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Short Research Article

Solid-phase synthesis of cyclic imines — potential for radiolabelling†

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Introduction

Solid supports may be useful as a means of localizing radioactivity, particularly if the final radiolabelled compounds are released in high purity upon cleavage from resin. Recently, we have developed a method by which simple resin-bound esters can be converted into a range of bioactive heterocycles (benzofurans,[1,2] indoles,[2] benzothiophenes,[3] and quinolines[4]) using titanium alkylidene reagents[5] **1** (Figure 1), which are Schrock carbenes. The heterocycles are produced in very high purity and require no chromatography and a radiolabel could potentially be incorporated into the target heterocycles at C-2 if a radiolabelled carboxylic acid is used.

Results and discussion

Radiochemical labelling of piperidine alkaloids and related compounds is of interest because of the range of biological activities that such compounds can have.

Indeed the piperidine alkaloids γ-coniceine **2** and (*S*)-coniine **3** were responsible for the toxic effects of the cup of hemlock used to execute the ancient Greek philosopher Socrates (Figure 2).[6] Furthermore, the

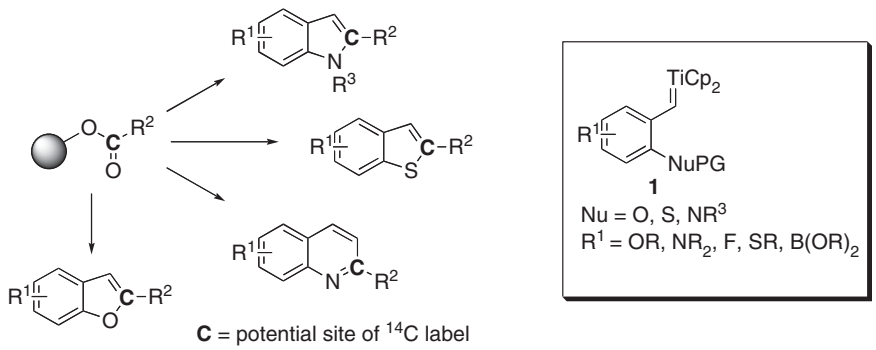

Figure 1 Versatility of organotitanium reagents.

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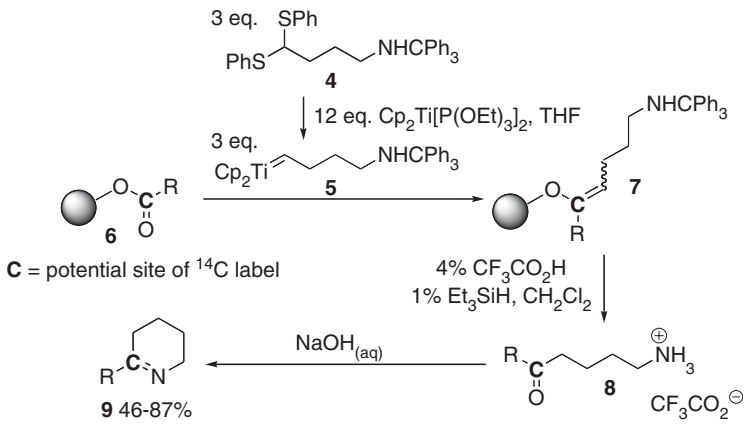
Figure 2 Piperidine alkaloids from hemlock.



Scheme 1

drug Ritalin that treats attention-deficit-hyperactivity-disorder[7] and the insect repellent Bayrepel[8] also contain a 2-substituted piperidine core. Therefore, we devised a route for the synthesis of 6-membered and 7-membered cyclic imines from resin-bound esters. In the six membered-ring series,[9] titanium alkylidene **5** was generated from thioacetal **4** and used to convert esters **6** into enol ethers **7**, which were cleaved with acid and the resulting ketones **8** cyclized in base to give imines in good purity and respectable yield (Scheme 1).

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REFERENCES

1. McKiernan GJ, Hartley RC. *Org Lett* 2003; **5**: 4389–4392.
2. Macleod C, McKiernan GJ, Guthrie EJ, Farrugia LJ, Hamprecht DW, Macritchie J, Hartley RC. *J Org Chem* 2003; **68**: 387–401.
3. Roberts CF, Hartley RC. *J Org Chem* 2004; **69**: 6145–6148.
4. Macleod C, Austin CA, Hamprecht DW, Hartley RC. *Tetrahedron Lett* 2004; **45**: 8879–8882.
5. Hartley RC, McKiernan GJ. *J Chem Soc Perkin Trans 1* 2002; 2763–2793.
6. Reynolds T. *Phytochemistry* 2005; **66**: 1399–1406.
7. Gilman V. *Chem Eng News* 2005; **83**(25): 108.
8. Badolo A, Ilboudo-Sanogo E, Ouedraogo AP, Constantini C. *Trop Med Int Health* 2004; **9**: 330–334.
9. Adriaenssens LV, Austin CA, Gibson M, Smith D, Hartley RC. *Eur J Org Chem* 2006; 4998–5001.