Synthesis of 4,5-Dihydro-oxazoles Immobilized on Silica Gel

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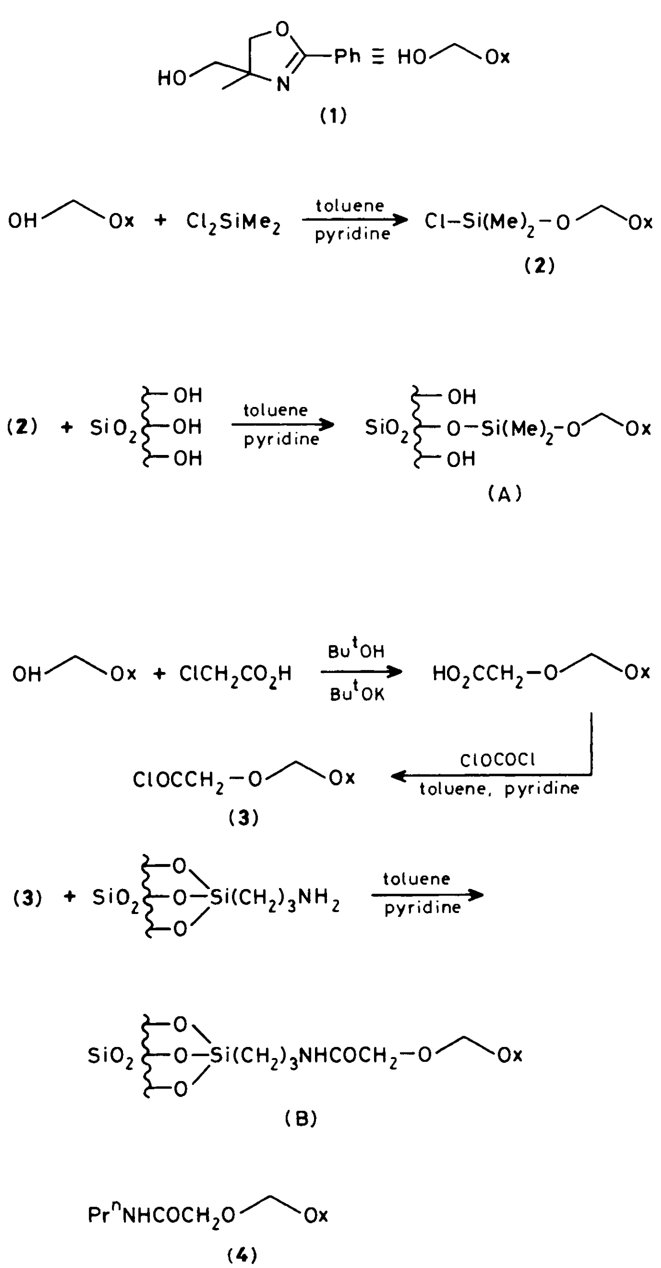
4,5-Dihydro-oxazole (**1**) has been anchored to silica gel, affording immobilized species that, in comparison with similar systems bound to polystyrene matrices, readily undergo hydrolytic cleavage of the oxazoline ring to give the supported amino alcohol and the free soluble carboxylic acid.

Functionalized polymers have proved to be of value in organic synthesis, *e.g.* Insoluble matrices have been used to immobilize reactive species[1] and as phase transfer catalysts.[2] Cross-linked polystyrene is the most commonly used support, along with inorganic oxides such as silica gel and alumina[3].

In this communication we report the synthesis of 4,5-dihydro-oxazoles[4] immobilized on silica gel, and our study of the hydrolysis reaction that affords the amino alcohol anchored to the matrix.

From the 4,5-dihydro-oxazole (**1**) (15.0 g, 0.08 mmol) and unfunctionalized silica gel (15.0 g), the supported dihydro-oxazoline (A) (19.6 g) was obtained (corresponding to 0.94 mmol oxazole g^{-1}) (Scheme 1).

Starting from a 3-aminopropylfunctionalized silica gel (5.0

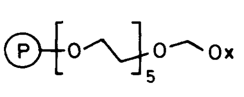


Scheme 1

g; 0.78 mequiv. NH_2 g^{-1}), a different supported species (B) was obtained (5.9 g; corresponding to 0.66 mmol oxazole g^{-1}), (Scheme 2).

Dilhydro-oxazoles bound to crosslinked polystyrene have been used in Mayers type reactions.[5] However we must report incomplete hydrolysis of the supported oxazoles in acidic medium.

Systems (A) and (B) undergo hydrolysis in acidic aqueous solution at 40 °C. The reaction mixture (functionalized silica gel, 3.0 g; 1M HCl, 3.0 ml; H_2O 47.0 ml) was shaken to produce a gentle vortex mixing action. After 3 h the reaction mixture was filtered and the support washed with Et_2O. The aqueous solution from the original filtrate was extracted with Et_2O, which combined with the other organic solution was then extracted with aqueous 10% $NaHCO_3$. The resulting basic aqueous layer was acidified using HCl at 0 °C to afford 0.30 g $PhCO_2H$ from 3 g (A) (corresponding to *ca.* 0.8 mmol $PhCO_2H$ g^{-1}), and 0.20 g of $PhCO_2H$ (corresponding to *ca.* 0.5 mmol g^{-1}) from 3 g (B).



(C)

Scheme 2

The ready opening of the oxazole ring (even if the recovery of the benzoic acid does not correspond to the original content of the support) is probably a consequence of the silica gel matrix. Its hydrophilic nature provides an environment more favourable to the hydrolysis reaction with aqueous HCl, compared with the hydrophobic polystyrene. The oxazole (**4**) was synthesised in order to obtain a soluble compound which could be compared to the supported species (B). This compound did not undergo the hydrolytic cleavage faster than the 4,5-dihydro-oxazole (**1**) under the same experimental conditions reported for the immobilized species (B) (*ca.* 90% ring opening after 3 h at 40 °C).

We have also synthesised a polystyrene-anchored dihydro-oxazole having an alkyl spacing chain inserted between the insoluble matrix and the ring, species (C). In this system, containing on average of five OCH_2CH_2 groups between support and oxazole moiety, the functionality is removed from the lipophilic organic matrix, and consequently the hydrolytic cleavage is less hindered.

Starting from 3.0 g of (C) (0.8 mmol oxazole g^{-1}), and carrying out the hydrolysis reaction according to the previously reported conditions,[5a] [tetrahydrofuran (190 ml), 3M HCl (12 ml)], after 10 h at 60 °C, 0.22 g of $PhCO_2H$ were recovered, corresponding to *ca.* 0.6 mmol $PhCO_2H$ g^{-1}.† Systems (A) and (B) do not need be previously swollen by standing in a suitable solvent either for the synthesis or the hydrolysis, making the reactions easier. However, the silica gel particles are fragile and must be stirred with care to avoid being reduced to powder.

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† In ref. 5a the polymer-bound oxazole was heated at 60 °C for 48 h; this suggests that it is the spacing chain that keeps the oxazole moiety far from the hydrophobic organic matrix.

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