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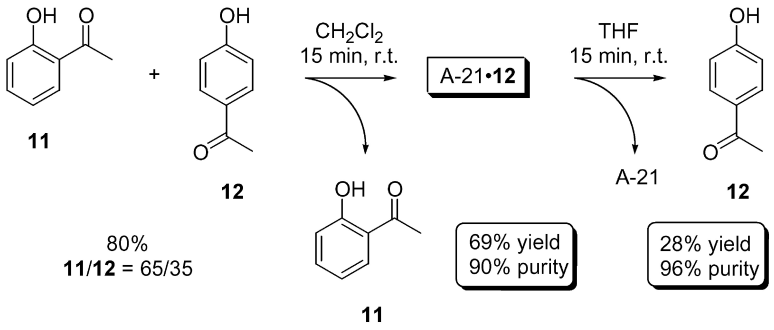

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Fast, Easy, and Efficient Method for the Purification of Phenolic Isomers Using a Selective Solid-Phase Scavenging Process

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The need for fast and efficient purification methods that can be easily handled and moreover automated is considerably increasing with the new techniques of high-throughput chemical synthesis. Following our previous work on the use of simple polymeric scavengers in fast reactions and purifications of organic substances, this article presents the results found during the development of a new method for the purification of phenolic substances. The purification method was found to be regulated by the interaction of acidic phenol groups with a basic polystyrene resin. Furthermore, the scavenging of phenolic isomers proved to be very selective for a given isomer. But the most interesting aspect of this method is that it is based on a simple contact in situ with the resin and that the adsorption/desorption process of the phenol was found to be solvent-dependent. The phenols can thus be freed from impurities, or other isomers, by a simple and fast contact with the resin in the first solvent, filtration, and washings, followed by liberation of the purified phenol by a last soaking in another solvent for desorption. The method was successfully applied to the purification of a crude reaction mixture issued from the Fries rearrangement of phenyl acetate, as well as to small libraries of phenolic derivatives.

Introduction

As a complementary approach to solid-phase organic synthesis (SPOS),[1] recent applications of well-known functionalized polymeric resins as supported reagents or scavenging polymers were published. Solid-phase scavenging (SPS), polymer-supported quench (PSQ), and complementary molecular reactivity and molecular recognition (CMR/R) were efficiently used in order to synthesize and purify organic substances in high-throughput approaches.[2] Our continuous research efforts to find new methodologies, as well as new purification methods, using the advantages of polymeric scavengers, promoted us to explore further the use of these techniques.

Phenols are very important organic compounds, both for their own structure and as an access to more complex products. They are used as starting materials or intermediates for the preparation of many aromatic derivatives, usually as directing groups for the entry of other functions or by transformation of the phenol itself.[3] Phenols are often found as an important feature in biologically and pharmacologically active substances, natural or synthetic, sometimes being responsible for the activity.[4] Phenols under their dimeric atropisomeric form, have been largely used as ligands, or ligand precursors, for organic catalysis and especially in their asymmetric versions with excellent results.[5]

The hydroxyl group in phenols is a very efficient ortho- and para-directing group that proved its usefulness in many electrophilic aromatic substitutions.[3] The orientation and activation effects in phenols are also responsible for the selectivities encountered in other reactions of phenols,[6] Friedel−Crafts acylation, and alkylation reactions as well as in Fries rearrangement of phenol derivatives.[7,8] The ortho/para ratio in these transformations is variable and is a function of the reaction or the substrate type. Even though selectivities can be very high, traces of unwanted isomers could still be present. Phenol isomers can be separated by techniques such as steam distillation, fractional distillation, recrystallization or chromatography, depending on the nature of the aromatic products. These purification techniques can sometimes be rather cumbersome for sensitive compounds when the isomers do not differ enough in physicochemical properties and more especially while working on small-scale reactions.

During a part of our projects, we became interested in finding fast and efficient purification methods for phenolic isomers and their derivatives, especially in the view of an application for the purification of samples issued from high-throughput organic synthesis. The required method should permit the removal of unwanted isomeric or residual phenols with ease from a reaction mixture or a crude product.

Results and Discussion

Insoluble nitrogen-based polystyrene resins have been successfully used for the removal of excess electrophilic reagents, as well as acidic products generated during solution-phase reactions. Resins loaded with primary and secondary amines have thus served to trap excess acid chlorides, or

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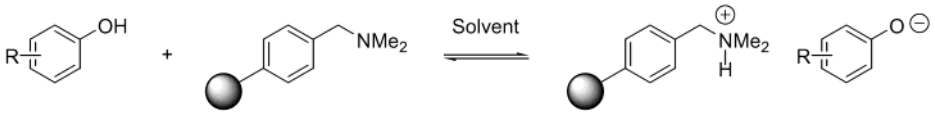
Scheme 1



Amberlyst A-21

R = 2-NO_2 (**1**), 3-NO_2 (**2**), 4-NO_2 (**3**), 2-Cl (**4**), 3-Cl (**5**), 4-Cl (**6**), 2-CH_3 (**7**), 3-CH_3 (**8**), 4-CH_3 (**6**).

other acylating reagents such as isocyanates, in ester, amide, and urea formation.[9] Tertiary amino-substituted polymers have also found application in the removal of mineral or carboxylic acids[10] and as efficient scavengers for acidic leaving groups of activated esters such as pentafluorophenol, *p*-nitrophenol, and *N*-hydroxysuccinimide.[11] Among them, the simple and well-known macroreticular polystyrene resins such as Amberlyst, Amberlite, Dowex, and others are the most attractive.[12] They are widely available at very low cost, with a variety of functionalities, high loading capacities, and different granulometries. Among commercial resins, we selected Amberlyst A-21 as the basic polymeric material for our study.

Preliminary Fixation Tests. The resin efficiency for phenol removal from solutions was first tested with a variety of compounds in different solvents. Basic Amberlyst A-21, a polystyrene grafted with a tertiary amino group, should react with the acidic phenols to form ammonium phenoxides on the polymer, thus removing phenols from the mixtures (Scheme 1).

Three different disubstituted phenols were selected for the study, and within the groups, all three isomers were tested. The substituents on the phenolic ring ranged from nitro (**1**−**3**), to chloro (**4**−**6**) and methyl (**7**−**9**). Solvents were chosen to be representative of polarity and structural panels, as well as typical reaction solvents. Thus, experiments were conducted in toluene, methylene chloride (CH_2Cl_2), and tetrahydrofuran (THF). The contact time between the resin and the phenol solution was selected to be only 15 min.[13] An excess of phenol was used in order to quantify the total loading capacity of the polymer by both weight increase of the resin and evaluation of residual phenol in the filtrate.

The results recorded for these experiments are presented in Table 1 according to phenol type and solvent. For all the phenols tested (**1**−**9**), fixation was found to be the best in toluene, intermediate in CH_2Cl_2, and the worst in THF, where just a few percent of phenol formed a salt on the resin. The nature of the solvent thus had a strong influence on the heterogeneous equilibrium between the phenol in solution and the phenoxide salt on the solid phase as depicted in Scheme 1. For toluene ($\epsilon = 2.4$; $E_T = 33.9$),[14,15] the least polar solvent used, the equilibrium was shifted to the right in such a way that the polar phenols preferred to leave the solution's nonpolar environment to form a salt with the basic solid and insoluble material. Increasing the polarity by the use of methylene chloride ($\epsilon = 9.0$; $E_T = 41.1$) established an equilibrium in which more of the phenol was found in solution. This cannot be attributed in this case to the basicity of the solvents implicated here. The differences between

Table 1. Phenol Fixation Tests on Amberlyst A-21 as a Function of the Solvent

			% phenol fixation on A-21 resin (mmol)[a]		
compd	phenol	pK_a [b]	toluene	CH_2Cl_2	THF
1	*o*-nitrophenol	7.00	21 (0.5)	8 (0.2)	8 (0.2)
2	*m*-nitrophenol	8.15	96 (2.3)	71 (1.7)	8 (0.2)
3	*p*-nitrophenol	6.85	100 (2.4)	87 (2.1)	12 (0.3)
4	*o*-chlorophenol	8.50	33 (0.8)	25 (0.6)	12 (0.3)
5	*m*-chlorophenol	8.80	67 (1.6)	62 (1.5)	8 (0.2)
6	*p*-chlorophenol	9.05	58 (1.4)	46 (1.1)	12 (0.3)
7	*o*-cresol	10.20	29 (0.7)	21 (0.5)	0 (0.0)
8	*m*-cresol	9.70	33 (0.8)	25 (0.6)	0 (0.0)
9	*p*-cresol	9.65	37 (0.9)	25 (0.6)	4 (0.1)

[a] The phenol (4.0 mmol) was incubated with Amberlyst A-21 (2.4 mmol amine) in the solvent for 15 min. The fixation was quantified by the resin's weight increase (see Experimental Section). [b] Values of pK_a (H_2O, 25 °C, titration) are issued from ref 18.

toluene and dichloromethane were such that approximately 60−75% of the amount of salt formation in toluene was observed in CH_2Cl_2. The use of THF ($\epsilon = 7.4$; $E_T = 37.4$), which is in the same polarity range as CH_2Cl_2, gave, however, a completely different behavior. Phenols formed salts on the solid phase at an extent of only ∼10% or lower. Thus, for THF, polarity is not the only influence that can account for such observations. In this case, this could be a result of the ionizing capacities of THF, through its basicity/*n*-donor character, that shift the equilibrium toward the left.[16,17]

Within each isomeric series (**1**−**3**, **4**−**6**, and **7**−**9**), the meta and para isomers were more scavenged by the resin than the ortho one, the order for the phenoxide formation being para > meta ≫ ortho. The differences between the isomers of a series of approximately the same pK_a can be attributed to steric hindrance of the substituent, especially when in the ortho position. The group in the 2-position could thus prevent the formation of an intimate ion pair, as is not the case for the meta and para isomers.

Finally, the acidity of the phenol obviously had an influence on salt formation. The more acidic nitrophenols (**1**−**3**) were more efficiently removed from solution than the chloro (**4**−**6**) and methyl (**7**−**9**) substituted ones. In the case of Amberlyst A-21, the amino substituent can be considered as a trisubstituted alkylamine with a pK around 10−11.[19] Nitrophenols (**1**−**3**) have pK_a of 7−8, which is 2−3 pK units higher than the base, resulting in good salt formation. For chlorophenols (**4**−**6**), the intermediate fixation should be the result of a lower acidity (pK_a = 8.5−9), being only 1−1.5 units stronger than the amine. In this series, the less acidic *p*-**6** isomer is not sequestered as efficiently as the more acidic

Scheme 2

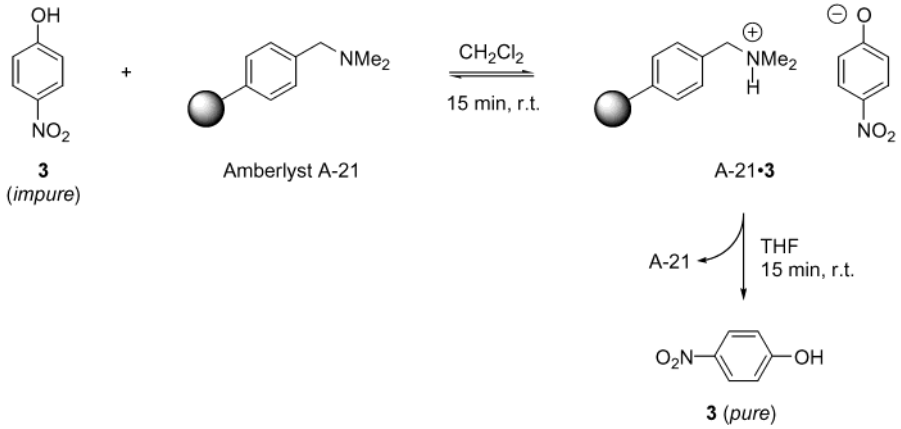


Table 2. Purification of *p*-Nitrophenol (**3**) Using Adsorption/Desorption with CH_2Cl_2 and THF

crude **3** (mg)	mp (°C)	mg of A-21 (equiv)[a]	mg of pure **3** (%)[b]	mp (°C)
278	109−112	500 (1.2)	183 (66)	
278	109−112	625 (1.5)	198 (71)	112−113
278	109−112	833 (2.0)	175 (63)	
278	109−112	1000 (2.4)	188 (68)	
1400	109−112	3100 (1.5)	1000 (71) 1200 (88)[c]	111−112

[a] The phenol (2 or 10 mmol) was first incubated with dry Amberlyst A-21 (4.8 mmol of amine/g) in CH_2Cl_2 to form the salt, and the isolated resin was soaked in THF to release the phenol (see Experimental Section). [b] Recuperation yield based on the initial amount of impure material. [c] Total yield after a second crop issued from a second treatment of A-21 with 1 equiv of AcOH in THF.

m-**5** one. The pK_a of the cresols (**7**−**9**) are in the range of 10, equivalent to the one of the solid-supported amine, explaining the weak interactions observed in these cases.

Evaluation of a Purification Technique by Adsorption/Desorption. The results obtained for the preliminary fixation tests clearly demonstrated the possibility of using Amberlyst A-21 for the removal of phenols from a solution. Moreover, the differences observed when passing from toluene and methylene chloride, where the fixations were the most efficient, to tetrahydrofuran, where phenols were almost unfixed, suggested a possible application of the phenomenon. The working hypothesis was that changing from a solvent to another could entitle us to selectively adsorb or desorb phenols, using a simple reversal of equilibrium. The technique was tested using an impure sample of *p*-nitrophenol (**3**) available in the laboratory (Scheme 2).[20]

Impure 4-nitrophenol (**3**) was first fixed on Amberlyst A-21 resin by contact in methylene chloride for 15 min.[21] The dried bright-yellow polymer issued from the filtration of the mixture (A-21•**3** salt) was then suspended in tetrahydrofuran, which was evaporated after the same contact time to obtain the purified phenol (Table 2). The use of 1.5 molar equivalents of Amberlyst A-21 resin gave the best results in terms of purification and recuperation of the pure phenol (71% based on impure starting material). The purification was first conducted on a small amount of phenol before being scaled up. The use of the technique on a larger scale (1.4 g, 10 mmol) gave the same good results in the purification of *p*-nitrophenol (**3**), with identical purification yield.

The purified phenol **3** had both the awaited aspect and melting point. The impure **3**, the filtrate from CH_2Cl_2 fixation, and the pure fraction were also analyzed by spectroscopy. The following figure presents the proton NMR spectra of the impure sample of **3** (Figure 1A) and the pure compound (Figure 1C), obtained after purification by adsorption/desorption on Amberlyst A-21. Traces of impurities that can be seen in Figure 1A (crude **3** NMR), but most of all in Figure 1B (CH_2Cl_2 filtrate), have completely disappeared from the spectrum of the purified *p*-nitrophenol (**3**, Figure 1C).

In the purification experiments, the residue left after evaporation of the methylene chloride fraction was less important with the increase of Amberlyst A-21 used (data not shown), starting at 19−14% when using 1.2−1.5 equiv and reaching a plateau around 2.0 equiv (10% of crude). On the basis of this residual phenol containing impurities, the fixation of pure phenol on the resin can be approximated to be between 81% and 90%, which is consistent with the 87% salt formation observed in the preliminary fixation tests (see Table 1). For the amount of the phenoxide of **3** left on the resin after THF treatment, easily observable by the bright-yellow coloration of the Amberlyst, the behavior is quite similar. The residual phenoxide on A-21 is becoming more important with the amount of the aminated polymer used. From 5% for 1.2 equiv of the resin, it passes through 18% (1.5 equiv) to a maximum of 26% (2.0−2.4 equiv). For the experiment on a 10 mmol (1.4 g) scale using 1.5 equiv of polymeric amine, the amount of phenol **3** on A-21 was evaluated to be 266 mg (19%). A part of this residual phenol can be displaced from the resin with the use of 1 equiv of acetic acid in THF based on the amine content of Amberlyst A-21 to obtain a second crop of purified *p*-nitrophenol (**3**). The recuperated phenol (241 mg, 17%) showed the same purity as the one obtained by simple treatment with tetrahydrofuran. The total yield based on the initial amount of impure material was thus 88% in phenol **3**.

Separation of Phenolic Isomers through Adsorption/Desorption. Another observation made in our initial study was that the fixation on Amberlyst A-21 resin was also very selective toward certain isomers of phenols. Since the para and meta isomers were much more captured by the resin than the ortho ones, a study on selective removal of isomeric phenol was conducted to evaluate the efficiency of such a

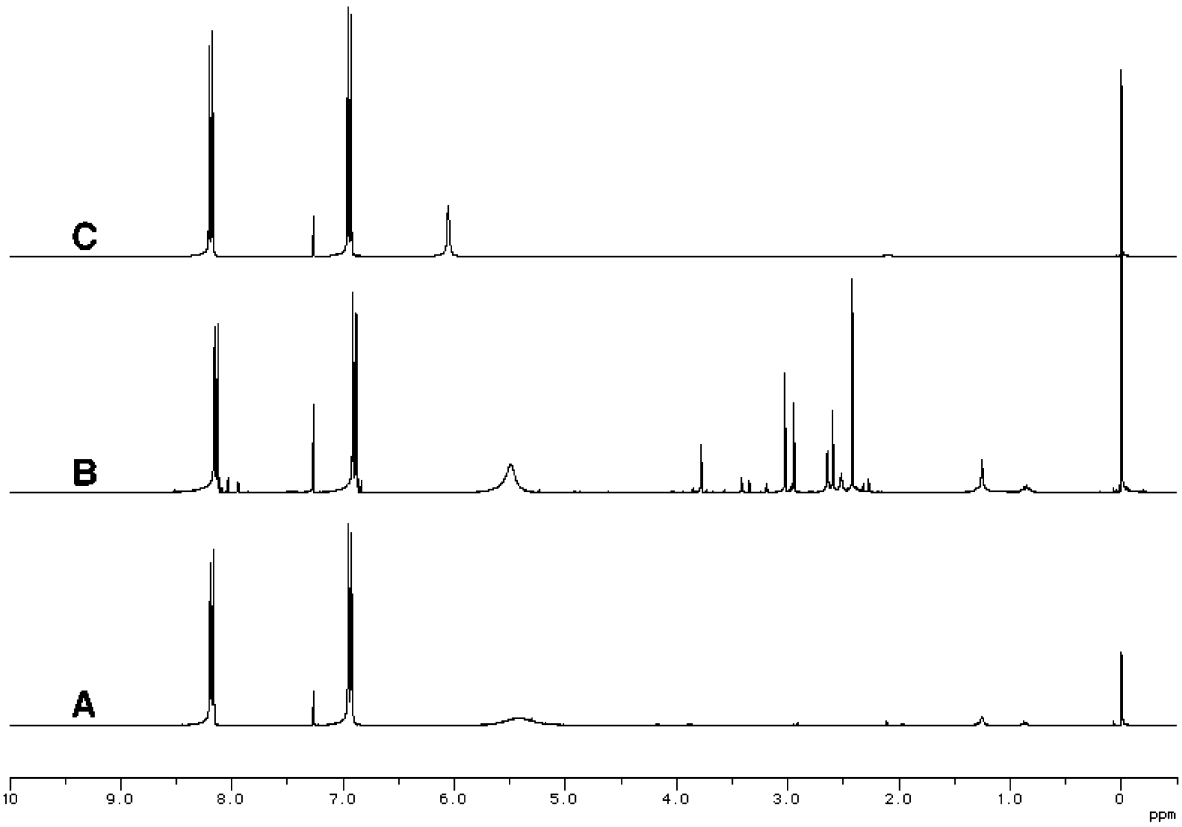
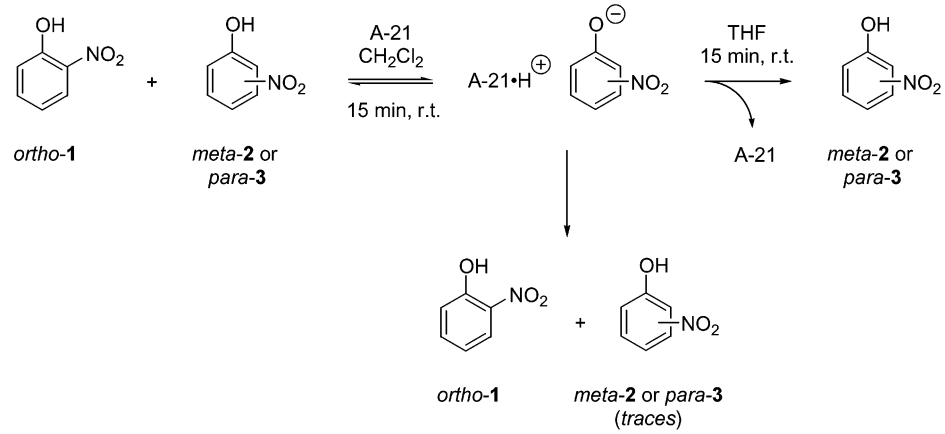


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$) spectra of (A) impure 4-nitrophenol (**3**), (B) the intermediate CH_2Cl_2 filtrate, and (C) pure **3** after purification on Amberlyst A-21.

Scheme 3



technique in the purification of phenol mixtures. Nitrophenols were chosen, and mixtures of ortho/meta (**1**/**2**) and ortho/para (**1**/**3**) isomers were tested in order to validate the approach (Scheme 3).

Mixtures of *o*-nitrophenol (**1**) and another isomer, consisting of equimolar amounts (2 mmol each), were treated with increasing quantities of Amberlyst A-21 in methylene chloride in order to remove the meta (**2**) and para (**1**) phenols from the mixtures. The results from these experiments are presented in Table 3 for the ortho/meta **1**/**2** (entries 1−4) and ortho/para **1**/**3** (entries 5−8) mixtures. For both mixtures, the increase from 1.2 to 4.8 equiv of the resin in regard to the phenol to be removed from the solution gave a decrease in the purity of the unfixed *o*-**1** isomer in CH_2Cl_2 filtrate. For mixtures with *m*-nitrophenol (**2**), entries 1−4 show that the proportion of this isomer **2** left with the *o*-**1** after treatment progressively decreased from 22% (1.2 equiv) to 17% (4.8 equiv). Purities of recuperated *o*-nitrophenol (**1**) were thus between 78% and 88%. Better results were obtained for the mixtures of *o*-**1** with *p*-nitrophenol (**3**), as shown in entries 5−8, where the mixtures isolated from methylene chloride started with a 19% (1.2 equiv) content of *p*-**3** to finally reach only 8% (4.8 equiv). The results thus show that the best results for the removal of the *m*-**2** or *p*-**3** isomer from mixtures with the *o*-**1** one were obtained with ∼5 equiv of Amberlyst A-21.[22] The isolated *o*-nitrophenol (**1**) shows acceptable purities in the range 83−92%.

Desorption of the scavenged isomers **2** and **3** using tetrahydrofuran was then conducted and led to the recovery of pure *m*-**2** (entries 1−4) and *p*-**3** (entries 5−8). The isolated

Table 3. Purification of Mixtures of Nitrophenols Using Amberlyst A-21 with CH_2Cl_2 and THF[a]

	A-21[b]	mixtures (mmol)		filtrate (%)[c]		desorption (mmol)		yield (%)[d]
entry	mmol (equiv)	*o*-**1**	other	*o*-**1**	other	*o*-**1**	other	other
1	2.4 (1.2)	2.0	2.0 (**2**)	78	22 (**2**)	0.00	1.23 (**2**)	61 (**2**)
2	4.8 (2.4)	2.0	2.0 (**2**)	82	18 (**2**)	0.00	1.33 (**2**)	66 (**2**)
3	7.2 (3.6)	2.0	2.0 (**2**)	81	19 (**2**)	0.00	1.48 (**2**)	74 (**2**)
4	9.6 (4.8)	2.0	2.0 (**2**)	83	17 (**2**)	0.00	1.60 (**2**)	80 (**2**)
5	2.4 (1.2)	2.0	2.0 (**3**)	81	19 (**3**)	0.00	1.41 (**3**)	70 (**3**)
6	4.8 (2.4)	2.0	2.0 (**3**)	85	15 (**3**)	0.00	1.46 (**3**)	73 (**3**)
7	7.2 (3.6)	2.0	2.0 (**3**)	91	9 (**3**)	0.00	1.71 (**3**)	85 (**3**)
8	9.6 (4.8)	2.0	2.0 (**3**)	92	8 (**3**)	0.00	1.83 (**3**)	91 (**3**)

[a] The phenol mixtures (2 mmol of each) were first incubated with dry Amberlyst A-21 (4.8 mmol of amine/g) in CH_2Cl_2 to form the salt. The resulting resin was then suspended in THF to release the phenol followed by a second treatment of the resin with AcOH (1 equiv) in the same solvent (see Experimental Section). [b] Number of equivalents calculated on the amount of phenol to remove from the mixtures. [c] Evaluated by ^{1}H NMR in $CDCl_3$ of the residue. [d] Recuperation yield based on the initial amount of *m*-**2** or *p*-**3** isomer in the mixture.

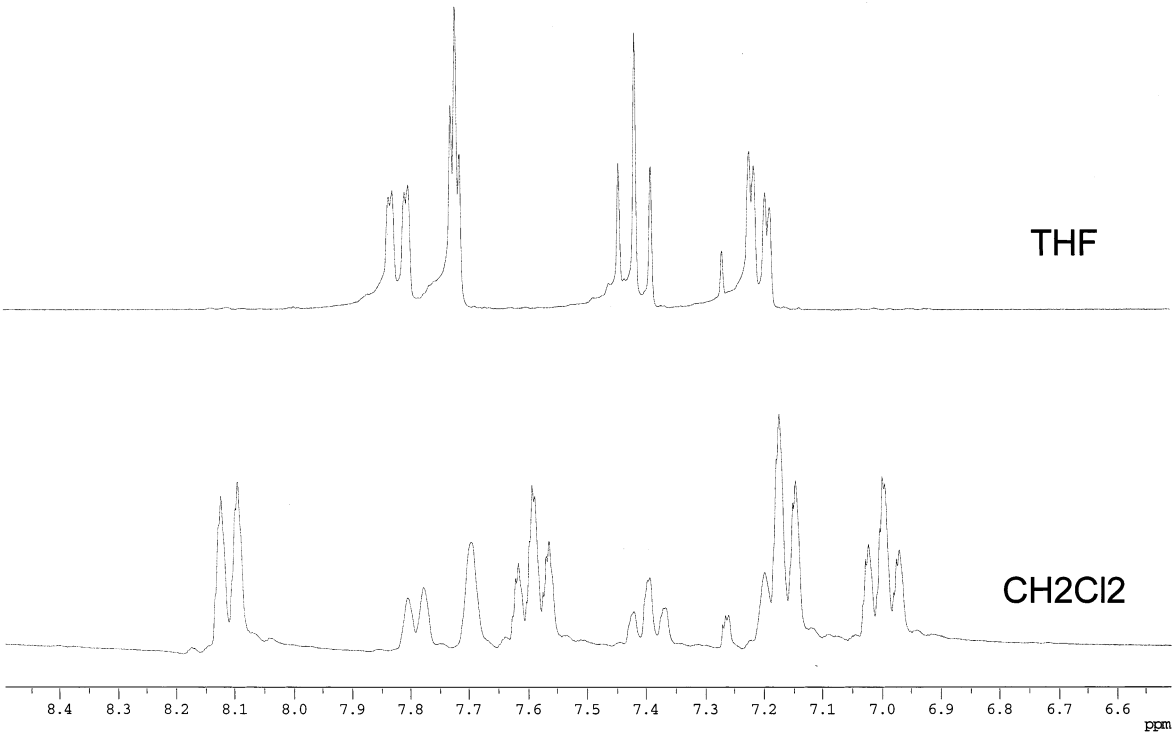


Figure 2. ^{1}H NMR (300 MHz, $CDCl_3$) spectra of CH_2Cl_2 filtrate (bottom) and pure *m*-nitrophenol (**2**) obtained from THF desorption (top) during the purification of *o***1** and *m*-nitrophenol (**2**) mixtures using 4.8 equiv of Amberlyst A-21.

m-**2** and *p*-**3** phenols contained only faint traces of the isomeric *o*-nitrophenol (**1**) for all the stoichiometries of aminated polymer used. For both mixture types, the total recuperation yield based on the initial amount of the isomer increased with the quantity of A-21 used. In the case of *m*-nitrophenol (**2**), the efficiency of the procedure varied from 61% to 80%, while for the *p*-**3** one it ranged between 70% and 91%.

Figures 2 and 3 present the proton nuclear magnetic resonance spectra for the two studied phenol mixtures in the aromatic region, when using 4.8 equiv of aminated polymer. In Figure 2, we can clearly see the composite signals arising from the presence of *o*-**1** and traces of *m*-nitrophenol (**2**) left (17%) on the bottom spectrum issued from methylene chloride filtrate. The product obtained from the tetrahydrofuran desorption (top spectrum), however, contains only the meta isomer **2**, with minute traces of the *o*-**1**. Figure 3 illustrates the results obtained during the purification of *o*-**1**/*p*-**3** mixtures. The bottom spectrum from evaporation of the methylene chloride fraction shows that *o*-**1** still contains little traces of *p*-**3** (8%), while the desorption with tetrahydrofuran (top) only left the pure *p*-nitrophenol (**3**), with only a small traces the *o*-isomer **1**.

The use of Amberlyst A-21 to preferentially fix the *p*-**3** or *m*-**2** isomer over the *o*-**1** one when the mixtures are dissolved in methylene chloride thus gave very good results. This treatment left, after filtration of the polymer, the unremoved ortho isomer **1** together with traces of the other one in the filtrate. The phenoxide salt formed on the polymeric material with **2** (or **3**) was then resuspended in THF and left, after evaporation, only the *m*-**2** (or *p*-**3**) isomer with very good recuperation yields and purities.

Application of the Technique for the Purification of the Isomeric Mixture Issued from Fries' Rearrangement of Phenyl Acetate (10). The purification procedure was then put to the test on a mixture issued from Fries' rearrangement

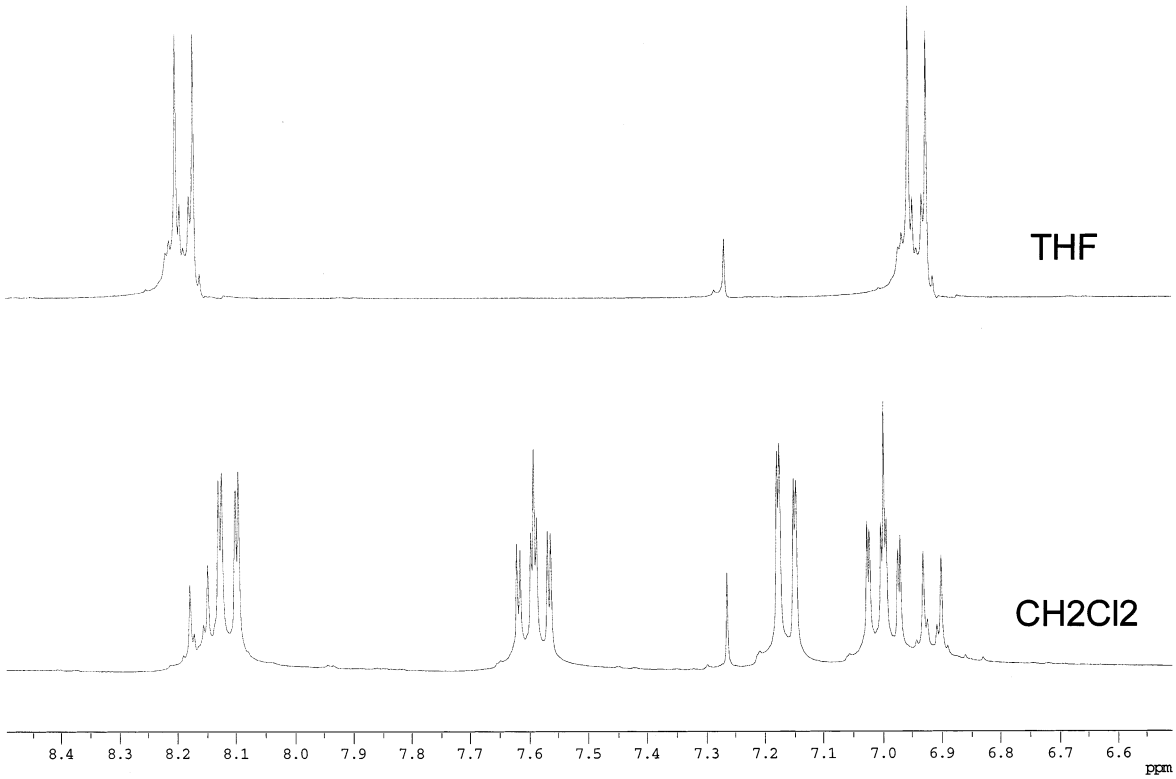
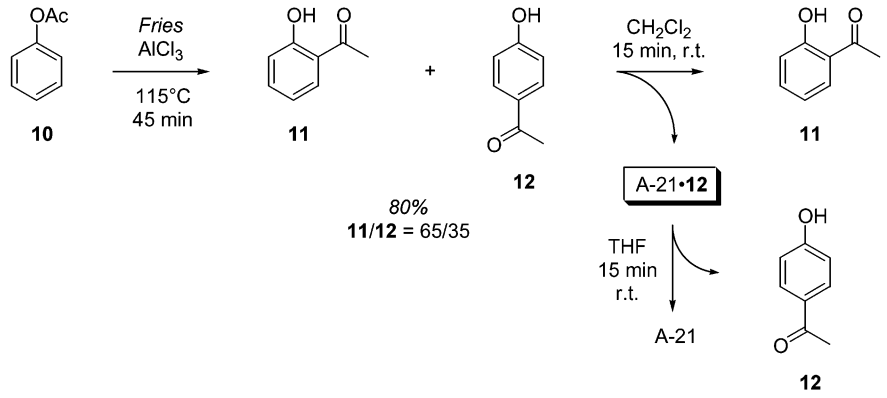


Figure 3. ^{1}H NMR (300 MHz, $CDCl_3$) spectra of CH_2Cl_2 filtrate (bottom) and pure *p*-nitrophenol (**3**) obtained from THF desorption (top) during the purification of *o***1** and *p*-nitrophenol (**3**) mixtures using 4.8 equiv of Amberlyst A-21.

Scheme 4



of phenyl acetate (**10**, Scheme 4).[23] The reaction produced a 65/35 mixture of 2-hydroxy- (**11**) and 4-hydroxyacetophenone (**12**) in 80% yield after workup. Purification of the crude from this type of rearrangement is usually done by distillation under vacuum to obtain only the 2-hydroxy isomer in low yield (around 30%), leaving the para isomer in the tars of the distillation flask.[23b,c]

The use of this new purification method can thus be considered in order to isolate both isomers by a simpler procedure and with hopefully a better yield. A literature survey indicated that the p*K* from the two isomers could be different enough for use of our method. For 2-hydroxyacetophenone (**11**), the p*K* is around 10.3, and for the 4-isomer **12**, it is about 7.8.[18,24]

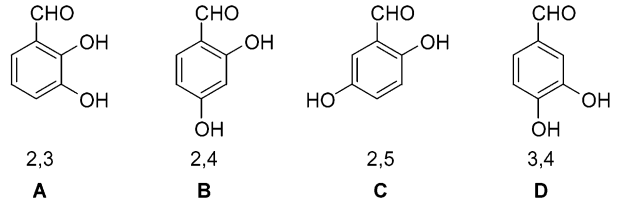
Fixation tests were first conducted on a 4 mmol scale (Table 4). The conditions selected were essentially the same as for the nitrophenol separations (vide supra). Thus, a mixture consisting of 65% of *o*-hydroxyacetophenone (**11**) and 35% of *p*-hydroxyacetophenone (**12**) was first treated with Amberlyst A-21 (4.8 equiv based on the amount of the *p*-**12** isomer to remove) as previously described (entry 1). The liquid residue from the methylene chloride filtrate was analyzed and found out to be the *o*-**11** isomer with a purity of 90%. THF desorption from A-21 resin led to the isolation of the solid *p*-**12** isomer showing a purity of 94%. The total recuperation yield, based on the initial amount of acetophenones, was 93%. An identical treatment was applied, but using 6.9 equiv of the resin, to try to improve the purity of each isomer (entry 2). Surprisingly, the results were essentially the same as for 4.8 equiv. The ortho-substituted compound **11** was isolated with a purity of 90%, while the para one (**12**) was 96% pure. The recuperation yield was, however, lower (90%). Another attempt was then realized using 4.8 equiv of A-21 (entry 3). The polymer was split into two

Table 4. Purification of Acetophenones **11** and **12** Mixtures by Adsorption/Desorption on Amberlyst A-21 with CH_2Cl_2 and THF[a]

entry	A-21[b] equiv (mmol)	% mixture (mmol)		filtrate (%)[c]		desorption (%)[c]		yield (%)[d]
		o-**11**	*p*-**12**	*o*-**11**	*p*-**12**	*o*-**11**	*p*-**12**	**11** + **12**
1	4.8 (6.7)	65 (2.6)	35 (1.4)	90	10	6	94	93
2	6.9 (9.6)	65 (2.6)	35 (1.4)	90	10	4	96	90
3	4.8 (6.7)[e]	65 (2.6)	35 (1.4)	88	12	4	96	99
4	4.8 (20)	65 (7.8)	35 (4.2)	88	12	4	96	97

[a] The acetophenones mixtures were placed in contact with dry Amberlyst A-21 (4.8 mmol of amine/g) in CH_2Cl_2 before removal of the solvent by filtration. The filtrate contained the isomer **11**. The recuperated resin was resuspended in THF alone to release the fixed acetophenone **12** and then by a second treatment of the resin with AcOH (1 equiv) in the same solvent (see Experimental Section). [b] Number of equivalents calculated on the amount the minor constituent to remove (*p*-hydroxyacetophenone **12**). [c] Composition estimated by ^{1}H NMR in $CDCl_3$ of the residue. [d] Total recuperation yield based on the initial amount of the acetophenones in the mixtures. [e] The hydroxyacetophenone mixture was treated twice by using half the indicated amount of polymer for each fixation.

Scheme 5



halves, and the first one was used to treat the acetophenones mixture. The methylene chloride filtrate obtained was then retreated with the second portion of A-21 and filtered again. The *o*-**11** isomer obtained by this procedure showed a purity of 88%. Desorption of the two portions of A-21 gave the *p*-**12** isomer with a purity of 96%. The total recovery of acetophenones was much better in this case (99%).

The mixture issued from Fries' rearrangement of phenyl acetate (**10**) was then subjected to purification using the procedure of entry 1, which is almost equivalent to the latest one (entry 3). The application of the technique on this larger scale (12 mmol) gave similar results in terms of purities (88% and 96%) and recuperation yield (97%). Other attempts to improve the already acceptable purity of these two isomers using this method did not gave better results. However, the purification technique is very efficient when compared to the existing procedures, especially in terms of rapidity, purity, and mostly recuperation yields.

Purification of Small Phenolic Libraries. The method was then applied to the purification of small libraries of phenolic isomers. The first series treated to this purpose is depicted in Scheme 5. Four isomeric dihydroxybenzaldehydes were mixed in 90/10 proportions and then purified by the previously described technique. Amberlyst A-21 was used in 4.8 equiv on the minor isomer (the 10% impurity). The results are presented in Table 5 for each mixture, showing the recuperation yield (*R*) and purity (*P*) of the major benzaldehyde isomer from the initial mixture, isolated from CH_2Cl_2 and THF filtrates.

From the fixation of each single isomer (diagonal of the table), the usual trends were still observed. Compounds with the most acidic hydroxyl groups in the 4-position are the ones that showed the best fixation on A-21 (**B** and **D**). The fixation of **D** was, however, lower because of steric demands and low solubility. For the two other isomers **A** and **C**, compound **C** with the less hindered OH group, as well as in a para relation to the 2-one, was found to be a little more scavenged by the resin. The fixation is thus in the order **B** > **D** > **C** ≫ **A**.

For mixtures where **A** was the major isomer (first line), this isomer was mostly recuperated in the CH_2Cl_2 filtrate (73−86%) with an increased purity of approximately 95%. Since all other isomers are more efficiently fixed on A-21, the THF filtrate containing the adsorbed hydroxybenzaldehyde was richer in the other isomer, with purities for **A** between 60% and 67%.

In the case of the 2,4-dihydroxy isomer (**B**, second line), which was showing the best fixation on the resin, the results are exactly the opposite. The hydroxybenzaldehydes were globally equally split between the CH_2Cl_2 and THF filtrates. The CH_2Cl_2 filtrates were composed of a lower purity **B** (80−97%), while the filtrate from THF desorption showed high purities (96−100%) for **B**, the only exception being the mixture with **D** (87%).

Isomer **C** purification was driven by fixation differences with the other isomer present as the impurity (third line). In the mixture with **A**, the better fixation of **C** gave a product issued from THF desorption with a higher purity (96%). The residue left after CH_2Cl_2 treatment was of a lower purity (82%). When isomers **B** and **D** were present as the minor constituent, the CH_2Cl_2 filtrate showed a better purity (96%) than the THF one (60%). This was the result of the higher affinity of the more acidic **B** and **D** isomers for the resin.

Finally, for the 3,4-dihydroxy isomer (**D**, fourth line), the purification was somehow complicated by solubility problems. Since this isomer was only slightly soluble in CH_2Cl_2, it was mainly recuperated manually after this first treatment and combined with the filtrate. The solid recuperated this way showed good purity, between 97% and 100%, when mixed with **B** and **C**. As a mixture with the **A** isomer, the purity was not improved. The THF filtrates consisted of very few dihydroxybenzaldehyde **D** of low purity (43−62%) except once again for the mixture with **A** where the purity was equivalent to the one with the CH_2Cl_2 content.

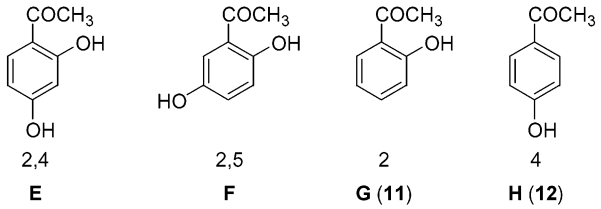
Another library composed of mono- and dihydroxyacetophenones was finally tested (Scheme 6). This library was generated and purified using A-21 by the same methods as previously described (vide supra). The different results gathered are displayed in Table 6.

Table 5. Purification of a Library of Dihydroxybenzaldehydes with the Adsorption/Desorption Technique on A-21[a]

	A	B	C	D[b]
A	**AA**[c] CH_2Cl_2 $R = 86\%$, $P = 95/5$ THF $R = 11\%$, $P = 99/1$	**AB** CH_2Cl_2 $R = 73\%$, $P = 95/5$ THF $R = 18\%$, $P = 60/40$	**AC** CH_2Cl_2 $R = 83\%$, $P = 94/6$ THF $R = 16\%$, $P = 67/33$	**AD** CH_2Cl_2 $R = 84\%$, $P = 100/0$ THF $R = 15\%$, $P = 61/39$
B	**BA** CH_2Cl_2 $R = 48\%$, $P = 80/20$ THF $R = 46\%$, $P = 100/0$	**BB** CH_2Cl_2 $R = 60\%$, $P = 97/3$ THF $R = 32\%$, $P = 100/0$	**BC** CH_2Cl_2 $R = 55\%$, $P = 88/12$ THF $R = 38\%$, $P = 96/4$	**BD** CH_2Cl_2 $R = 40\%$, $P = 89/11$ THF $R = 33\%$, $P = 87/13$
C	**CA** CH_2Cl_2 $R = 26\%$, $P = 82/18$ THF $R = 68\%$, $P = 96/4$	**CB** CH_2Cl_2 $R = 60\%$, $P = 96/4$ THF $R = 31\%$, $P = 60/40$	**CC** CH_2Cl_2 $R = 84\%$, $P = 99/1$ THF $R = 16\%$, $P = 99/1$	**CD** CH_2Cl_2 $R = 70\%$, $P = 100/0$ THF $R = 24\%$, $P = 79/21$
D	**DA** CH_2Cl_2 $R = 85\%$, $P = 92/8$ THF $R = 15\%$, $P = 92/8$	**DB** CH_2Cl_2 $R = 83\%$, $P = 100/0$ THF $R = 14\%$, $P = 43/57$	**DC** CH_2Cl_2 $R = 83\%$, $P = 97/3$ THF $R = 19\%$, $P = 62/38$	**DD** CH_2Cl_2 $R = 83\%$, $P = 93/7$ THF $R = 17\%$, $P = 97/3$

[a] Hydroxybenzaldehydes mixtures (90/10) were first incubated with dry Amberlyst A-21 (4.8 equiv/minor isomer) in CH_2Cl_2 to form the salt, and the isolated resin was soaked in THF to release the benzaldehyde(s) (see Experimental Section). Yield (*R*) and purity (*P*) major/minor isomer are indicated. [b] Compound **D** is only slightly soluble in CH_2Cl_2. [c] The first letter refers to the major isomer in the mixture.

Scheme 6



For the fixation, starting with individual acetophenones (diagonal line of the table), the yields (*R*) and purities (*P*) were also determined by analysis of CH_2Cl_2 and THF filtrates. From the analyses, acetophenones **E** and **H** were found to be scavenged to the same extent by A-21. These acetophenones bearing an OH group in the fourth position were supposed to be the most acidic and thus very efficiently removed by A-21 from the solution. For the relatively acidic isomer **F**, by analogy to the **C** one, good fixation on the resin should had been observed. However, this compound, being only sparingly soluble in CH_2Cl_2, did not show the expected behavior. Isomer **G** was not fixed at all on A-21 under these conditions.

During the purification of **E** (line 1), the mixture with 10% of **F** gave a CH_2Cl_2 filtrate with a slight improvement in purity (91%). In this case, a small amount of **F** was dissolved and captured by the resin together with **E**, giving a THF filtrate of lower **E** purity (82%). With **G**, which is not fixed by A-21, its presence in the CH_2Cl_2 filtrate led to a lower purity (89%) when compared to the residue isolated from THF (100%). For the mixture with **H**, which is equally fixed on the polymer, both filtrates showed almost the same yield (54% and 43%) and purity (75% and 88%).

For the **F** isomer (line 2), its low solubility ruled out the issue of purification. Admixed with **E**, compound **F** was more pure in CH_2Cl_2 (94%) than in THF (34%), where more **E** was present. With **G**, the result is reversed with a low-purity CH_2Cl_2 filtrate (84% in **F**) and a 96% pure **F** from THF in poor recuperation yield. Finally, the separation for **H** was not successful with CH_2Cl_2 and THF filtrates of equivalent composition (47% and 58% purity).

The purification of the **G** mixture was obviously more efficient (line 3). Since this isomer is not well fixed on A-21, all the CH_2Cl_2 filtrate contained **G** with high purity (88−94%). The compounds isolated from THF desorption led to contents of only around 10% **G**. It means that the other isomer, initially present as the 10% impurity, reached 90% purity in THF filtrate.

Purification of the last isomer **H** (line 4) gave only slight differences when mixed with 10% **E** or **F**. The purity of both filtrates was almost identical for **E** (92−81%) and **F** (86−88%) because of the competition between these acidic acetophenones. The mixture with **G** gave, of course, a better result, with an improved purity of **H** in THF (100%) when compared to that in CH_2Cl_2 (87%).

Conclusion

The study of salt formation of phenols on Amberlyst A-21 in various solvents presented here gave the opportunity to get a better understanding of the behavior of these systems. The observations obtained using different phenols and solvents gave the efficiencies of phenol removal based on the conditions used. The ease of fixation was identified to be dependent on the phenol acidity, its substitution pattern, and the nature of the solvent used. Furthermore, an interesting unprecedented phenomenon was uncovered while working with different systems that permitted us to fix the phenols as their salts in one solvent type and desorb them in another one. This entitled us to free phenols from impurities as well as to effect isomer separations with some efficiency.

The purification method presented here is simple and straightforward, giving the opportunity to purify the products

Table 6. Purification of a Library of Hydroxyacetophenones with the Adsorption/Desorption Technique on A-21[a]

	E	F[b]	G	H
E	**EE**[c] CH_2Cl_2 $R = 74\%$, $P = 100/0$ THF $R = 22\%$, $P = 100/0$	**EF** CH_2Cl_2 $R = 50\%$, $P = 91/9$ THF $R = 33\%$, $P = 82/18$	**EG** CH_2Cl_2 $R = 75\%$, $P = 79/21$ THF $R = 25\%$, $P = 93/7$	**EH** CH_2Cl_2 $R = 54\%$, $P = 75/25$ THF $R = 43\%$, $P = 88/12$
F	**FE** CH_2Cl_2 $R = 92\%$, $P = 95/5$ THF $R = 9\%$, $P = 34/66$	**FF** CH_2Cl_2 $R = 95\%$, $P = 97/3$ THF $R = 4\%$, $P = 90/10$	**FG** CH_2Cl_2 $R = 88\%$, $P = 41/59$ THF $R = 9\%$, $P = 100/0$	**FH** CH_2Cl_2 $R = 88\%$, $P = 47/53$ THF $R = 11\%$, $P = 58/42$
G	**GE** CH_2Cl_2 $R = 92\%$, $P = 94/6$ THF $R = 9\%$, $P = 10/90$	**GF** CH_2Cl_2 $R = 94\%$, $P = 94/6$ THF $R = 5\%$, $P = 10/90$	**GG** CH_2Cl_2 $R = 88\%$, $P = 100/0$ THF $R = 0\%$, $P =$ _	**GH** CH_2Cl_2 $R = 93\%$, $P = 88/12$ THF $R = 6\%$, $P = 13/87$
H	**HE** CH_2Cl_2 $R = 84\%$, $P = 92/8$ THF $R = 15\%$, $P = 81/19$	**HF** CH_2Cl_2 $R = 82\%$, $P = 86/14$ THF $R = 18\%$, $P = 88/12$	**HG** CH_2Cl_2 $R = 83\%$, $P = 87/13$ THF $R = 16\%$, $P = 100/0$	**HH** CH_2Cl_2 $R = 79\%$, $P = 100/0$ THF $R = 21\%$, $P = 100/0$

[a] Hydroxyacetophenones mixtures (90/10) were first incubated with dry Amberlyst A-21 (4.8 equiv/minor isomer) in CH_2Cl_2 to form the salt, and the isolated resin was soaked in THF to release the benzaldehyde(s) (see Experimental Section). Yield (*R*) and purity (*P*) major/minor isomer are indicated. [b] The coumpound **F** is sparingly soluble in CH_2Cl_2. [c] The first letter refers to the major isomer in the mixture.

without any cumbersome techniques. No special chemical or physical treatments other than contact with the polymer in easily removable solvents are needed. The method implies very short contact time, with all the operations at room temperature and with the use of only filtrations and evaporations. The procedure was used with success for the separation of the isomeric mixtures issued from the Fries rearrangement of phenyl acetate.

The method was successfully used for the purification of two small libraries of hydroxylated benzaldehydes and acetophenones. The efficiency of the method was evaluated and demonstrated for isomeric substances. If differences of acidity and steric hindrance, and sometimes solubility as well, were large enough between the isomers, the separation technique would work perfectly. For some mixtures, the limits of the scope for this purification technique were reached. However, many examples were more than efficiently purified by this simple method, showing once again relatively wide application possibilities.

We are confident that this straightforward method for the purification of phenolic isomers, using an easily available resin, filtrations, and solvent changes for the adsorption/desorption of the substances, can find application in the purification of samples from high-throughput chemical synthesis.

Experimental Section

General Methods. Phenols and other reagents were purchased from Aldrich or Fluka and used without further purification. Commercially available Amberlyst A-21 resin from Aldrich (water content, ~57%) was dried accordingly to the procedure described in the Experimental Section before being used. Toluene (spectrometric grade) was purchased from SDS and used as such. Dichloromethane was treated with phosphorus pentaoxide at reflux (1 h) before being distilled. Tetrahydrofuran was distilled from sodium/benzophenone ketyl radical under nitrogen prior to use. Melting points were measured on a microscope equipped with a heated plate and are not corrected. Infrared spectroscopy (FTIR) was performed on a single-beam Nicolet 205 Fourier transform spectrometer, and absorptions are reported in cm^{-1}. Nuclear magnetic resonance (NMR) was recorded on a Brucker Avance 300 spectrometer in deuteriochloroform with tetramethylsilane (0.1%) as an internal standard. Chemical shifts (δ) are reported in ppm relative to TMS (0 ppm), and coupling constants (*J*) are reported in hertz.

Preparation of Dry Amberlyst A-21 Resin. Commercial wet Amberlyst A-21 resin (20−50 mesh, 100 g) was suspended in MeOH (500 mL) for 0.5 h and filtered (3 times) and then soaked in methylene chloride (500 mL) for 0.5 h and again filtered (3 times). The resulting resin was placed in a round-bottom flask on a rotoevaporator and dried at 50 °C under 10 mmHg until it was free-flowing. The dried resin was then kept overnight in vacuo in a desiccator over P_2O_5. Specifications from the manufacturer indicate that the polymer contains 4.8 mequiv of amine/g of dry resin.

Tests for the Formation of Phenoxide Salts on Amberlyst A-21 Resin. The phenol (4 mmol) was dissolved in the appropriate solvent (10 mL) and placed in contact with 500 mg (2.4 mmol of amine) of dry Amberlyst A-21 resin for 15 min. The resin was filtered off and washed with the solvent (2 × 10 mL) before being dried (0.01 mmHg, 40 °C, overnight). The increase in weight was then measured to evaluate the loading in phenol on the resin. The filtrate was evaporated and the residue weighed in order to compare the results. Since some phenols have a tendency to sublimate, or form an azeotropic mixture with the solvent, the latter measure was in some cases different and thus less reliable than weighing the resin.

Purification of 4-Nitrophenol (3) Using Adsorption/Desorption in CH_2Cl_2 and THF. Impure *p*-nitrophenol (**3**, 97%, mp 109−112 °C, 1.4 g, 10 mmol) was dissolved in CH_2Cl_2 (50 mL) and placed in contact with Amberlyst A-21 (4.8 mequiv/g, 3.1 g, 15 mmol, 1.5 equiv) for 15 min with gentle shaking. The resin was filtered and washed with CH_2Cl_2 (2 × 25 mL) before being air-dried. The filtrate when evaporated left an oily, brownish residue. The resulting yellow polystyrene was then resuspended in THF (50 mL) for 15 min under agitation. The THF was recuperated by filtration, and the resin was rinsed with the same solvent (2 × 25 mL). The THF was rotoevaporated in vacuo to leave pure **3** as a pale-yellow solid (1.0 g, 71%), mp 111−112 °C (lit.[25] 113−114 °C). A second crop of *p*-nitrophenol (**3**) was obtained from the resin issued from the THF wash, which was resuspended in THF (50 mL) and treated with glacial acetic acid (875 μL, 910 mg, 15.1 mmol). The polymer turned instantaneously from bright-yellow to beige, and evaporation of the volatiles in vacuo left another 241 mg (17%) of *p*-nitrophenol (**3**), for a total yield of 88% for the purification.

Separation Tests of Phenolic Isomers through Adsorption/Desorption. Nitrophenol isomers (2 mmol, 278 mg each) were dissolved in CH_2Cl_2 (10 mL) and treated with dry Amberlyst A-21 resin (4.8 mmol of amine/g) for 15 min. The resin was filtered off and washed with two portions of the solvent (10 mL each). The filtrate was evaporated, weighed, and analyzed by NMR spectrometry. The resulting resin was then suspended in THF (10 mL) for 15 min before being filtered and washed with THF (2 × 10 mL). The resin was resuspended in THF (10 mL) and treated with an amount of acetic acid corresponding to 1 equiv in regard to the amino content. The resin was filtrated again, and the volatiles were rotoevaporated to give the purified phenol. Its purity was evaluated by ^{1}H NMR spectrometry.

Purification of an *o*- and *m*-Nitrophenol (1 and 2) Mixture. By use of the general procedure with 2.0 g of A-21 (9.6 mmol of amine, 4.8 equiv), the CH_2Cl_2 filtrate contained 280 mg (2.01 mmol) of the phenols as a 83:17 mixture of the ortho (**1**) and meta (**2**) isomers (^{1}H NMR analysis). Desorption of the phenoxide from the resin using THF and THF/AcOH (572 L, 600 mg, 10.0 mmol) provided 221 mg (1.60 mmol, 80%) of pure *m*-nitrophenol (**2**) as a yellow solid: mp 96−97 °C (lit.[25] 97 °C); FTIR (KBr) 3393 (ν OH), 3103 and 3088 (ν CH Ar), 1632 (ν C═C), 1520 and 1351 (ν NO_2), 882, 794, and 671 (δ CH meta) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, ls, OH-1), 7.21 (1H, dt, J = 0.9, 1.5, 8.1 Hz, H-6), 7.42 (1H, t, J = 8.1 Hz, H-5), 7.72 (1H, d, J = 2.1 Hz, H-2), 7.81 (1H, dd, J = 0.8, 8.1 Hz, H-4) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 110.6 (C-2), 116.0 (C-4), 122.1 (C-6), 130.4 (C-5), 145.5 (C-3), 156.4 (C-1) ppm.

Purification of an *o*- and *p*-Nitrophenol (1 and 3) Mixture. According to the previous procedure and working with 2.0 g of A-21 (9.6 mmol of amine, 4.8 equiv), the residue obtained from CH_2Cl_2 evaporation weighed 280 mg (2.01 mmol) and was identified as a 92:8 mixture of *o*-**1** and *p*-nitophenol (**3**) by ^{1}H NMR spectrometry. Treatment of the bright-yellow resin by THF and THF/AcOH (572 μL, 600 mg, 10.0 mmol) followed by evaporation of the volatiles led to 254 mg (1.83 mmol, 91%) of the pure para isomer (**3**) as a yellow solid: mp 113−114 °C (lit.[25] 113−114 °C); FTIR (KBr) 3364 (ν OH), 3129 and 3093 (ν CH Ar), 1614 and 1600 (ν C═C), 1500 and 1350 (ν NO_2), 836 (δ CH para) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (1H, ls, OH-1), 6.94 (2H, dd, J = 1.1, 9.1 Hz, H-2,6), 8.19 (2H, dd, J = 1.1, 9.1 Hz, H-3,5) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 115.8 (C-2,6), 126.4 (C-3,5), 141.7 (C-4), 161.4 (C-1) ppm.

Synthesis of 2-Hydroxyacetophenone (11) and 4-Hydroxyacetophenone (12) by Fries Rearrangement of Phenyl Acetate (10) Followed by Purification on Amberlyst A-21.[23] Anhydrous $AlCl_3$ (5.3 g, 40 mmol) was added at once to phenyl acetate (**10**, 2.0 g, 15 mmol) in a round-bottomed flask equipped with a reflux condenser connected to Durand bottles filled with 0.1 M sodium hydroxide solution (CAUTION! Vigorous evolution of HCl). The yellow slurry was heated to 115 °C for 45 min before being cooled and hydrolyzed carefully by dropwise addition of cold water (20 mL). The solution was then poured in a mixture of ice (100 mL) and 12 N HCl (5 mL) and was extracted with ether (3 × 30 mL). Combined organic phases were dried over $MgSO_4$ and rotoevaporated. The resulting liquid (1.6 g, 12 mmol, 80% yield) analyzed by ^{1}H NMR was a 65:35 mixture of 2-hydroxyacetophenone (**11**) and 4-hydroxyacetophenone (**12**). The oil was diluted in CH_2Cl_2 (30 mL) and treated with dry Amberlyst A-21 (4.2 g, 20.2 mmol of amine) for 15 min under magnetic stirring. The mixture was filtered, and the resin was washed with CH_2Cl_2 (2 × 15 mL) and set aside to dry.

The filtrate was evaporated to give 1.122 g (69% of total initial amount) of 2-hydroxyacetophenone (**11**) as a colorless liquid with a purity of 88%. For the major constituent: R_f (heptane/AcOEt, 1/1) = 0.3; FTIR (film, NaCl) 3050 (br, ν OH), 1636 (ν C═O), 1614 and 1579 (ν C═C), 750 (δ CH ortho) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (3H, s, CH_3), 6.90 (1H, td, J = 1.0, 7.6 Hz, H-5), 6.97 (1H, dd, J = 1.1, 8.4 Hz, H-3), 7.47 (1H, td, J = 1.6, 7.7 Hz, H-4), 7.73 (1H, dd, J = 1.6, 8.0 Hz, H-6), 12.26 (1H, s, OH-2) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.6 (CH_3), 118.4 (C-3), 118.9 (C-5), 119.8 (C-1), 130.7 (C-6), 136.4 (C-4), 162.5 (C-2), 204.5 (C═O) ppm.

The dried resin was suspended in THF (30 mL) and was stirred for 15 min before being filtered off and rinsed with THF (2 × 15 mL). The resin was suspended again in the same amount of THF and treated with glacial acetic acid (1.2 mL, 1.2 g, 20.2 mmol) for 15 min before being filtered off and washed. Evaporation of the combined filtrates gave 456 mg (28% of total initial amount) of 4-hydroxyacetophenone (**12**) as a white solid that is 96% pure. For the major constituent: R_f (heptane/AcOEt, 1/1) = 0.6; mp 105−106C (lit.[26] 109−110 °C); FTIR (KBr) 3307 (ν OH), 3071 and 3000 (ν CH), 1657 (ν C═O), 1607 and 1579 (ν C═C), 850 (δ CH para) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (3H, s, CH_3), 6.97 (2H, dd, J = 1.8, 8.6 Hz, H-3,5), 7.93 (2H, dd, J = 1.7, 8.6 Hz, H-2,6), 8.20 (1H, ls, OH-4) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.3 (CH_3), 115.6 (C-3,5), 129.7 (C-1), 131.3 (C-2,6), 161.5 (C-4), 198.7 (C═O) ppm.

Purification of Libraries of Hydroxylated Benzaldehydes and Acetophenones. Mixtures of two isomers in 90/10 proportions (4 mmol) were treated by Amberlyst A-21 (400 mg, 1.92 mmol, 4.8 equiv on the 10% impurity) in CH_2Cl_2 (10 mL) in plastic syringes fitted with a valve and a septum on an orbital shaker for 15 min. The CH_2Cl_2 was drained out, and the resin was washed with another 10 mL of solvent. The combined extracts were evaporated to give the CH_2Cl_2 filtrate.

The dried resin was then resuspended in THF (10 mL) and treated the same way for 15 min. The THF was recuperated, and the resin was treated with another 10 mL of THF containing 115 μL of AcOH. This wash was combined with the previous one and evaporated to yield the THF filtrate. The two resulting products were weighed and analyzed by ^{1}H NMR in methanol-d_4.

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