Proceedings of the Estonian Academy of Sciences,
2024, **73**, 1, 1–5
https://doi.org/10.3176/proc.2024.1.01
Available online at www.eap.ee/proceedings

ORGANIC CHEMISTRY

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

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Received 8 June 2023, accepted 17 July 2023, available online 19 September 2023

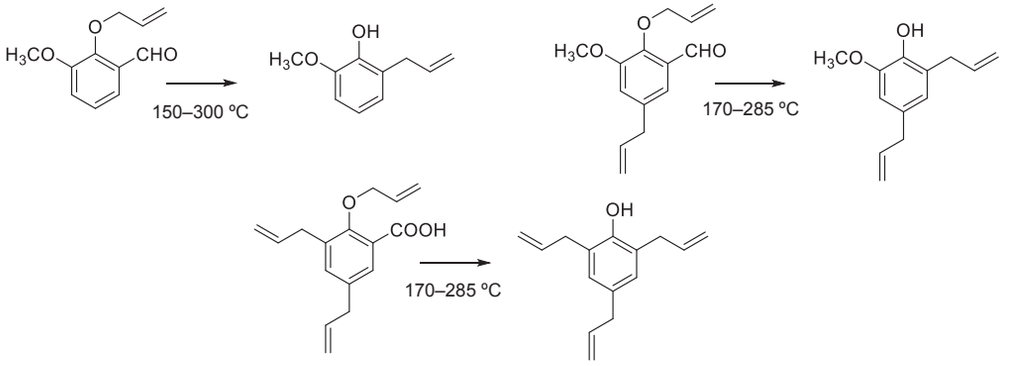
Abstract. 4-formyl phenols with electron donating groups in *ortho*-position react with active alkyl halides in three directions: Williamson reaction up to 48%, aromatic substitution of the formyl group up to 36%, and addition to the *ortho*-position with dearomatization of the ring up to 10%. The ratio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

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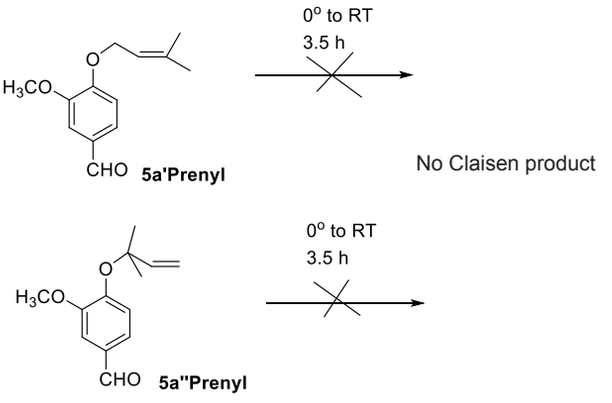
MATERIALS AND METHODS

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 $MgSO_4$. 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).



Scheme 3. No Claisen rearrangement reaction of phenol ethers **5a** at our alkylation conditions.

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).

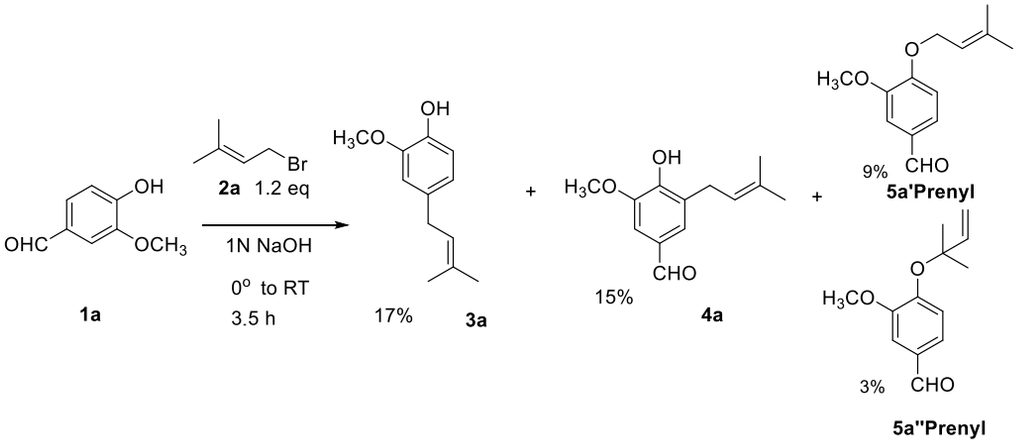
In order to elucidate whether this is a Claisen-type rearrangement process, the phenol ethers **5a'Prenyl** and **5a''Prenyl** were subjected at RT to alkali solution for 3.5 h. No reaction was observed (Scheme 3).

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.

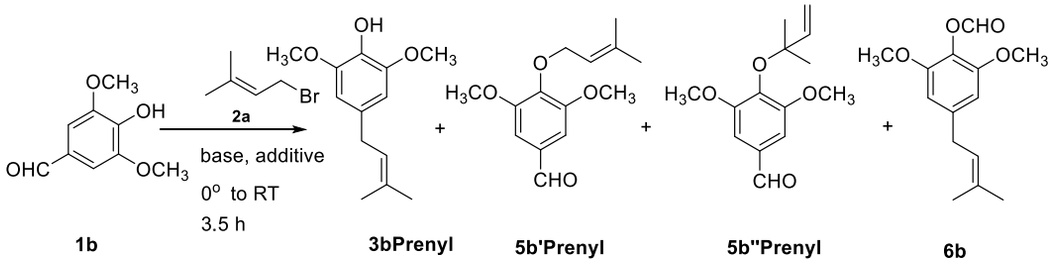
In order to broaden the scope of the alkylation reaction, the substituted 4-formyl phenols **1b** and **1c** were alkylated with benzyl bromide **2b**. Typical experimental conditions are included in Note 4. The results are presented in Table 2. The NMR spectra of the products are presented in Note 3.

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 OCH_3 groups in the ring (substrate **1b**), the ether



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

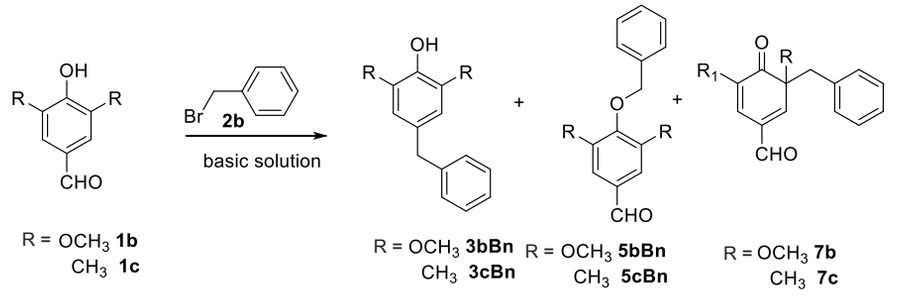
Table 1. Alkylation of 2,6-dimethoxy-4-formyl phenol **1b** with prenyl bromide **2a** in NaOH and KOH solution



No.	Base 1N 1 eq.	Additive	Products					
			O-alkylation			*C*-alkylation		
			5b'Prenyl %	**5b''Prenyl** %	Sum	**3bPrenyl** %	**6b** %	Sum
1	NaOH	Py* 1.2 eq	9	10	19	8	8	16
2	KOH	Py 1eq	11	12	22	9	14	23
3	KOH	–	9	6	15	19	1	20
4	NaOH	$CaCO_3$ 1 eq	8	11	19	18	–	18

* Py – pyridine

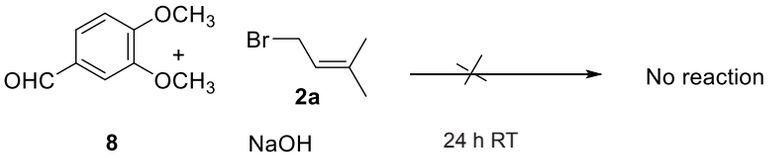
Table 2. Alkylation of substituted 4-formyl phenols **1** with benzyl bromide **2b**



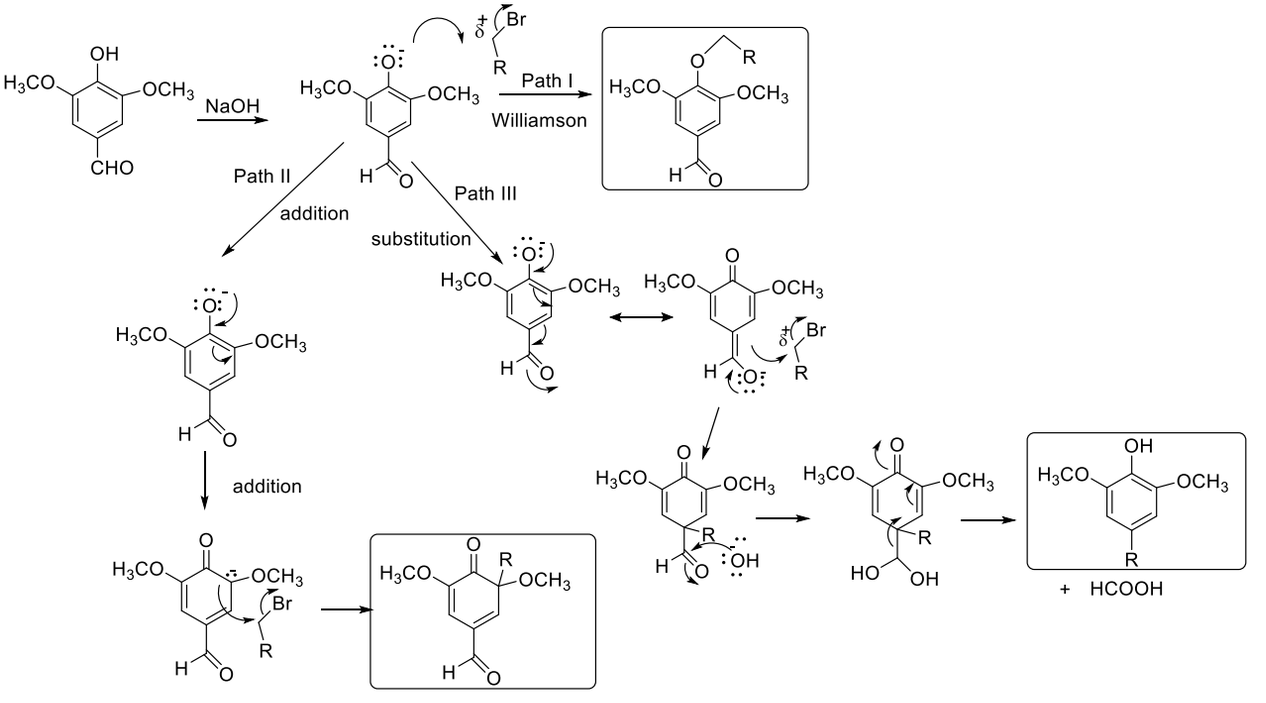
No	Substituted 4-formyl phenol; R	Base; Equiv.	Additive	**2b** Equiv.	Products			
					3; %	**5**; %	**7**; %	*C*-alkylation
1	**1b**; OCH_3	1N NaOH; 1	1N $NaHCO_3$	1.5	**3bBn**; 15	**5bBn**; 37	**7b**; 6	21
2	**1b**; OCH_3	1N LiOH; 1	–	1.2	**3bBn**;1 4	**5bBn**; 40	**7b**; 7	21
3	**1b**; OCH_3	0.5N LiOH; 1	–	1.2	**3bBn**; 17	**5bBn**; 48	**7b**; 8	25
4	**1c**; CH_3	0.6N LiOH; 1.2	–	1.5	**3cBn**; 36	**5cBn**; 15	**7c**; 10	46

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



Scheme 4. No reaction of 2-methoxy-4-formyl phenol with prenyl bromide.



Scheme 5. The possible chemical mechanism of alkylation of substituted 4-formyl phenols with alkyl halides.

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, naptholates 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),

3.29 (d, J = 7.3 Hz, 2H), 1.78–1.72 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 143.7, 133.9, 132.4, 123.7, 120.9, 114.3, 111.0, 56.0, 34.1, 25.9, 17.9. **4a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.31–7.27 (m, 2H), 6.33 (s, 1H), 5.33 (tdq, J = 7.3, 2.9, 1.4 Hz, 1H), 3.94 (s, 3H), 3.39 (d, J = 7.3 Hz, 2H), 1.77–1.71 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 149.5, 147.0, 133.8, 129.1, 127.8, 127.7, 121.3, 106.9, 56.3, 27.9, 25.9, 17.9. **5a':** ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.46–7.37 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 5.50 (tdq, J = 7.0, 2.8, 1.4 Hz, 1H), 4.66 (d, J = 6.7 Hz, 2H), 3.91 (s, 3H), 1.81–1.74 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 154.0, 150.0, 138.8, 130.0, 126.9, 119.0, 111.7, 109.1, 66.0, 56.1, 26.0, 18.4. **5a'':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.39 (d, J = 1.9 Hz, 1H), 7.31 (dd, J = 8.2, 2.0 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 6.15 (dd, J = 17.6, 10.9 Hz, 1H), 5.26–5.13 (m, 2H), 3.88 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 152.5, 151.7, 143.7, 130.9, 125.5, 119.9, 114.2, 109.9, 81.8, 56.0, 27.0.

2. NMR spectra of the compounds: **3bPrenyl**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 2H), 5.36 (s, 1H), 5.30 (dddt, 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); ^{13}C NMR (101 MHz, CDCl3) δ 147.1, 133.0, 132.9, 132.6, 123.5, 104.9, 56.4, 34.6, 25.9, 18.0. **5b'Prenyl**: ^{1}H NMR (400 MHz, CDCl3) δ 9.86 (s, 1H), 7.11 (s, 2H), 5.53 (tdq, 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); ^{13}C NMR (101 MHz, CDCl3) δ 191.3, 154.3, 142.7, 139.1, 131.9, 120.3, 106.8, 69.8, 56.4, 26.0, 18.0. **5b''Prenyl**: ^{1}H 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). **6bPrenyl**: ^{1}H NMR (400 MHz, CDCl3) δ 8.24 (s, 1H), 6.44 (s, 2H), 5.31 (tdq, 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); ^{13}C 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: **3bBn:** ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 141.4, 133.2, 132.2, 128.8, 128.6, 126.2, 105.8, 56.4, 42.1. **3c:** ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 141.9, 132.9, 129.2, 128.9, 128.5, 126.0, 123.1, 41.2, 16.0. **5bBn:** ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 154.1, 142.5, 137.3, 132.0, 128.6, 128.4, 128.2, 106.8, 75.2, 56.4. **5c:** ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 161.3, 137.0, 132.5, 132.4, 130.9, 128.8, 128.4, 128.0, 74.3, 16.7. **7b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.21 (dd, J = 4.9, 1.9 Hz, 3H), 7.12–7.07 (m, 2H), 6.70 (d, J = 1.7 Hz, 1H), 6.31 (d, J = 1.7 Hz, 1H), 3.68 (s, 3H), 3.20 (s, 3H), 3.07 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 189.1, 153.1, 148.9, 137.1, 133.5, 130.5, 128.1, 127.6, 104.3, 85.5, 56.0, 55.2, 46.8. **7c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.17 (dd, J = 5.1, 1.9 Hz, 3H), 7.12 (dt, J = 3.0, 1.5 Hz, 1H), 7.02 (dd, J = 2.2, 0.8 Hz, 1H), 7.00–6.95 (m, 2H), 3.28 (d, J = 13.2 Hz, 1H), 2.89 (d, J = 13.2 Hz, 1H), 1.86 (dd, J = 1.6, 0.6 Hz, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7, 189.8, 159.2, 136.1, 135.2, 133.4, 131.5, 129.5, 128.2, 127.1, 52.3, 46.5, 24.3, 15.7.

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.

ACKNOWLEDGEMENTS

We thank the Estonian Ministry of Education and Research (grant Nos PRG657 and PRG1031), the Centre of Excellence in Molecular Cell Engineering (grant No. 2014-2020.4.01.15e0013) and the European Regional Development fund (grant No. 2014-2020.4.02.16-0050) for supporting this work. The publication costs of this article were partially covered by the Estonian Academy of Sciences.

REFERENCES

1. Claisen, L. and Eisleb, O. Über die umlagerung von phenolallyläthern in die isomeren allylphenole (On the rearrangement of phenol allyl ethers into the isomeric allyl phenols). *Justus Liebigs Ann. Chem*., 1913, **401**(1), 21–119. https://doi.org/10.1002/jlac.19134010103
2. Tarbell, D. S. The Claisen rearrangement. In *Organic Reactions*, **II**. John Wiley & Sons, New York, 1944, 1–48.
3. Damodar, K., Kim, J.-K. and Jun, J.-G. Synthesis and pharmacological properties of naturally occurring prenylated and pyranochalcones as potent anti-inflammatory agents. *Chin. Chem. Lett.*, 2016, **27**, 698–702. https://doi.org/10.1016/j.cclet.2016.01.043
4. Lopušanskaja, E., Kooli, A., Paju, A., Järving, I. and Lopp, M. Towards *orto*-selective electrophilic substitution/addition to phenolates in anhydrous solvents. *Tetrahedron*, 2021, **83**, 131935. https://doi.org/10.1016/j.tet.2021.131935
5. Kooli, A., Shalima T., Lopušanskaja E., Paju A. and Lopp M. Selective *C*-alkylation of substituted naphthols under non-aqueous conditions. *Tetrahedron*, 2021, **95**, 132278. https://doi.org/10.1016/j.tet.2021.132278
6. Lopušanskaja, E., Paju, A., Järving, I. and Lopp, M. A direct alkylation of resorcinols. *Synth. Commun.*, 2023, **53**, 1216–1226. https://doi.org/10.1080/00397911.2023.2214645