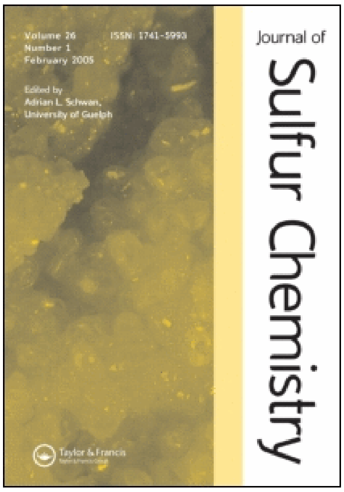

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COMMUNICATION

4-(4-Sulfamoylphenylazo)benzoic acid as a red safety-catch linker

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A red azo-dye, 4-(4-sulfamoylphenylazo)benzoic acid, is suggested as an alternative for the Kenner safety-catch linker. The deeply coloured molecule allows for naked-eye bead-property estimation with regard to loading level and linker integrity without affecting the functionality of the safety-catch linker. A practical synthesis of the title compound is reported.

Keywords: Naked-eye; Safety-catch linker; Bead-property estimation

1. Introduction

On-bead reaction monitoring suffers from the notorious limitations associated with the analysis of insoluble polymer-bound intermediates. Many methods developed so far to gain the necessary information are either destructive, time consuming, or require expensive analytical hardware. On-resin NMR [1, 2], IR [3–5], MS [6, 7], and electrochemical impedance spectroscopy (EIS) [8] experiments are valuable tools but tend to be elaborate, especially when quantitative information is sought. Colorimetric techniques, however, often offer fast, cheap, and simple access to bead-property estimation. Thus, colorimetric approaches can represent practical tools to qualitatively or quantitatively monitor solid-phase reactions [9–11].

2. Results and discussion

Support-bound primary amines present in aminomethylated polystyrene have commonly been detected with ninhydrin [12] and other classical reagents (recently reviewed [9]). The still widely used destructive Kaiser ninhydrin test is suited to indicate the absence of amino groups and can thus serve to monitor the degree of formation of amide bonds between sulfamoyl-functionalised carboxylic acids and aminomethylated polystyrene resins. Moreover, addition

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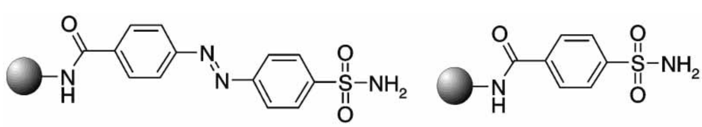
of the pH indicator bromophenol blue allows the course of amide-bond formation to be followed by continuous visual examination [13]. The change in colour of the coupling solution from deep violet to blue and finally greenish yellow indicates the consumption of free amino groups and can serve as a signal that the reaction proceeds as anticipated. This simple but elegant standard procedure, widely used for reaction control during synthesis of the construct **2**, requires that no bases other than the amino group of the polymer taking part in the bond formation be present in the reaction mixture. Novel supports like the recently proposed ULTRA-resins invented by Rademann and Barth [14] contain minor amounts of tertiary amine within their functional backbone. Tertiary amino groups cannot be subjected to amide-bond formation in a preceding capping step and therefore obstruct the use of pH-indicating dyes such as Bromophenol Blue for reaction control in this case. As this newly developed type of high-loading resin will undoubtedly gain widespread use in the near future, novel techniques for visual reaction monitoring are needed.

Using polymer-bound 4-(4-sulfamoylphenylazo)benzoic acid **1** (figure 1) as a surrogate for the Kenner safety-catch linker **2** analogue 4-sulfamoylbenzoic acid proposed by Ellman and co-workers [15], deeply coloured particles are obtained. The depth of the colour allows for a rough but easy and fast estimation of the loading level by naked-eye inspection.

By tuning the amount of azo-dye **5** applied in the coupling step that yields linker **1** from 0.07 to 4.0 equivalents, a row of resin samples with varied loading levels could successfully be prepared. Elemental analysis of the sulfur content indicated loading values ranging from zero to 0.92 mmol/g. We could observe the desired change in colour very well, starting with white, through orange, up to a deep red. After the preparation of a test sample with unknown loading level, the test resin was first compared with the previously composed test row and we predicted a loading level of 0.70–0.75 mmol/g based on the visual comparison. To verify our prediction, the sample was subjected to elemental analysis as well, and the sulfur content turned out to be 0.71 mmol/g.

It is apparent that the incorporation of an azo-functionality requires special precautions and that the novel red linker has limitations with respect to possible chemical transformations, especially as regards stability towards reducing agents. However, it is not the focus of this report to present a novel linker with broad applicability. Instead, we intend to demonstrate the astonishingly simple but useful novel concept of dyeing the beads by using coloured linker molecules. Hitherto known techniques using polymer-bound dyes to monitor reaction processes may, for example, attach surplus dyes on sites distant from anchor groups. This is conceptually different from the idea of replacing existing linkers by coloured analogues that are able to yield the same products that would have been obtained using the established, colourless anchor groups.

The red colour of our beads is not pH dependent. Neither addition of 2% TFA nor that of 2% DIPEA to the swollen polymer resulted in a shift of colour or colour depth. At the same time, the deep red colour can easily be destroyed by treatment with $SnCl_2$ hydrate in DMF. Should additional colour tests downstream in the reaction sequence appear necessary, a small aliquot of the beads can be decolourised by this widely used reduction reagent. Upon reduction, the



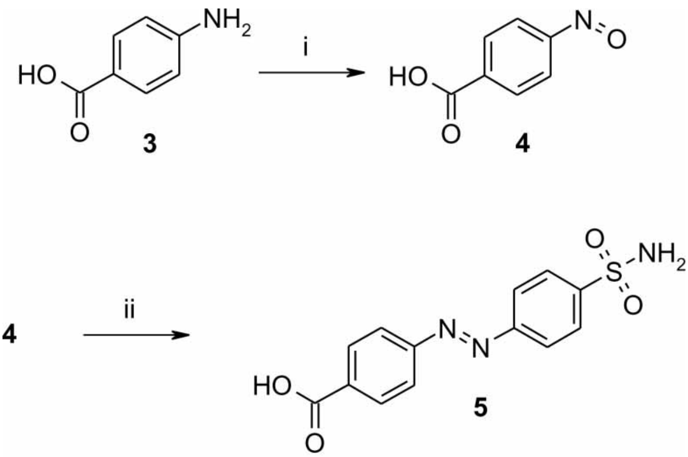
1 2

Figure 1. Polymer-bound 4-(4-sulfamoylphenylazo)benzoic acid **1** and Ellman's Kenner safety-catch linker variant **2**

azo functionality will be destroyed but the linker bound construct remains attached to the polymer bead. The structure of this putative polymer-bound phenylhydrazine derivative (not shown) is currently under investigation.

Subsequently, colour tests can be performed and are not hampered by the strong colour of the beads.

Since the required known 4-(4-sulfamoylphenylazo)benzoic acid **5** is not available commercially, a practical synthesis using cheap reagents starting from 4-aminobenzoic acid **3** was established, combining already known reactions (scheme 1) [15].



i. H_2O_2, Na_2WO_4, $Bu_4N^+Br^-$, H_3PO_4, 35-40 °C, 3h
ii. sulfanilamide, acetic acid, 110-120 ºC, 4 h

SCHEME 1 Synthetic pathway leading to 4-(4-sulfamoylphenylazo)benzoic acid **5**

3. Conclusions

The title construct **1** is suggested as a novel red safety-catch linker. It has already proved to be useful in the preparation of a series of compounds intended for a medicinal chemistry project. Experimental details and biological evaluation data will be reported in due course.

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