

The Use of Anion Exchange Resins for the Synthesis of Combinatorial Libraries Containing Aryl and Heteroaryl Ethers

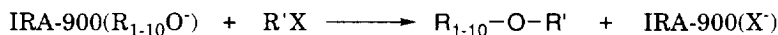
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Abstract: Quaternary ammonium exchange resins (Amberlite® IRA-900) were prepared that contained each a mixture of ten aryloxides and heteroaryloxides. The feasibility of generating combinatorial libraries containing aryl and heteroaryl ethers was demonstrated by reacting the resin's with a single electrophile (*n*-butyl bromide) to afford mixtures of ether products. The advantages of using quaternary ammonium exchange resins over solution phase chemistry to prepare this library are discussed.

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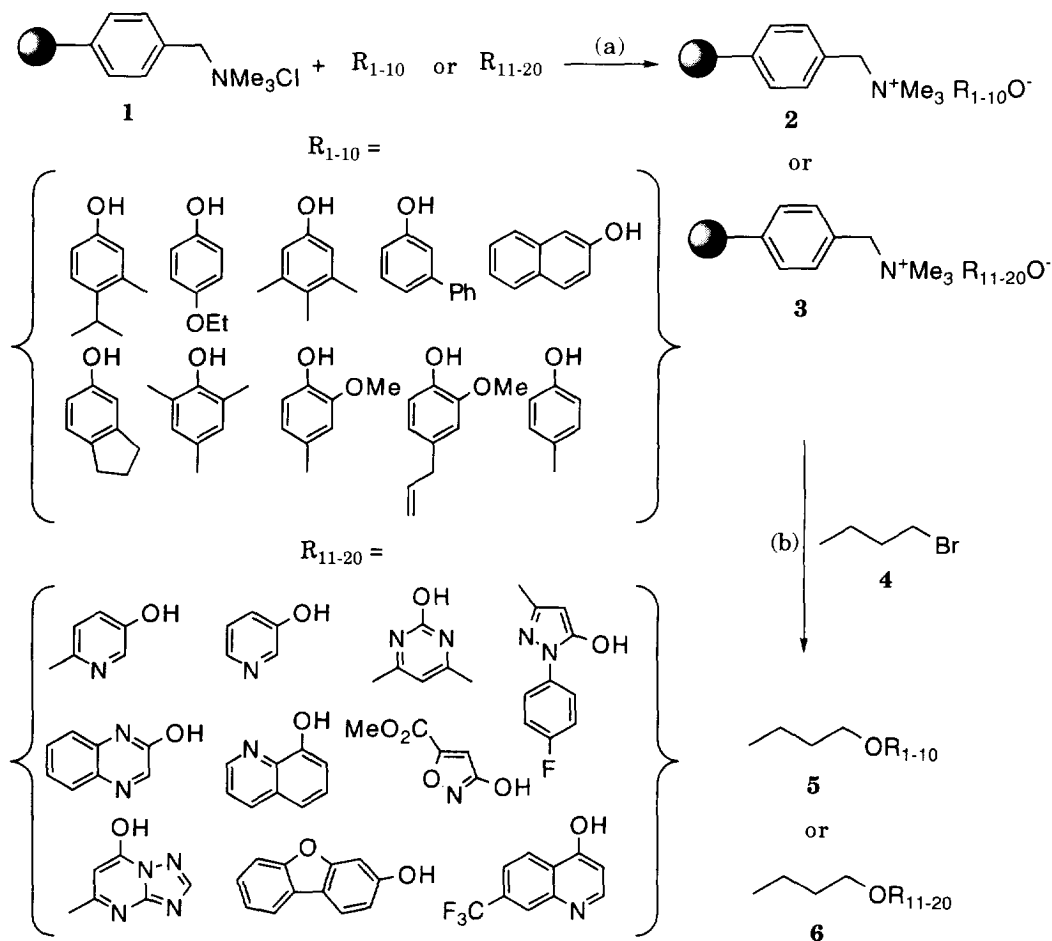
Polymer-bound reagents have been widely utilized for many chemical transformations in organic chemistry. Two of the most significant advantages of these reagents over their soluble counterparts are their ability to drive the reaction to completion by using excess and the ease of their separation from the desired product by filtration. Anion-exchange resins, specifically, have been used in various organic reactions.^{1,2,3} A benefit from this system is the nucleophilic power of the anions is greatly increased due to the ionic nature of the species. The quaternary ammonium exchange resins have been used to prepare aryl ethers⁴ and diaryloxymethanes.⁵ Thus, it has been demonstrated that Amberlite® IRA-900(ArO⁻) resins can be used to prepare pure single component products and this approach has been successfully utilized in our laboratories as well.¹ With the explosion of combinatorial chemistry,^{6,7} we have recently explored the feasibility of preparing aryl and heteroaryl ether libraries by using Amberlite IRA-900 resins that contain multiple components. The design of the library is based on reacting a single electrophile with a mixture of polymer bound nucleophiles to produce mixtures of ethers as shown in Scheme 1.



Scheme 1

Preparation of two batches of Amberlite® IRA-900(ArO⁻) resin containing ten components each is shown in Scheme 2. A known amount of the chloride form of Amberlite® IRA-900 is packed in a column and flushed with water, 10% aqueous sodium hydroxide, water until effluent is neutral, 95% ethanol, and finally with absolute ethanol. A solution of an equimolar mixture of ten phenols or ten hydroxy heterocycles (1.1 total equivalents based on polymer used) in ethanol is circulated through the column for five hours and the resin is washed with ethanol, tetrahydrofuran, ether and dried in vacuo and stored ready for use. To assure an equal distribution of products from a reaction of an electrophile with the polymer-bound nucleophiles, the mixture of

nucleophiles used to prepare the resins are selected by their relative reactivity, especially if an excess of polymer is used. For example, a set of ten electron rich phenols are placed on a batch of polymer or a set of ten phenols containing electron withdrawing groups are attached on a batch of polymer, etc. For the two examples below, the selection of R₁₋₁₀ is a representative case in which the phenols are substituted with electron donating groups. The second case R₁₁₋₂₀ is not grouped by their relative reactivity but its purpose is to demonstrate the variety of hydroxy heterocycles one could use.



Scheme 2. a) 1,000 mL of Amberlite[®] IRA-900(Cl⁻) (1) was packed in a column and flushed with 1 L of water, 3 L of 10% aqueous sodium hydroxide, water until effluent is neutral, 1 L of 95% ethanol, and finally with 1 L of absolute ethanol. A solution of an equimolar mixture of ten phenols (0.10 moles of each 4-isopropyl-3-methylphenol, 4-ethoxyphenol, 3,4,5-trimethylphenol, 3-phenylphenol, 2-naphthol, 5-indanol, 2,4,6-trimethylphenol, 2-methoxy-4-methylphenol, 4-allyl-2-methoxyphenol, 4-cresol) or ten hydroxy heterocycles (0.10 moles of each 5-hydroxy-2-methylpyridine, 3-hydroxypyridine, 4,6-dimethyl-2-hydroxypyrimidine, 1-(4-fluorophenyl)-5-hydroxy-3-methylpyrazole, 2-quinoxalinol, 8-hydroxyquinoline, methyl 3-hydroxy-5-isoxazolecarboxylate, 5-methyl-s-triazolo[1,5-a]pyrimidin-7-ol, 2-hydroxydibenzofuran, 7-(trifluoromethyl)-4-quinolinol) in ethanol is circulated through the column for 5 hours and the resin is washed with ethanol, tetrahydrofuran, ether and dried in vacuo; b) Amberlite[®] IRA-900(R₁₋₁₀O⁻) (2) or Amberlite[®] IRA-900(R₁₁₋₂₀O⁻) (3) (0.40 g, excess) and *n*-butyl bromide (90.4 mg, 0.66 mmol) in tetrahydrofuran (BHT free), 65°C, 6 h.

The Amberlite® IRA-900 resin (2) or (3) is then reacted with a known amount of *n*-butyl bromide (4) in tetrahydrofuran (BHT free) at 65°C for six hours (Scheme 2).⁸ The solution is filtered and the polymer is rinsed with tetrahydrofuran until no more product is eluted. The solvent is removed to give 123.8 mg (95% yield) and 100.8 mg of the desired mixture of ethers (5) and (6)⁹ respectively.¹⁰ The reaction is run such that an excess of resin (2) or (3) is used over the electrophile. This allows addition of polymer (2) or (3) without precise measurement for the reaction which becomes advantageous during automation and the excess of resin (2) or (3) also ensures the total consumption of the electrophile. The product mixtures (5) and (6) were analyzed and each of the expected molecular weights of the ten ethers of (5) and (6) are observed through gas chromatography and mass spectrometry. Figure 1 shows the GC/MS profile of the reaction product mixture (5). Although it is difficult to quantitate the relative amounts of each product, the mixture is close to equimolar. Other electrophiles have been explored and the same results were accomplished as with those cited by Gelbard⁴ with yields in the range of 62-100%.

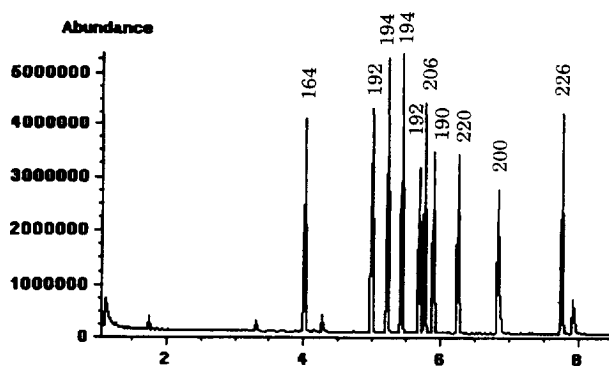


Figure 1. GC-MS of product mixture (5).¹¹

This method utilizing an anion exchange resin provides the advantage of solid phase reagents as well as anionic activation to yield product mixtures in excellent yields and in pure form, free from salts that would otherwise require an extra step for removal (i.e. extraction). In addition, the resin can be recycled simply by converting it back to the chloride form by treatment with a solution of hydrochloric acid. The simplicity and efficiency of this method is clear and makes it very attractive for automation in generating combinatorial libraries.

Other quaternary ammonium exchange resins have been prepared in our laboratories which contain mixtures of β -dicarbonyl compounds, mixtures of sulfinates, and mixtures of carboxylic acids to yield product mixtures of oxygen and carbon alkylated β -dicarbonyl compounds, sulfones, and carboxylic esters respectively. These resins are currently being used to prepare combinatorial libraries and will be reported in a future publication.

References and Notes

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8. The loading of the resins were in the range of 1.3-3.0 meq./g. This was calculated from a variety of resins, prepared in our laboratories, by elemental analysis of a common atom which was present in each of the nucleophiles (S,N, or a halogen) on a single batch of resin.
9. Products of mixture **6** that contained a potential nucleophilic nitrogen were not characterized to determined if alkylation occurred on the nitrogen or oxygen.
10. The 95% yield for product mixture **5** is based on equimolar amounts of products. No yield is reported for product mixture **6** since an equimolar mixture of products is not expected.
11. GC/MS was performed using a 5890 Hewlett Packard gas chromatograph and a Hewlett Packard 5970 Series Mass Selective Detector.
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