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Synthesis of 1,3-Dioxolanes from Substituted Benzaldehydes of the Vanillin Series

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Abstract—Condensation of substituted benzaldehydes of the vanillin series with propane-1,2-diol and 3-chloropropane-1,2-diol in boiling benzene in the presence of FIBAN K-1 sulfonated cation exchanger as catalyst gave the corresponding substituted 1,3-dioxolanes.

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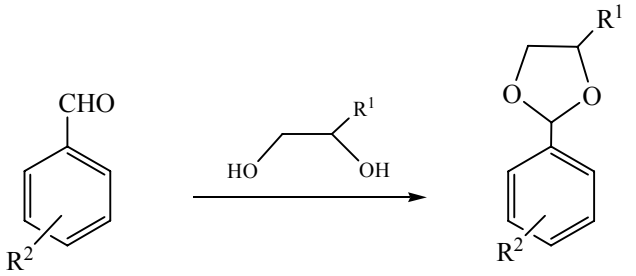
Vanillin and its closest homologs and analogs, such as *o*-vanillin, isovanillin, vanillal, anisaldehyde, and veratraldehyde, are convenient and accessible substrates for chemical modification and starting materials for the preparation of biologically active compounds with a broad spectrum of practical uses [1–5]. We previously reported on the synthesis of substituted 1,3-dioxolanes that are derivatives of propane-1,2-diol [6]. Some 1,3-dioxolane derivatives were found to exhibit strong biological activity [7–9].



I **IIa, IIb** **IIIa–IIIq, IVa–IVm**

II, R^1 = Me (**a**), $ClCH_2$ (**b**); **III**, R^1 = Me, R^2 = 2-HO-3-MeO (**a**), 3-HO-4-MeO (**b**), 3-AcO-4-MeO (**c**), 3,4-$(MeO)_2$ (**d**), 3-MeO-4-Me$(CH_2)_8$COO (**e**), 3-MeO-4-Me$(CH_2)_{11}$COO (**f**), 3-MeO-4-Me$(CH_2)_{16}$COO (**g**), 3-MeO-4-PhCOO (**h**), 3-MeO-4-(2,4-$Cl_2C_6H_3$COO) (**i**), 3-MeO-4-(3-$O_2NC_6H_4$COO) (**j**), 3,4-$(MeO)_2$-5-Br (**k**); 3-EtO-4-MeO (**l**), 3-EtO-4-(4-MeC_6H_4COO) (**m**), 4-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**n**), 4-methoxy-3-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**o**), 3-methoxy-4-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**p**), 3-ethoxy-4-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**q**); **IV**, R^1 = $ClCH_2$, R^2 = H (**a**), 3-HO-4-MeO (**b**), 3-AcO-4-MeO (**c**), 3-MeO-4-HO (**d**), 3,4-$(MeO)_2$ (**e**), 3-MeO-4-AcO (**f**), 3-MeO-4-(2,4-$Cl_2C_6H_3$COO) (**g**), 3,4-$(MeO)_2$-5-Br (**h**), 3-EtO-4-MeO (**i**), 4-(4,5-dichloro-1,2-tjiazol-3-ylcarbonyloxy) (**j**), 4-methoxy-3-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**k**), 3-methoxy-4-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**l**), 3-ethoxy-4-(4,5-dichloro-1,2-thiazol-3-ylcarbonyloxy) (**m**).

In the present article we describe a preparative procedure for the synthesis of new substituted 1,3-dioxolanes **IIIa**–**IIIq** and **IVa**–**IVm**, including those containing a 4,5-dichloroisothiazole fragment (compounds **IIIn**–**IIIq** and **IVj**–**IVm**). The procedure is based on the condensation of substituted benzaldehydes **I** of the vanillin series with propane-1,2-diol (**IIa**) or 3-chloropropane-1,2-diol (**IIb**) in boiling benzene in the presence of FIBAN K-1 sulfonated cation exchanger as catalyst [6, 10]. Water liberated

Yields, densities and refractive indices or melting points, elemental analyses, and molecular weights of substituted 1,3-dioxolanes **IIIa**–**IIIq** and **IVa**–**IVm**

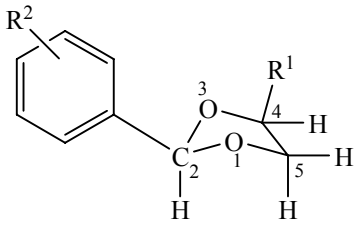
Comp. no.	Yield, %	d_{20}^{20}	n_D^{20}	Found, %		Formula	Calculated, %		*M*	
		mp, °C		C	H		C	H	found	calculated
IIIa	86	1.0567	1.5368	63.12	6.79	$C_{11}H_{14}O_4$	62.85	6.71	202	210
IIIb	88	1.2598	1.5320	63.10	6.85	$C_{11}H_{14}O_4$	62.85	6.71	204	210
IIIc	90	1.2501	1.5162	62.28	6.46	$C_{13}H_{16}O_5$	61.90	6.39	243	252
IIId	92	1.1442	1.5302	64.56	7.34	$C_{12}H_{16}O_4$	64.27	7.19	209	224
IIIe	84	1.1429	1.4912	69.71	9.02	$C_{21}H_{32}O_5$	69.20	8.85	354	364
IIIf	80	1.0633	1.4908	71.19	9.48	$C_{24}H_{38}O_5$	70.90	9.42	397	406
IIIg	82	33–34		73.46	10.27	$C_{29}H_{48}O_5$	73.07	10.15	462	477
IIIh	84	83–84		69.12	5.90	$C_{18}H_{18}O_5$	68.78	5.77	304	314
IIIi[a]	91	1.3622	1.5672	56.80	4.39	$C_{18}H_{16}Cl_2O_5$	56.41	4.21	372	383
IIIj[b]	92	1.3411	1.5574	60.37	4.93	$C_{18}H_{17}NO_7$	60.17	4.77	345	359
IIIk[c]	88	1.4549	1.5568	47.82	5.16	$C_{12}H_{15}BrO_4$	47.54	4.99	288	303
IIIl	90	32–33		65.76	7.68	$C_{13}H_{18}O_4$	65.53	7.61	230	238
IIIm	88	1.1253	1.5458	70.43	6.67	$C_{20}H_{22}O_5$	70.16	6.48	331	342
IIIn[d]	86	1.3625	1.5718	46.88	3.20	$C_{14}H_{11}Cl_2NO_4S$	46.68	3.08	348	360
IIIo[e]	86	1.3512	1.5728	46.85	3.54	$C_{15}H_{13}Cl_2NO_5S$	46.17	3.36	381	390
IIIp[f]	84	1.3540	1.5745	46.28	3.50	$C_{15}H_{13}Cl_2NO_5S$	46.17	3.36	377	390
IIIq[g]	86	1.3520	1.5708	47.90	3.91	$C_{16}H_{15}Cl_2NO_5S$	47.54	3.74	390	404
IVa[h]	88	1.3086	1.5312	60.84	5.67	$C_{10}H_{11}ClO_2$	60.46	5.58	192	199
IVb[i]	90	1.2325	1.5455	54.42	5.58	$C_{11}H_{13}ClO_4$	45.00	5.36	232	245
IVc[j]	92	1.2655	1.5270	54.73	5.39	$C_{13}H_{15}ClO_5$	54.46	5.27	278	287
IVd[k]	89	1.2149	1.5489	54.35	5.40	$C_{11}H_{13}ClO_4$	45.00	5.36	238	245
IVe[l]	89	1.2479	1.5462	55.94	6.05	$C_{12}H_{15}ClO_4$	55.71	5.84	244	259
IVf[m]	90	1.3266	1.5301	54.80	5.50	$C_{13}H_{15}ClO_5$	54.46	5.27	281	287
IVg[n]	86	1.3785	1.5649	52.13	3.78	$C_{18}H_{15}Cl_3O_5$	51.76	3.62	404	418
IVh[o]	87	1.5125	1.5622	42.97	4.38	$C_{12}H_{14}BrClO_4$	42.69	4.18	328	338
IVi[p]	85	1.2294	1.5372	57.20	6.36	$C_{13}H_{17}ClO_4$	57.25	6.28	260	273
IVj[q]	88	64–65		42.88	2.69	$C_{14}H_{10}Cl_3NO_4S$	42.61	2.55	387	395
IVk[r]	85	1.3638		43.02	3.06	$C_{15}H_{12}Cl_3NO_5S$	42.42	2.85	405	425
IVl[s]	85	88–89		42.67	2.94	$C_{15}H_{12}Cl_3NO_5S$	42.42	2.85	416	425
IVm[t]	86	1.3445		44.12	3.28	$C_{16}H_{14}Cl_3NO_5S$	43.80	3.22	422	439

[a] Found Cl, %: 18.11. Calculated Cl, %: 18.50. [b] Found N, %: 3.58. Calculated N, %: 3.90. [c] Found Br, %: 25.92. Calculated Br, %: 26.36. [d] Found, %: Cl 19.36; N 3.49; S 8.45. Calculated, %: Cl 19.68; N 3.89; S 8.90. [e] Found, %: Cl 17.90; N 3.22; S 7.89. Calculated, %: Cl 18.17; N 3.59; S 8.22. [f] Found, %: Cl 17.87; N 3.34; S 7.81. Calculated, %: Cl 18.17; N 3.59; S 8.22. [g] Found, %: Cl 17.09; N 3.00; S 7.35. Calculated, %: Cl 17.54; N 3.46; S 7.93. [h] Found Cl, %: 17.38. Calculated Cl, %: 17.85. [I] Found Cl, %: 14.15. Calculated Cl, %: 14.49. [j] Found Cl, %: 11.99. Calculated Cl, %: 12.37. [k] Found Cl, %: 14.08. Calculated Cl, %: 14.49. [l] Found Cl, %: 13.35. Calculated Cl, %: 13.70. [m] Found Cl, %: 12.06. Calculated Cl, %: 12.37. [n] Found Cl, %: 25.16. Calculated Cl, %: 25.46. [o] Found [Cl+Br], %: 33.87. Calculated [Cl+Br], %: 34.17. [p] Found Cl, %: 12.85. Calculated Cl, %: 13.00. [q] Found, %: Cl 26.58; N 3.18; S 7.66. Calculated, %: Cl 26.95; N 3.55; S 8.12. [r] Found, %: Cl 24.86; N 2.87; S 7.18. Calculated, %: Cl 25.04; N 3.30; S 7.55. [s] Found, %: Cl 24.77; N 2.82; S 6.97. Calculated, %: Cl 25.04; N 3.30; S 7.55. [t] Found, %: Cl 24.03; N 2.86; S 6.81. Calculated, %: Cl 24.24; N 3.19; S 7.31.

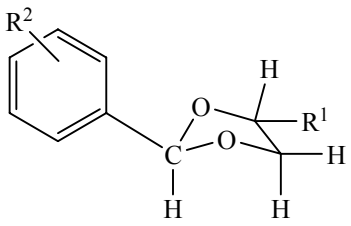
during the process was removed from the reaction mixture by azeotropic distillation using a Dean–Stark trap. The reaction time was 16–18 h, and the yields ranged from 80 to 92% (see table). The selected conditions allowed to completely avoid hydrolysis or alcoholysis of ester groups present in compounds **IIIc**, **IIIe**–**IIIj**, **IIIm**–**IIIq**, **IVc**, **IVf**, **IVg**, and **IVj**–**IVm**.

1,3-Dioxolanes **IIIa**–**IIIq** and **IVa**–**IVm** were isolated as colorless or slightly colored liquids or crystalline substances which contained no impurities of initial compounds and required no additional purification. Their structure was confirmed by elemental analysis, IR and ^{1}H NMR spectroscopy, and determination of their molecular weights by cryoscopy (see table).

The IR spectra of **IIIa**–**IIIq** and **IVa**–**IVm** contained the following absorption bands, ν, cm^{-1}: 3080–3000 and 870–720 ($C–H_{arom}$), 2970–2870 ($C–H_{aliph}$), 1765–1720 ($C=O_{ester}$), 1600±5 and 1510±5 ($C=C_{arom}$), and 1275–1008 cm^{-1} (C–O); no absorption band was observed at 1695–1680 cm^{-1}, i.e., in the frequency range typical of stretching vibrations of the carbonyl group in initial aldehydes.



(2*R*,4*S*)-2-Aryl-4-R^1-1,3-dioxolane



(2*R*,4*R*)-2-Aryl-4-R^1-1,3-dioxolane

As followed from the ^1H NMR spectra, the products were formed as mixtures of approximately equal amounts of (2*R*,4*S*)- and (2*R*,4*R*)-diastereoisomers. Signals from protons in the 1,3-dioxolane ring appeared as two singlets at δ (ppm) 5.40–6.10 (2-H) and multiplets at δ 3.90–4.55 (5-H) and 3.20–3.95 (4-H). Protons in the R^1 group gave rise to two doublets at δ 1.10–1.60 ($R^1 = CH_3$, **IIIa**–**IIIq**) or a multiplet at δ 3.95–4.20 ppm ($R^1 = CH_2Cl$, **IVa**–**IVm**). Aromatic protons resonated in the region δ 7.30–7.90 ppm; signals from protons in MeO (δ 3.70–3.90 ppm, s) and EtO groups (δ 0.85–1.40, t, and 3.60–4.40 ppm, q) were also present. In addition, 1,3-dioxolanes **IIIa**–**IIIq** and **IVa**–**IVm** displayed in the IR and ^1H NMR spectra absorption bands and proton signals corresponding to the ester fragments.

EXPERIMENTAL

The IR spectra were recorded from films or KBr pellets on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^1H NMR spectra were measured on a Tesla BS-587A instrument (100 MHz) from 5% solutions in chloroform-*d* using tetramethylsilane as internal reference. The molecular weights were determined by cryoscopy in benzene.

Substituted 1,3-dioxolanes IIIa–IIIq and IVa–IVm (*general procedure***).** A 100-ml one-neck round-bottom flask equipped with a Dean–Stark trap and a reflux condenser was charged with 0.01 mol of the corresponding substituted benzaldehyde **I**, 0.025 mol of propane-1,2-diol (**IIa**) or 3-chloropropane-1,2-diol (**IIb**), 0.2 g of FIBAN K-1 cation exchanger, and 75 ml of benzene. The mixture was heated for 16–18 h under reflux, the progress of the reaction being monitored by the amount of water separated in the Dean–Stark trap (about 0.2 ml). The catalyst was removed by filtration through a porous glass filter, the filtrate was washed with water to remove excess of propanediol **IIa** and **IIb** and with a saturated solution of sodium chloride, and the solvent was distilled off under reduced pressure. The residue was finally purified by column chromatography on silica gel (60–100 μm) using benzene as eluent.

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