



Clean and efficient synthesis of azo dyes using polymer-supported reagents

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Summary

The recent technological advancements in polymer-supported reactions have led to the propagation of combinatorial chemistry as a method for the rapid and efficient preparation of novel functionalised molecules. An interesting and fast growing branch of this area is polymer-supported reagents. Here we describe the principles of generating diazonium salts and their coupling using polymer-supported reagents and sequestering agents, to form azo dyes in a clean manner.

Introduction

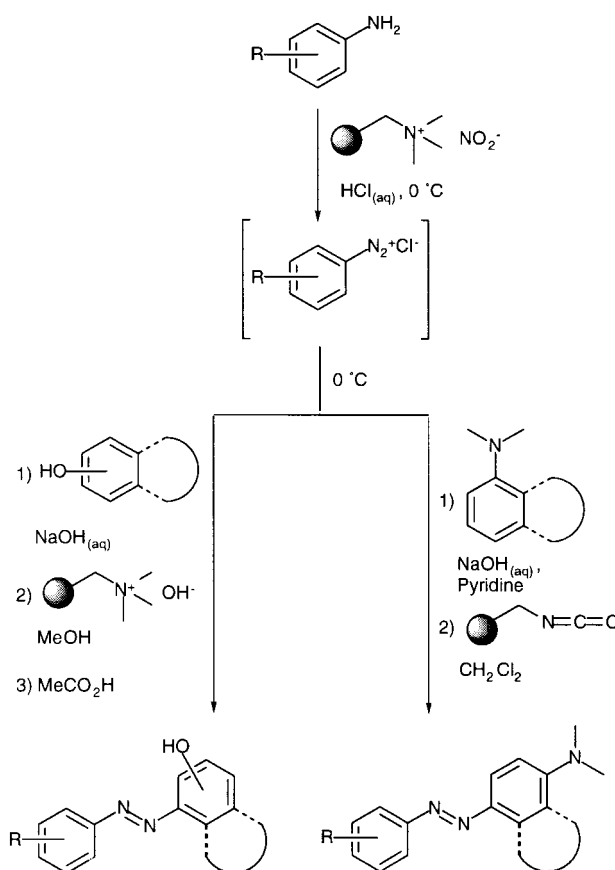
The application of combinatorial methods for the generation of novel chemical libraries, for use in the pharmaceutical and agrochemical industries, is now commonplace.¹ Increasingly, these methods are also being adopted by other sectors of the chemical industry in order to prepare novel materials for application in many diverse areas, especially catalysis.²

Many of these chemical libraries are obtained by carrying out linear synthetic sequences on polymer-supported substrates. While this approach has been very successful, there are still many associated problems and limitations which have not been fully addressed. Therefore, we have chosen to adopt a different strategy which allows us to synthesise a large number of compounds in solution, in a linear³ or convergent fashion,⁴ through the sequential use of polymer-supported reagents in a multi-step process. By adopting this approach we have previously been able to prepare a number of heterocyclic systems, including a small library of hydroxamic acid derivatives⁵ and some natural products.⁶ The advantage of this approach includes the ease of reaction monitoring (*i.e.* TLC, LC-MS) and the fact that with the appropriate design of sequences, clean products may be obtained using only simple filtrations rather than conventional work-up/purification techniques.

As a further demonstration of the potential of this approach we sought to synthesise a library of azo dye substances which are the most prevalent class of synthetic colourants. Although the textile, cosmetic and reprographics industries are by far the largest users of dyes, other applications range from analytical chemistry to the biomedical field in bacteriological work.⁷ The most common process for their preparation involves the diazotisation of an aromatic primary amine and the coupling of the resultant diazonium salt with a phenol or an aromatic amine. This is traditionally achieved using conventional wet chemistry which leads to large quantities of down stream waste. With the ever increasing environmental restrictions and control on the release of effluent the ability to effect a clean and efficient synthesis of the azo-compound is of considerable environmental and commercial importance.

Results and discussion

For the generation of the diazonium salts a selection of anilines were reacted with a polymer-supported nitrite (Scheme 1). The



Scheme 1 Preparation of the azo dyes.

preparation of this supported reagent⁸ was achieved by ion exchange of the tetraalkylammonium chloride resin (Amberlyst A-26) with an aqueous solution of NaNO₂.

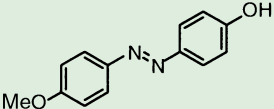
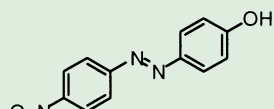
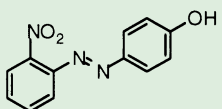
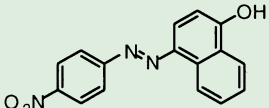
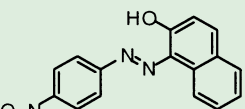
The generation of the diazonium salts was carried out on four aniline derivatives which were dissolved in HCl (37%), cooled to

Green Context

The clean production of azo dyes is a classical chemistry problem. The manufacture of this industrially important family of compounds is traditionally associated with large volumes of hazardous and coloured waste. The authors of this article have applied modern synthetic methodology to produce a more efficient and cleaner preparation of these compounds. The paper touches on clean synthesis, waste minimisation, the replacement or control of hazardous substances and novel improved separation technologies.

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Table 1 Diazo dyes derived from phenolic coupling

Product	Yield ^a (%)	Purity ^b (%)	LC-MS	pH = 0	pH = 14
	90	> 98	197.10(-)	Yellow	Yellow
	62	85	229.31(+)	Orange	Orange
	80	> 98	224.15(-)	Yellow	Red
	quant.	> 98	242.13(-)	Yellow	Orange
	78	80	292.19(-)	Orange	Blue
	quant.	> 98	292.16(-)	Yellow	Violet

^a Yields are based on the amount of phenolic derivative used. ^b Purity was determined by 400 MHz ¹H NMR spectroscopy.

0 °C and then the polymer-supported nitrite was added. The suspension was stirred for 5 min before the resin was removed by filtration. The filtrate was added dropwise at 0 °C to a solution of the phenolic derivative in NaOH (10%) with vigorous stirring which produced a coloured solution and a precipitate. The suspension was filtered with the filtrate being discarded and the precipitate then dissolved in MeOH. As the reactions were carried out with an excess of aniline, the methanolic solution contained the azo-derivative and unreacted aniline. In order to obtain the clean final product, the solution was subjected to a catch-and-release work-up which involved shaking the coloured solution with Dowex(OH). This captured only the product leaving a colourless solution after filtration. The isolated resin was subsequently washed with acetic acid releasing the pure product (Table 1). A slightly modified procedure was used for the preparation of the dimethylaniline series (Table 2). The solution of diazonium salt, prepared as described above, was added at 0 °C to a vigorously stirred solution of the dimethylaniline derivative in NaOH (10%) and pyridine.⁹ Following the addition, the pyridine was removed *in vacuo* and the resulting precipitate was removed by filtration. The excess of unreacted aniline was selectively removed from the product by dissolving the solid in methylene chloride and shaking the solution with a polymer-supported isocyanate.¹⁰ Filtration of the solution gave, after evaporation, the clean product. An attempt to couple the diazonium salt derived from 4-methoxyaniline with dimethylaniline gave no product. This result is in accordance with data for the relative rates of coupling for diazonium salts of aniline deriva-

tives: 4-NO₂:H:4-CH₃O 1300:1:0.1¹¹

As expected the products obtained acted as indicators and showed the characteristic change of colour at extremes of pH. All of the reactions produced essentially clean products as shown by LC-MS and ¹H NMR spectroscopy.

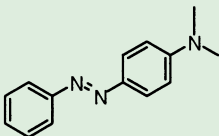
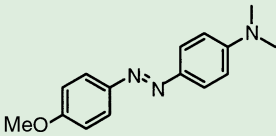
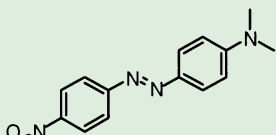
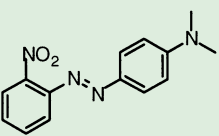
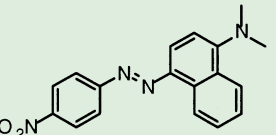
Conclusion

In conclusion, we have shown the possibility of using polymer-supported reagents for the generation of dyes without the need for conventional work-up and purification procedures. Moreover, the scheme of reaction demonstrates several different ways in which solid supported reagents can be used; their use as reagents, their use as scavengers in order to remove excess reactants or by-products and their use in catch-and-release procedures for purification. We believe that as the procedure only involves simple filtrations the reaction scheme could also be adopted for use in robotic systems in order to generate a large number of compounds. This would be of value in the generation of novel azo dye substances where rapid optimisation of the desired colour or properties are necessary.

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Table 2 Diazo dyes derived from dimethylaniline coupling

Product	Yield ^a (%)	Purity ^b (%)	LC-MS	pH = 0	pH = 14
	92	> 98	226.26(+)	Pink	Yellow
	—	—	—	—	—
	quant.	> 95	271.26(+)	Red	Orange
	quant.	> 98	271.21(+)	Red	Orange
	92	> 92	321.27(+)	Orange	Organge

^a Yields are based on the amount of dimethylaniline derivative used. ^b Purity was determined by 400 MHz ¹H NMR spectroscopy.

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