



A simple colorimetric test for the detection of polymer-supported tertiary alcohols

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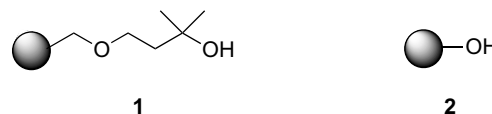
Received 5 June 2001; accepted 20 June 2001

Abstract—A simple, rapid method for the detection of polymer-supported tertiary alcohols is described. © 2001 Elsevier Science Ltd. All rights reserved.

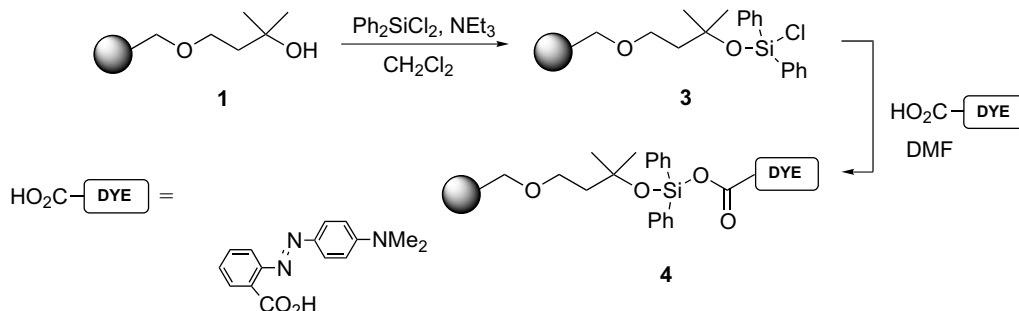
As part of our studies directed towards the development of novel linkers for solid-phase organic synthesis, we synthesised the polymer-supported tertiary alcohol (**1**) from Merrifield resin.¹ For the rapid, qualitative determination of the success of this reaction, two colour tests for the detection of polymer-supported alcohols were available to us.^{2,3} The first of these tests involves reaction of the polymer-supported alcohol with cyanuric chloride to form an activated ether derivative to which a dye (Mordant Orange 1) can be coupled. Despite the reported success of this test with tertiary alcohols, in our hands negative or ambiguous results were obtained.

The second test reported for the detection of polymer-supported alcohols involves reaction of the alcohol with *p*-toluenesulfonyl chloride followed by nucleophilic displacement of the resulting tosylate with 4-(4-nitrobenzyl)pyridine (PNBP). This method was unsuitable for our systems as it is known to give positive tests for Merrifield resin and, hence, residual chloromethyl groups from the synthesis of **1** would interfere with the test result. Regardless of the suitability of this test, we were perplexed by the authors' claim that positive

results were obtained for polymer-supported phenols despite negative results being obtained for phenols in solution phase. As the Wang linker was used for the literature studies with PNBP, it is more likely that residual hydroxymethyl groups from the linker interfered with the colour test. This was confirmed upon taking a small sample of freshly prepared phenol resin⁴ (**2**) and subjecting it to PNBP test conditions, whereupon a negative result was obtained.



Given the failure or unreliability of the reported colour tests for the detection of tertiary alcohols, there is clearly impetus for the development of alternative methods. We now report a new procedure specifically designed for the detection of polymer-supported tertiary alcohols.⁵ This method relies on the reaction of readily available, inexpensive diphenyldichlorosilane with polymer-supported tertiary alcohols such as **1** to form a polymer-supported diphenylsilylchloride ether (**3**) as an intermediate (Scheme 1). Subsequent treat-



Scheme 1.

Keywords: solid phase synthesis; detection methods; tertiary alcohols; colour test.

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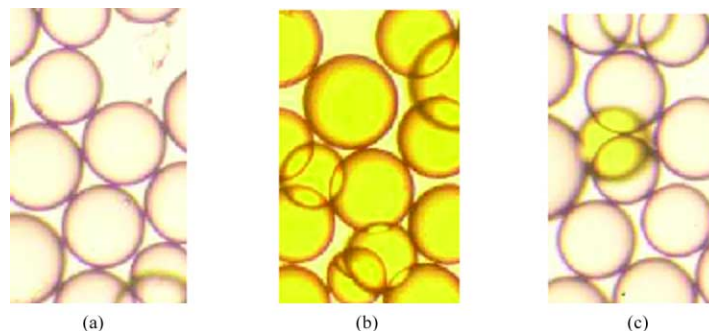
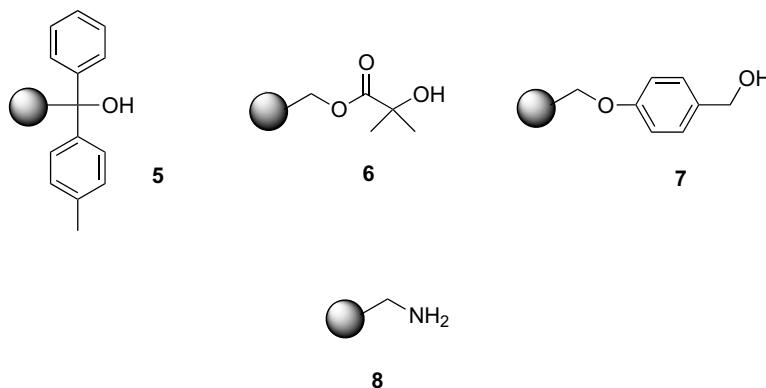


Figure 1. (a) Control experiment: resin **1** after treatment with methyl red followed by thorough washing; (b) detection test: resin **1** after treatment with dichlorodiphenylsilane and methyl red followed by thorough washing; (c) mixture of beads from control and detection test.

ment of **3** with methyl red affords the tethered dye (**4**) and results in a readily distinguishable orange/red colouration of the beads (Fig. 1).

In addition to **1**, this detection method gave positive results for other tertiary alcohols such as 4-methyltrityl alcohol resin (**5**) and polymer-supported 2-hydroxyisobutyric acid (**6**). The scope of the diphenyldichlorosilane/methyl red system was further demonstrated by positive test results being obtained for other alcoholic polymer supports such the Wang (**7**) and phenol (**2**) resins, as well as for aminomethyl polystyrene resin (**8**).



In order to establish a detection limit for the colour test, the polymer-supported alcohol **1** was capped using different quantities of acetic anhydride. The remaining free hydroxyl groups were quantified by treating the resin with diphenyldichlorosilane followed by cinnamyl alcohol. Subsequent TBAF cleavage and GC analysis of cinnamyl alcohol then gave the loading of unacetylated hydroxyl groups. Each of the acetylated resins was also subjected to the methyl red colour test. As shown in Table 1, staining of the resin is still easily detectable for loadings of approximately 0.07 mmol g^{-1} .

Attempts were also made to quantify the loading of **1** by performing an acidic cleavage of the dye from the resin and subsequent analysis by UV spectrometry. However, the loading obtained was significantly lower than the loading as determined by the cinnamyl alcohol method. This is due, in part, to low hydrolytic stability of the silyl ester linkage, as evidenced by the slow leaching of colour from the polymer beads into solution upon prolonged standing.

In summary, an efficient, unambiguous method for the qualitative detection of hindered polymer-supported alcohols has been developed. Significantly, this simple detection method is also applicable to a range of less hindered alcohols, including phenols, and can be used for low loadings of free hydroxyl groups on polymer supports. Therefore the present method for the detection of alcohols surpasses the reported methods for monitoring conversions involving transformations of polymer-supported alcohols.

Acknowledgements

The authors wish to acknowledge the supporting partners of the Centre for Combinatorial Chemistry for financial support. The funding partners are: Nycomed Amersham, AstraZeneca, GlaxoSmithKline, Lilly, CN Biosciences, Inc., Organon, Pfizer and Roche. We are also indebted to Mr. Martyn Fisher for the generous donation of phenol resin.

Table 1. Effect of loading of tertiary hydroxyl groups on detection with methyl red

Loading of free alcohol on 1 after acetylation (mmol g^{-1})	Test result
0.60	Positive
0.42	Positive
0.20	Positive
0.07	Positive

References

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2. Attardi, M. E.; Falchi, A.; Taddei, M. *Tetrahedron Lett.* **2000**, *41*, 7395.
3. Kuisle, O.; Lolo, M.; Quiñoà, E.; Riguera, R. *Tetrahedron* **1999**, *55*, 14807.
4. Phenol resin was prepared via Friedel–Crafts acylation of commercially available PS-DVB followed by Baeyer–Villager oxidation using MCPBA. Subsequent hydrolysis of the resulting ester afforded **2** with a loading of 2.1 mmol g⁻¹.
5. In a typical experiment a small sample of resin (5 mg) was swollen in 10% triethylamine in dry CH₂Cl₂ (200 μL) and treated with diphenyldichlorosilane (100 μL) for 10 minutes. The resin was then isolated by filtration, washed twice with 10% triethylamine in CH₂Cl₂ (500 μL) and re-suspended in a solution of 0.75% (w/v) of methyl red in DMF (300 μL) and agitated for 10 minutes. The resin was then collected by filtration and washed with DMF (5×500 μL×1 minute) and CH₂Cl₂ (5×500 μL×1 minute), by which time the washings were colourless and an orange colour persists on the resin beads, darkening to orange/red upon standing. If desired the resin can also be rinsed once with 500 μL of formic acid in order to develop a purple colouration of the beads. It is important to note that in some cases (e.g. resin **6**), further washing was necessary to remove the unreacted dye from the resin. For this reason it is recommended that for each test a blank experiment be run in parallel where the resin is treated only with dye to ensure the resin is adequately washed.