Selective Synthesis of 4-Aryl-1,3-dioxanes from Arylalkenes and Paraformaldehyde using an Ion Exchange Resin as Catalyst; Extension to Natural Compounds

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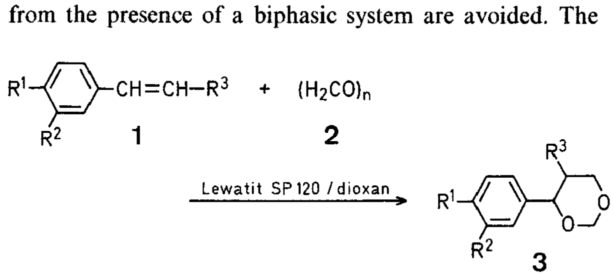
The Prins reaction – the condensation of an alkene with an aldehyde, generally formaldehyde – can lead to various products depending on the reaction conditions. Mineral acids are usually used as catalyst and the reaction proceeds with poor selectivity to give 1,3-dioxanes[1]. We have previously shown that the presence of a third solvent and the use of an ion exchange resin as catalyst in the reaction of styrene with aqueous formaldehyde leads to the highly selective formation of 4-phenyl-1,3-dioxane (quantitative yield)[2].

We now report on the use of paraformaldehyde and an ion exchange resin as catalyst in the Prins reaction. Advantages of this modification are that an aqueous solution is not necessary and the many difficulties arising at various stages from the presence of a biphasic system are avoided. The reaction between an arylalkene **1** and paraformaldehyde (**2**) in an organic solvent is shown in the scheme.



We present here results obtained under optimized conditions. The reaction leading to **3** as the sole product is rapid in a solvent such as dioxane with the acidic form of the macroporous cation exchange resin Lewatit SP 120 as catalyst. In the case of styrene itself the reaction time is reduced to 6 h as compared to 12 h when using aqueous formaldehyde. The reactivity of styrene derivatives of natural origin is especially noteworthy; they undergo quantitative transformation within 1–2 h under these conditions. The case of anethole[4] appears to be most significant (0.5 h) under these easy and soft conditions.

The reactants are used in stoichiometric amounts in contrast to some of the literature reports. The progress of the highly selective reaction can be conveniently followed by G.L.C. analysis. As soon as the styrene is consumed the corresponding product **3** can be obtained in a good degree of purity by filtration of the resin and evaporation of the solvent. The resins can also be effectively used in reactions with aqueous formaldehyde on account of their permanent porosity[3,5,6].

The catalytic activity of the resin remains unchanged after the reaction and the resins can be reused many times without regeneration. However, the water content of the resin must be carefully controlled and should not exceed 500 mg of water per gram of resin otherwise the yield decreases. A limitation of the method is shown in the reaction with nitrostyrene, i.e. when the double bond is strongly deactivated.

The substituted 1,3-dioxanes are an important class of compounds which find use in many branches of the chemical industry. The high yields, high selectivity, and easy experimental procedure favour its application to many differing substrates and for large scale preparations. Natural

Table. 4-Aryl-1,3-dioxanes **3a–j** prepared

Product	R¹	R²	R³	Reaction time [h]	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. m.p. or b.p./torr	¹H-N.M.R. (CDCl₃)[c] δ (O–CH₂–O) [ppm]		
								$\delta_{H eq}$	$\delta_{H ax}$	$J_{H eq, H ax}$
3a	H	H	H	5	91[d]	76°/1	95°/2[7]	5.17	4.80	6.25 Hz
3b	F	H	H	5	94	95°/1	$C_{10}H_{11}FO_2$ (182.2)	5.19	4.83	6.0 Hz
3c	Cl	H	H	5	83	102°/1	$C_{10}H_{11}ClO_2$ (198.6)	5.17	4.80	6.25 Hz
3d	Br	H	H	5	78	67°	$C_{10}H_{11}BrO_2$ (243.1)	5.18	4.82	6.25 Hz
3e	O_2N	H	H	5	15	85°	86°[8]	5.18	4.81	6.25 Hz
3f[e]	H	H	CH_3	5	95	80°/1	82–84°/1.1[9]	5.18	4.77	6.25 Hz
3g[e]	H_3CO	H	CH_3	0.5	97[f]	130°/0.5	142–144°/0.7[4]	5.16	4.80	6.25 Hz
3h[e]	HO	H_3CO	CH_3	2	94	145°/0.5	$C_{12}H_{16}O_4$ (224.3)	5.16	4.80	6.25 Hz
3i[e]	O–CH₂–O		CH_3	1	97	138°/0.5	$C_{12}H_{14}O_4$ (222.3)	5.15	4.78	6.25 Hz
3j[g]	H_3CO	H	n-C_3H_7	2	98	140°/0.5	$C_{14}H_{18}O_3$ (234.3)	5.17	4.78	6.25 Hz

[a] Yields estimated by G.L.C. using a non-polar column (Varian 101) with xylene as internal reference and corrected after separation of pure products.

[b] The microanalyses of all products were in satisfactory agreement with the calculated values (C ±0.38, H ±0.13, halogen ±0.7, N ±0.35).

[c] The ¹H-N.M.R. spectra were in accord with proposed structures[3].

[d] The condensation of paraformaldehyde with styrene in the presence of sulfuric acid gave 78% of compound **3a** and 22% of by-products[7]. By comparison, the use of sulfuric acid instead of Lewatit SP 120 led us to obtain after 6 h of reaction 73% of **3a** together with tarry by-products.

[e] Commercially available.

[f] The use of sulfuric acid instead of Lewatit SP 120 led us to obtain after 6 h of reaction 61% of **3g** together with tarry by-products.

[g] Compound **3j** is synthesized by a modified Wittig reaction of anisole with butyltriphenylphosphonium bromide[3].

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compounds such as isoeugenol, isoafrole, anethole, etc. are particularly suitable as substrates and the products can be used as starting materials for further syntheses.

1,3-Dioxanes 3; General Procedure:

A 500 ml flask is fitted with a mechanical stirrer, a thermometer, and a reflux condenser. A mixture of the alkene **1** (0.1 mol), paraformaldehyde (**2**; 6 g, 0.2 mol of formaldehyde monomer), Lewatit SP 120, acidic form (10 g, containing 0.2 g water/g dried resin) in dioxane (100 ml) is charged into the flask. The mixture is heated at 60 °C for the time given in the Table. The resin is then filtered off, the solvent evaporated, and the residue redistilled in vacuum to give the dioxane **3** (Table).

Compound **3d** crystallizes at room temperature after evaporation of the solvent and is redissolved in hot ethanol and allowed to crystallize slowly at room temperature.

The water content of the ion exchange resin is determined by a Karl Fischer titration slightly modified for the lower water levels[10,11,12].

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