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An Environmentally Friendly Route for the Synthesis of Benzofurane Derivatives using Selective Ring Acylation of Resorcinol

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Abstract The synthesis of 2,2-dimethyl-2,3-dihydrobenzofuran-6-ol, an important intermediate for benzofurane derivatives having pharmaceutical activity, is achieved by an environmentally friendly pathway. Whereas the current synthesis method, based on resorcinol dimethylether, uses or produces harmful, corrosive and dangerous reagents/materials, the procedure proposed here achieves 60% preparative yield for the selective direct ring acylation of resorcinol with isobutyryl chloride, using a solvent-free reaction catalysed by solid acids.

Keywords Clays · Acylation · Resorcinol · Solvent-free reaction · Benzofurane precursor

1 Introduction

One of the bases of the modern chemical technologies is to avoid the formation of hazardous effluents, instead of eliminating (usually by further chemical treatment) these effluents already arised. This principle is the base of our activity on new and environmentally friendly synthetic methods, e.g. for the preparation of dihydroxyphenyl ketones, which are important intermediates for drugs and perfumery.

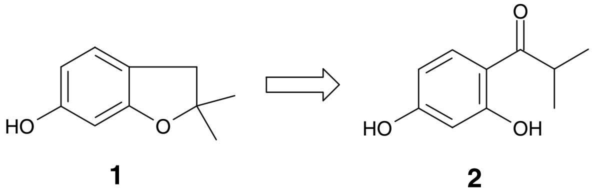
The environmentally friendly preparation of the key intermediate 1-(2,4-dihydroxyphenyl)-2-phenylethanone for the synthesis of Ipriflavone, an antiosteopenic drug, has been reported earlier [1]. In contrast with the classical reaction based on Lewis acids such as $AlCl_3$, the chemoselective Friedel-Crafts ring acylation of resorcinol with phenylacetyl chloride was achieved in solvent-free conditions, using a solid acid catalyst, and the method could be scaled up.

We present here the synthesis of the precursor **2** of 2,2-dimethyl-2,3-dihydro-benzofuran-6-ol (**1**) (Scheme 1), another important compound from pharmacological point of view, obtained by an environmentally friendly way, from resorcinol and isobutyryl chloride.

2 Strategy for an Environmentally Friendly Synthesis

2.1 Choice of the Synthesis Route

Benzofurane derivatives such as e.g. Carbofurane are important antioxidants and efficient pesticides. These compounds play a significant role also as essential constituents of 5-HT_1 antagonists (**3**) [2] (Scheme 2).



Scheme 1 Retrosynthetic route for benzofuranol from resorcinol

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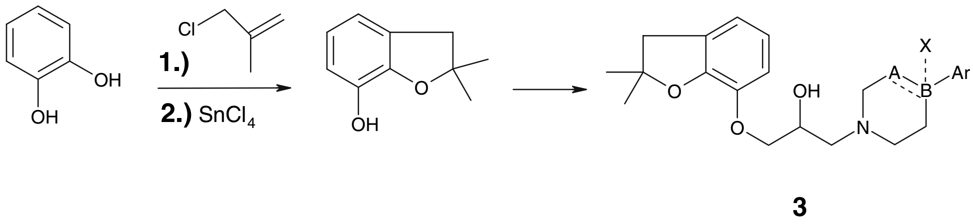
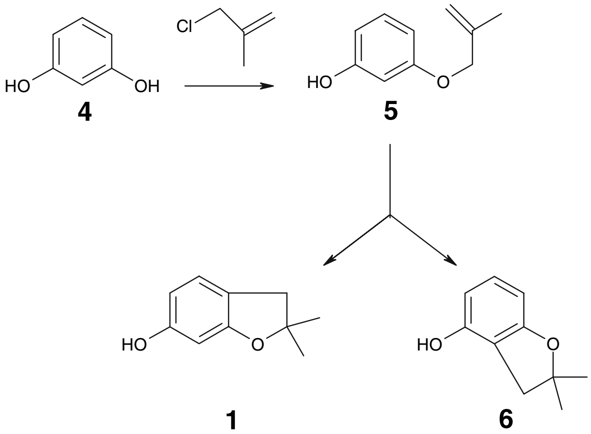
Scheme 2 Benzofurane derivatives having biological activity



The synthesis of the structural isomers of **3** was necessary for the elucidation of the relation between chemical structure and biological activity or selectivity. This purpose required the synthesis of the benzofuranol derivative **1**. According to literature data [3] the Lewis acid catalysed Claisen rearrangement of 3-methallyloxy-phenol (**5**) (Scheme 3) does yield the target compound **1** (by analogy with the Carbofurane synthesis [4] from 2-methallyloxy-phenol). However this reaction produces also an equimolar amount of isomer **6** which cannot be separated by the usual methods of recrystallization and distillation, but needs expensive and solvent consuming chromatography. Handling a great quantity of solvent (regeneration, eventual destruction by burning) brings up environmental problems.

The preparative method available nowadays for **1** is based on resorcinol dimethylether (**7**) (Scheme 4). **7** is acylated by isobutyryl chloride (**8**) in carbon disulfide or nitrobenzene as solvent, and the resulting **9** isobutyryl derivative is reduced with $NaBH_4$ to alcohol **10**. Boiling **10** with concentrated HBr the two methyl-groups are removed by hydrolysis, the OH-group is eliminated and the intermediate resorcinol derivative **11** is cyclized in the strongly acid medium, yielding the desired product **1**.

For industrial applications, the multistep process and the formation of 2 mol CH_3Br, the use of highly corrosive concentrated HBr, as well as the use of hazardous solvents such as carbon disulfide or nitrobenzene are drawbacks. Moreover CH_3Br is noxious for environment and responsible for the ozone hole.



Scheme 3 Claisen rearrangement of 3-methallyloxy-phenol

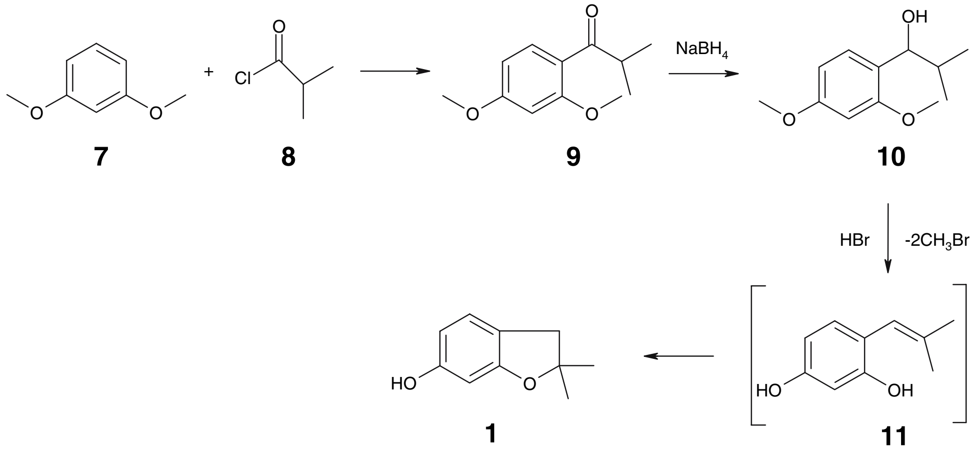
The direct *C*-acylation of resorcinol (**4**) with isobutyryl chloride using a solid acid catalyst is then interesting. Up to now this reaction has been performed only with classical Lewis acid such as $AlCl_3$, with moderate yield [5]. Another method for the synthesis of **2**, by-passing the use of nitrobenzene, is the acylation of resorcinol with isobutyric acid (in excess) instead of isobutyryl chloride, applying gaseous BF_3 as catalyst [6]. This method produces extremely dangerous HF at the decomposition of the Friedel-Crafts complex.

2.2 Acylation by Heterogeneous Catalysis

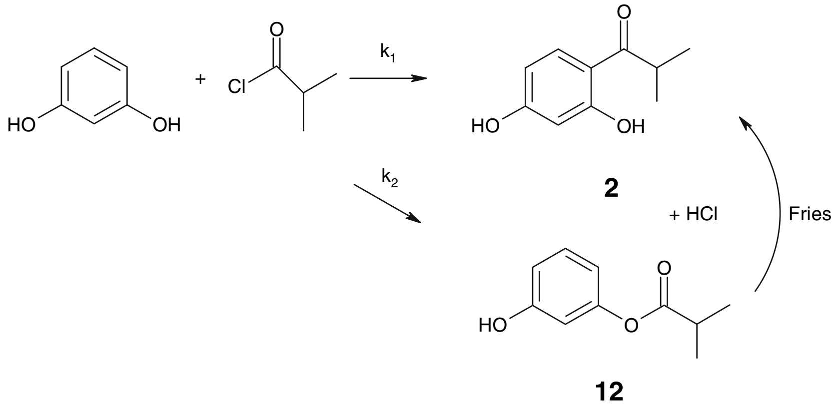
The direct *C*-acylation of phenol and naphthol derivatives has been reported for the preparation of 2-hydroxyphenyl or 2-hydroxynaphthyl ketone derivatives [7, 8], but the acylation of diphenols is much less documented. In the Friedel-Crafts ring acylation of diphenols with acid chlorides as commonly used acylating agents the classical Lewis acid catalysts are complexed by the phenol and then required in more than equimolar amount. The treatment of the aluminium residue induces environmental problems, and the drastic reaction conditions causes undesired side reactions. The substitution of these Lewis acids by solid ones would then significantly reduce the environmental pollution, and introduce some further advantages such as easier work-up of the reaction mixture and better safety due to lower corrosion.

One of the problems of selectivity in this reaction is the formation of ester (**12**) (Scheme 5). This ester has to be either separated or further isomerised to ketone by Fries rearrangement. The ring acylation of phenol has been reported in the literature using ZSM-5 [9–13] or BEA [14, 15] zeolite as catalyst, but the reaction of diphenols has been scarcely investigated. With bulky reactants, large pore solids are preferred and we report here the acylation of resorcinol on reducible transition metal cations deposited on a mesoporous support K10.

Another objective related to environment is the desire to work without solvent. The elimination of the solvent changes the kinetics of the reaction and may require a change of catalyst. For instance Sn^{2+}–K10, which was reported as good catalyst for the acylation of crown ethers by acetyl chloride



Scheme 4 Synthesis of benzofuranol **1** from resorcinol dimethylether



Scheme 5 Acylation of resorcinol by isobutyryl chloride

[16], was a poor one for the reaction of resorcinol with phenylacetyl chloride [1]. Therefore the choice of the cation is controlled by the reactivity of the substrates.

3 Experimental

The supports used were the K-series from Süd-Chemie including KSF, KSF/0, K0, KP10, K10 and KS. They were exchanged as described earlier [17] with Cu^{2+}, Fe^{3+}, Mn^{2+}, Sn^{2+}, Zn^{2+}. Cation exchange was performed by gradually adding the clay to a stirred solution of the cation at room temperature and stirring for 24 h. After exchange the suspensions were filtered and washed with deionized water to eliminate physisorbed salts. The resulting solids were dried on a thin bed at 373 K and ground. The exchanged K is the catalyst designated as Me^{n+}–K*x*.

The chemical composition was determined by ICP after dissolution of the solid. The compositions, textural properties and acidities are reported in Table 1. The acid properties were determined by adsorption of pyridine as probe molecule on self-supported wafers obtained by compressing the powders under 5 ton/cm^2. The determination of the Lewis/Brønsted ratio was carried out by integrating the surface area corresponding to the infrared lines at 1450 and 1545 cm^{-1}, normalized to the bands at 1920–1827 cm^{-1} relative to montmorillonite.

The standard reactions were performed in a glass flask equipped with a condenser. 10 mmol of resorcinol (or hydroquinone) were introduced in the reactor with 0.5 g catalyst freshly activated in air at 250 °C for 5 h. The mixture was heated to the reaction temperature, then 10 mmol of isobutyryl chloride was added at once. For the reaction with a solvent 1,2-dichloroethane was used and the concentration of reactants was fixed at 0.25 mol/L diphenol or acid chloride. The reaction temperature was 84 °C in the presence of solvent and 120 °C in solvent-free conditions.

The concentration of diphenol and products was determined as a function of time using HPLC (C18 reversed phase column, UV detection at 254 nm, eluent CH_3OH/H_2O = 35:65 v/v).

4 Results and Discussion

The K10 acid-activated clay supplied by Süd-Chemie has a cation exchange capacity (CEC) in the dry form equal to 0.55 mequiv/g [18]. The amount of cations fixed by the

Table 1 Characteristics of the catalysts used for acylation of diphenols

Catalyst	Textural characteristics		Analysis (wt.%)			Charge exchanged (mequiv/g)	Acidity	
	Specific surface area (m^2/g)	Mean pore diameter (Å)	Al	Fe	Exchanged cation		IR rel. intensity	
							Brønsted	Lewis
K10	229	56	7.71	1.99			0.33	0.29
KP10	169	71	6.87	1.49			0.34	0.06
Zn^{2+}–K10	213		7.50	1.94	1.19	0.36	0.16	0.73
Cu^{2+}–K10	236		7.79	2.04	1.24	0.39	0.13	0.68
Fe^{3+}–K10	239		7.54	2.92	0.93	0.54	0.35	0.34
Sn^{2+}–K10	240		6.84	1.61	10.1		0.27	0.45
Mn^{2+}–K10	254		7.7		0.9	0.33	0.36	1.0

clay, reported on Table 1, depends on several factors, including the tendency of the cations to hydrolyse at a neutral pH. While Zn^{2+}, Cu^{2+} or Mn^{2+} are retained by the clay in low amounts, corresponding to about 65% of the cationic exchange capacity, the amount of Fe^{3+} retained by the clay corresponds to the CEC and that of Sn^{2+} exceeds by far the exchange capacity. Indeed Sn^{2+}-salts hydrolyse easily and form polycations by intermolecular dehydration. Silico-aluminates show a higher selectivity for the exchange of cations of high charge, and this can account for the high amount of Sn retained by the clay.

The reaction yields two products, the ketone **2** formed by acylation of the ring and the ester **12** formed by *O*-acylation. In the presence of solvent the reactions are fast and reach about 70–80% conversion in less than 30 min at 84 °C, as illustrated in Fig. 1. After this time the conversion remains constant, which shows an inhibition of the reaction by the products. The selectivity into ester decreases as a function of time with an increase of the selectivity into ketone. Ion-exchanged catalysts therefore catalyse the Fries rearrangement of isobutyryl ester **12**, which was not observed in the case of the acylation of resorcinol by phenylacetyl chloride [1]. In the presence of solvent at 84 °C the ester content goes through a slight maximum, observed with both Fe and Sn clays. In solvent-free conditions at 120 °C, the pure ester could be partially transformed into ketone on Fe^{3+}–K10.

The comparison of different catalysts is reported in Fig. 2: K10 and KP10 alone show a measurable and comparable activity, but a low selectivity to ring acylation. Introducing Cu or Zn does not modify the product quantities. The addition of Fe, Mn or Sn induces changes mainly on selectivity: on K10, the yield in ketone **2** is increased by Fe addition, but decreased by Sn modification, which promotes the formation of ester **12**. This increase of ester production does not seem to be related to a change of acidity, in contrast to the results earlier reported on the acylation of crown ether by acetic anhydride [19] or the alkylation of toluene with benzyl alcohol [17]. By contrast the addition of Mn changes little the properties of K10 in diluted conditions.

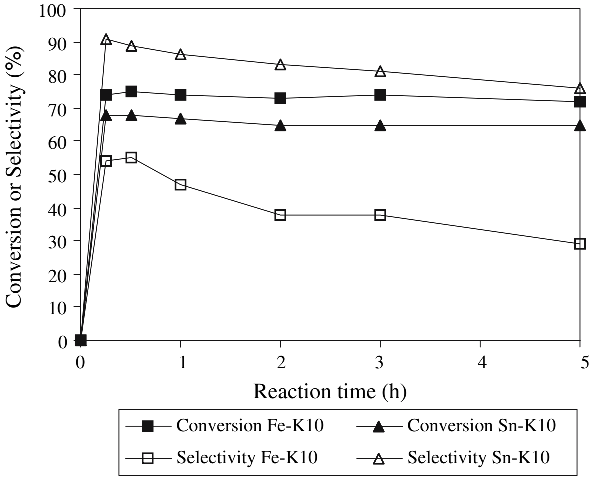


Fig. 1 Variations of conversion and ester selectivities as a function of time for Sn^{2+}–K10 and Fe^{3+}–K10

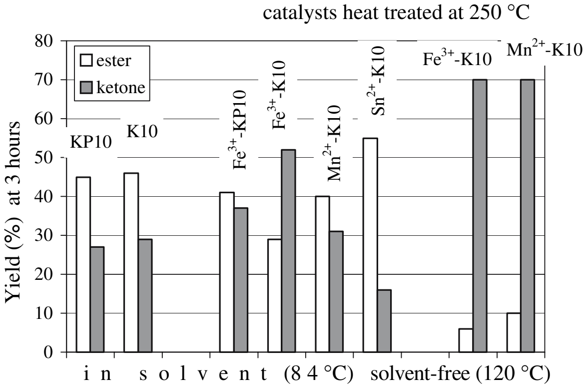


Fig. 2 Comparison of the yields for the acylation of resorcinol after 3 h of pure supports with exchanged clays

In the absence of solvent, the reaction is mainly oriented towards the formation of ketone, and ester formation is decreased on both Fe^{3+}–K10 and Mn^{2+}–K10. The two reactions then show a different order relative to the reactant concentration.

The solvent-free reaction was scaled up at the 0.1 mol level with Fe^{3+}–K10 or Mn^{2+}–K10 catalyst. A good reproduction was achieved with 65% ketone yield (HPLC). After separation of the ketone from the ester and from the non reacted resorcinol, a 60% preparative yield was obtained, and the catalysts could be reused with an efficiency level of 85% after washing with 1,2-dichloroethane and drying.

An attempt was made to extend the reaction to hydroquinone, with little success due to the sensitivity of the substrate to oxidation. A by pass could be to acylate the dimethyl ether: the yield reaches 18% in ketone in a solvent-free reaction at 120 °C.

It is noteworthy that Mn^{2+}–K10, containing as Fe^{3+}–K10 a variable valency cation and never used before in a similar Friedel-Crafts reaction, shows the same outstanding efficiency. Accordingly the mechanism suggested for the reaction of isobutyryl chloride on resorcinol involves the formation of an acyl cation by oxidation of the chloride as proposed earlier [16, 20]. This mechanism agrees with the results reported for acylations and alkylations catalysed by indium, gallium and thallium oxides or chlorides supported on alumina and zeolites [21–23]. It can be pointed out that a selectivity for ketone **2** [ketone/(ketone + ester)] as high as 92% can then be reached by heterogeneous catalysis.

As a practical result, the elaborated and scaled up new acylation procedure is as follows.

To the well stirred melt of 11.0 g (0.1 mol) resorcinol and 5 g freshly activated Fe^{3+}–K10 (or Mn^{2+}–K10) catalyst at 120 °C 10.65 g (0.1 mol) isobutyryl chloride is added at once. The mixture is stirred for further 3 h at 120 °C. The formed HCl is led away and absorbed in a water solution of 10.6 g (0.1 mol) Na_2CO_3. The warm reaction mixture is diluted with 100 mL 1,2-dichloroethane, after 5 min boiling it is filtered and the catalyst on the filter is washed with 2 × 10 mL warm 1,2-dichloroethane. The filtrate is cooled to 20 °C and extracted with 4 × 40 mL water. The organic solvent is evaporated under atmospheric pressure and the residue is distilled in vacuo. A first fraction (1.8–2.1 g) is collected until 145 °C at 0.4 mbar. The yield of ketone **2**, distilled between 150–152 °C at 0.4 mbar (Ref. [5] 150–151 °C/0.3 torr) is 10.72 g (59.5%). This product is easily crystallised, m.p. 67 °C (Ref. [24] 67–68.5 °C).

5 Conclusion

Acid treated clays exchanged by transition metal cations are interesting catalysts for the selective ring acylation of resorcinol by isobutyryl chloride, not with the traditional environment pollutant Lewis acids but using a heterogeneous catalytic, solvent-free reaction. The scale up of the reaction at the 0.1 mol level gives a good idea of the potentialities: 60% yield after isolation of the product, with 92% selectivity. The recyclability of the catalyst is also noticeable.

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