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Supported diazonium salts—convenient reagents for the combinatorial synthesis of azo dye

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Resin supported diazonium salts were synthesised. These were observed to be stable to storage and to provide a convenient means of compound handling and were employed in the solution synthesis of a 6 × 6 azo dye library.

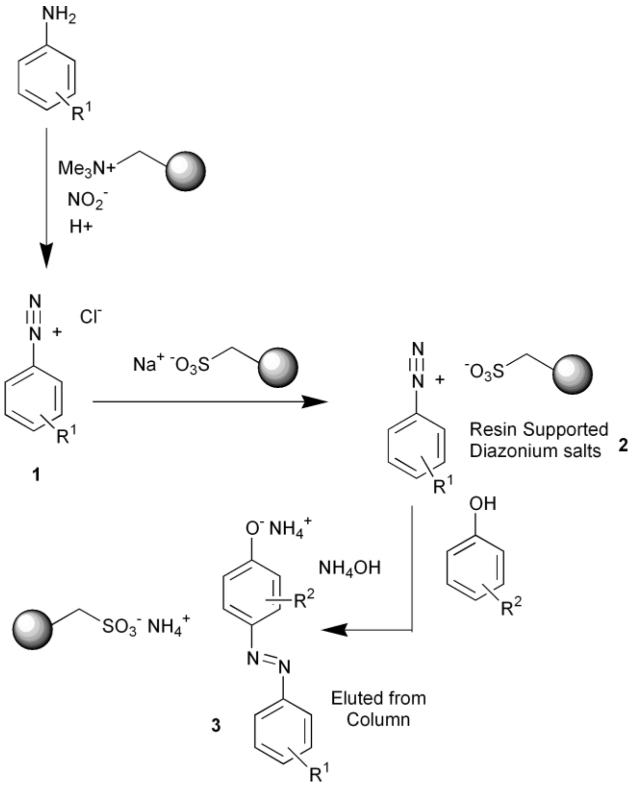
The use of combinatorial techniques is now firmly embedded in the research strategy of the pharmaceutical and agrochemical industry for the generation of libraries of small molecules.[1] The original work in the area of combinatorial chemistry[2] involved reactions on compounds covalently attached to polystyrene supports on which high reaction yields could be obtained through the use of high reactant concentrations, the excess of which could be removed after the reaction by thorough matrix washing. Solid phase synthesis is still a widely used technique but it has its disadvantages, which include the extra steps involved in substrate attachment to and detachment from the resin as well as the effects of the matrix environment on the outcome and kinetics of the reaction. Despite recent advances in MS[3] and NMR[4] techniques some difficulties are still encountered in analysing polymer-supported products.

An alternative to supported solid phase synthesis for a parallel combinatorial approach to new compounds is the use of polymer-supported reagents and scavengers.[5] Polymer supported reagents are materials ionically associated with, or covalently immobilised to insoluble matrices which can be added to a solution phase reaction, and later removed by filtration. Mass action can again be applied, while spent and excess resin can be removed by filtration. Ion exchange resins can be added to reactions to allow selective removal of either excess reagents or the desired product, or elimination of by-products in a parallelisation of classical ion-exchange purification methodology. An example of this methodology for the solution synthesis of azo dyes using an ion exchange resin-supported nitrite to generate the diazonium salts and purification by scavenger resins was recently reported while our work was in progress.[6]

Here we describe the preparation of stable ion-exchange resin supported diazonium species, and demonstrate their use as powerful reagents in the synthesis of azo dye libraries. This approach was achieved using two macroporous polystyrene ion-exchange resins allowing the use of aqueous based chemistry; Amberlyst A-15, which is a sulfonate acid based resin and Amberlyst A-26, which is functionalised with tetraalkylammonium groups.[7] In order to prepare the Amberlyst A-15 supported diazonium species, the free diazonium salt **1** was first generated (see Scheme 1). The aromatic amine was dissolved in concentrated HCl, followed by treatment with an excess of polymer-supported nitrite at 0 °C (this is a convenient and easy to handle source of nitrite).[5] The diazonium salt **1** was sequestered using an excess of Amberlyst A-15 to give polymer supported diazonium salt **2**.

The synthetic process was completed by mixing an excess of the Amberlyst A-15 supported diazonium species **2** with phenol at pH 9 to give the azo dye **3** in good purity (Fig. 1). The diazonium resins generated had a loading of between 0.6–1.0 mmol g^{-1} of diazonium salt.

In order to assess the stability of resin **2** a sample was dried and stored at −4 °C in the dark. Samples were removed over time and treated with phenol, and the azo dye generated was quantified by HPLC. The material was not observed to lose reactivity over an 8-day period. However after 12 weeks a reduction of 79% in yield was observed.



Scheme 1 Azo dye preparation.

The properties of Amberlyst A-15 and A-26 allow them to be used in series in order to sequester or release charged reagents, such as those involved in the diazotisation reaction. During the reaction of diazonium salt **2** to azo dye **3**, the species bound to the resin changes from cationic (diazonium) to anionic (phenolate anion), which should effect its release from the anionic resin sites of Amberlyst A-15.

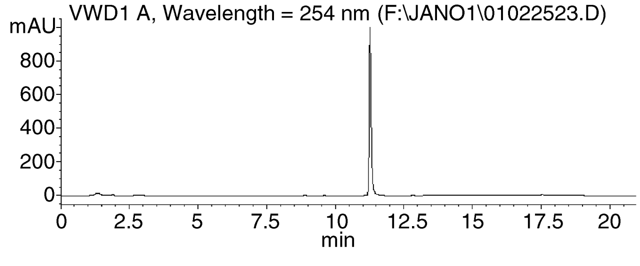


Fig. 1 HPLC of azo dye generated from diazonium resin **2**. Column conditions: 5 μm, C-18 150 × 4.6 mm column. 0.5 mL min^{-1}, 100% water to 100% acetonitrile over 10 min; 100% acetonitrile for 5 min.

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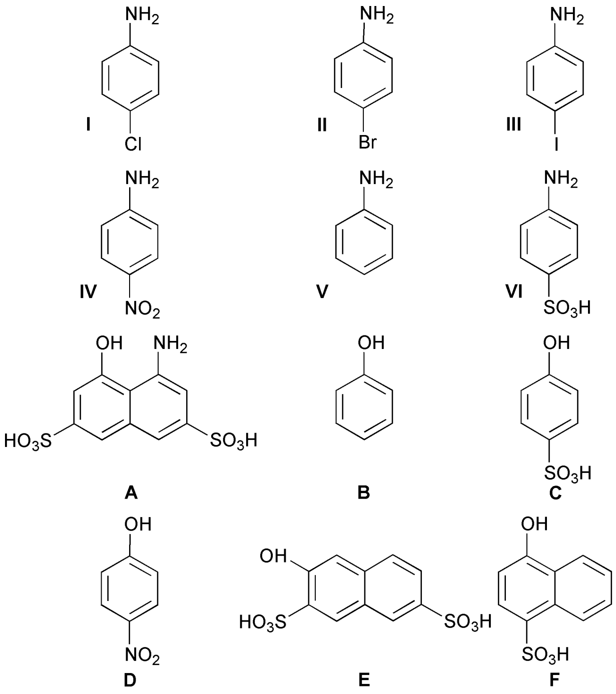

Fig. 2 Phenols **A**–**F**, aromatic amines **I**–**VI**.

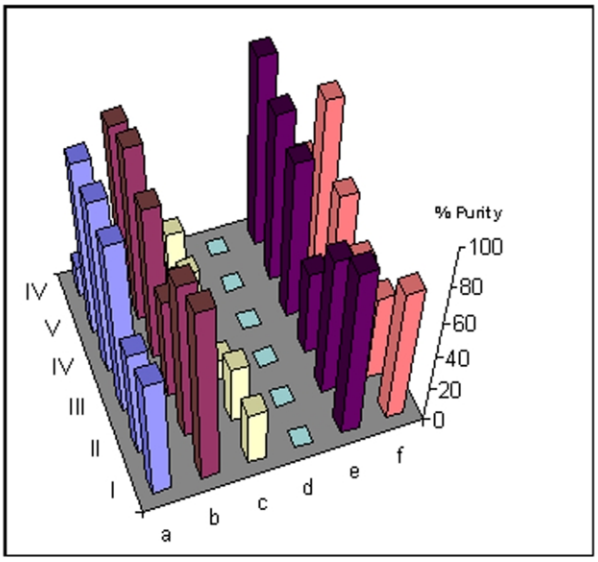

Fig. 3 Purity of dye library as monitored at 254 nm.

In order to demonstrate the validity of this approach a library of azo dyes (6 × 6) was synthesised. Thus 6 ion-exchange resin immobilised diazonium salts were prepared from 6 anilines (**I**–**VI**), and were treated with 6 phenols (**A**–**F**) in a parallel synthesis format (Fig. 2).†

The library was analysed by HPLC and MS (all $[M + H^+]^+$ were observed) and the results are presented in Fig. 3.

High purity was observed in series **A**, **B** and **E**, in accordance with the nucleophilicity of the phenols used in those series. The 4-hydroxybenzenesulfonic acid (series **C**) gave low purities/reaction yields possibly due to poor accessibility into the Amberlyst A-15 sulfonic acid based resin. As expected no reaction was observed with 4-nitrophenol (series **D**) due to their poor reactivity. The spectral properties of the dyes are shown in Fig. 4.

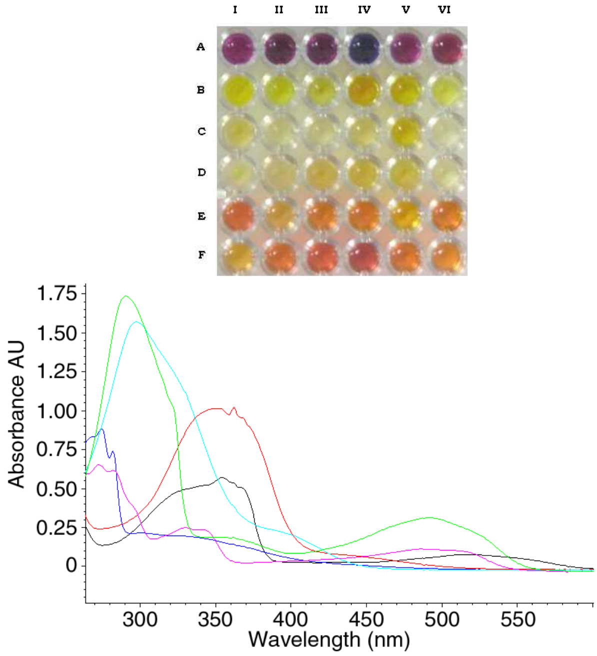

Fig. 4 UV/Vis spectra of dyes **VI–A** to **VI–F**, and visual analysis of full library.

In conclusion, the library synthesis demonstrates the use of polymer-supported diazonium salts as powerful agents for introducing diversity into azo dye libraries.

Notes and references

† **I** *p*-chloroaniline, **II** *p*-bromoaniline, **III** *p*-iodoaniline, **IV** *p*-nitroaniline, **V** aniline, **VI** sulfanilic acid. **A** 8-aminonaphthol-3,6-disulfonic acid (H-acid), **B** phenol, **C** 4-hydroxybenzenesulfonic acid, **D** 4-nitrophenol, **E** 2-naphthol-3,6-disulfonic acid, **F** 1-naphthol-4-sulfonic acid.

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7 A-15; 300–50 µm polystyrene beads with 11% DVB cross-linking and a loading of 4.7 mmol g^{-1}, and A-26; 300–850 µm polystyrene beads with 11% DVB cross-linking and a loading of 4.2 mmol g^{-1}, supplied by Avocado.