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Rapid detection of hydroxyl groups on solid-phase

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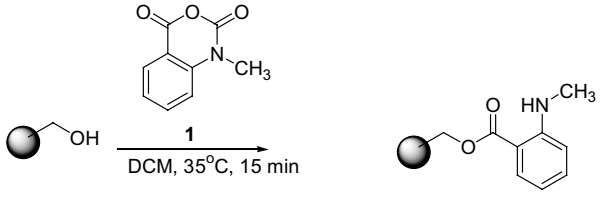
Abstract—A rapid method for the qualitative detection of hydroxyl groups on solid-phase has been developed. The method employs *N*-methylisatoic anhydride to derivatise resin-bound substrates possessing free hydroxyl functionality. The resultant fluorescent ester can be detected by visualisation under a standard laboratory UV lamp at 365 nm excitation.

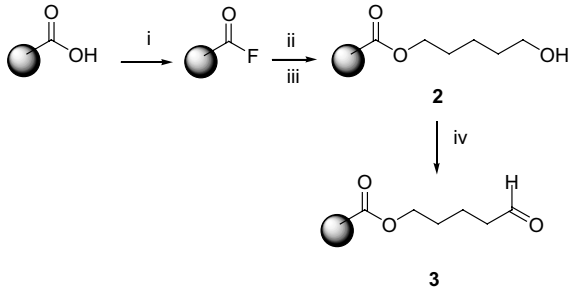
The synthesis of organic compounds on the solid-phase (SPOS) has grown rapidly in the last 10 years and progress of reactions is often monitored qualitatively by using colour tests to indicate the presence or otherwise of specific functional groups. Colour tests for resin-bound amines are well established and widely used, these include Kaiser,[1] chloranil[2,3] and TNBSA[4] tests. In contrast, although resin-bound hydroxyl groups are valuable intermediates in SPOS, there are no rapid, inexpensive tests to detect the presence or absence of this functional group on substrates bound to resin beads. Current methods are limited to either multistep derivatisation[5–7] or a single step derivatisation with an expensive fluorescent label, 9-anthroylnitrile.[8]

N-Methylisatoic anhydride (NMA) **1**, is an inexpensive fluorescent probe that has been used for the derivatisation of hydroxyl groups[9] to give a fluorescent ester with an excitation maxima of ~ 350 nm. We have exploited this reaction as a rapid and relatively inexpensive method to detect hydroxyl groups during SPOS (Scheme 1).

In order to demonstrate the scope of this reagent for detecting resin-bound hydroxyl groups, carboxypolystyrene (Novabiochem, 1.24 mmol g^{-1}) was converted to the resin-bound alcohol **2** (Scheme 2). A small quantity of beads was transferred into a glass vial, five drops of *N*-methylisatoic anhydride solution (2% in dichloromethane) were added and the mixture heated to 35 °C for 15 min. The beads were filtered, washed with dichloromethane and visualised at 365 nm under a standard laboratory UV lamp. Intense fluorescence was observed. Resin-bound alcohol **2** was treated with *o*-iodoxybenzoic acid (IBX) to furnish the resin-bound aldehyde **3,** [10] the NMA test was repeated and no visible fluorescence was detected.



Scheme 1. Reaction of resin-bound hydroxyl group with *N*-methylisatoic anhydride.



Scheme 2. (i) Cyanuric fluoride (5 equiv), pyridine (2 equiv), dichloromethane, 18 h. (ii) 5-(*t*-Butyldimethylsilyloxy)-1-pentanol (3 equiv), pyridine (2 equiv), DMAP (2 equiv), dichloromethane, 18 h. (iii) TBAF (1 M in THF) (4 equiv), acetic acid (4 equiv), 18 h. (iv) IBX (2 equiv), DMSO, 18 h.

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Table 1. Detection of aliphatic hydroxyl groups with NMA

Maximum pentanol loading ($\mu mol\,g^{-1}$)	Result
121	+
37	+
12	+
6	+
3	+
0	–

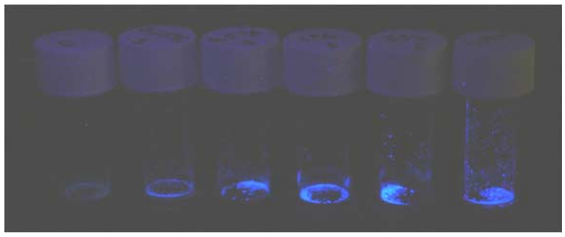
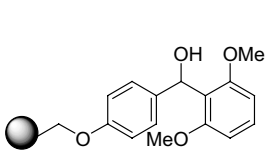


Figure 1. Beads under 365 nm fluorescent light, loading 0–121 $\mu mol\,g^{-1}$ from left to right.

In order to determine the sensitivity of this test we took resin-bound acid fluoride and coupled pentanol doped with a varying percentage of 5-(*t*-butyldimethylsilyloxy)-1-pentanol. The silyl group was removed with TBAF to reveal resin-bound pentanol. The resins were treated with NMA solution, the results show that the NMA test is extremely sensitive, detecting loading down to 3 $\mu mol\,g^{-1}$ (Table 1, Fig. 1).

In addition to the unhindered primary alcohol **2**, the reagent could detect the secondary hydroxyl group on Rink acid resin **4** but was unable to detect unequivocally the sterically hindered tertiary hydroxyl group on trityl alcohol resin **5**. The reagent gave a positive result with resin-bound phenol (Adv. Chem. Tech. phenol resin). Consistent with other literature tests for hydroxyl groups, amine functionality (Novabiochem aminomethyl polystyrene) gave a positive result.[6–8] A negative result was obtained with resin-bound carboxylic acid (Novabiochem carboxypolystyrene).



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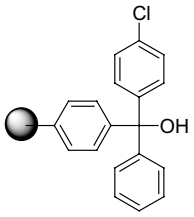

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In conclusion we have outlined a simple qualitative test for the detection of hydroxyl groups on solid-phase.

Acknowledgements

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References and notes

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10. The IR spectrum of **3** showed a gain in aldehyde (C–H stretch 2728 cm^{-1}), the absence of OH stretching in the spectrum was inconclusive.