDCl₃) δ 191.3, 154.3, 142.7, 139.1, 131.9, 120.3, 69.8, 56.4, 26.0, 18.0. 

bPrenyl: 1H NMR (400 MHz, CDCl₃) δ 9.86 (s, 1H), 7.09 (s, 2H), 6.16 (dd, J = 17.6, 10.8 Hz, 1H), 5.12 (dd, J = 17.6, 1.1 Hz, 1H), 4.99 (dd, J = 10.8, 1.1 Hz, 1H), 3.86 (s, 6H), 1.48 (s, 6H). 

bPrenyl: 1H NMR (400 MHz, CDCl₃) δ 9.86 (s, 1H), 7.11 (s, 2H), 5.31 (td, J = 7.3, 3.0, 1.5 Hz, 1H), 3.82 (s, 6H), 3.36–3.29 (m, 2H), 1.77 (q, J = 1.3 Hz, 3H), 1.72 (d, J = 1.3 Hz, 3H); 13C NMR (101 MHz, CDCl₃) δ 159.4, 151.9, 141.1, 133.4, 125.8, 122.7, 104.9, 56.2, 34.9, 25.9, 18.0. 

3. NMR spectra of the compounds: 

bBn: 1H NMR (400 MHz, CDCl₃) δ 7.33–7.26 (m, 2H), 7.24–7.16 (m, 3H), 6.42 (s, 2H), 5.39 (s, 1H), 3.92 (s, 2H), 3.84 (s, 6H); 13C NMR (101 MHz, CDCl₃) δ 147.1, 141.4, 133.2, 132.2, 128.8, 128.6, 126.2, 105.8, 56.4, 41.2, 31c. 

bBn: 1H NMR (400 MHz, CDCl₃) δ 7.34–7.27 (m, 2H), 7.24–7.18 (m, 3H), 6.83 (s, 2H), 4.50 (s, 1H), 3.87 (s, 2H), 2.23 (s, 6H); 13C NMR (101 MHz, CDCl₃) δ 150.6, 141.9, 132.9, 129.2, 128.3, 128.5, 126.0, 123.1, 41.2, 16.0. 

bBn: 1H NMR (400 MHz, CDCl₃) δ 9.86 (s, 1H), 7.50–7.43 (m, 2H), 7.39–7.25 (m, 3H), 7.11 (s, 2H), 5.13 (s, 2H), 3.90 (s, 6H); 13C NMR (101 MHz, CDCl₃) δ 191.3, 154.1, 142.5, 137.3, 132.0, 128.6, 128.4, 128.2, 106.8, 75.2, 56.4, 3c. 

bBn: 1H NMR (400 MHz, CDCl₃) δ 9.90 (s, 1H), 7.60–7.57 (m, 2H), 7.50–7.34 (m, 5H), 4.88 (s, 2H), 2.35 (d, J = 0.7 Hz, 6H); 13C NMR (101 MHz, CDCl₃) δ 191.8, 161.3, 137.0, 132.5, 132.4, 130.9, 128.8, 128.4. 

Typical reaction conditions: the phenolate was generated by using LiOH or NaOH at 0 °C in water solution and the reaction was carried out at RT for 24 h.

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