A Concise Synthesis of the Natural Product Carpanone Using Solid-Supported Reagents and Scavengers.

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Abstract: Polymer-supported reagents have been applied to the synthesis of the natural product carpanone resulting in a clean and efficient synthesis without the requirement for conventional purification techniques.

Key words: natural products, cyclization, polymer-supported reagents

The synthesis of the natural product carpanone **1** has been reported previously.[1] The most obvious approach to this and related molecules, is based upon an oxidative coupling of an electron rich *o*-hydroxystyrene derivative and subsequent intramolecular Diels-Alder cyclization. More recently this approach has been elegantly adapted to a general solid-phase synthesis of carpanone-like molecules.[2]

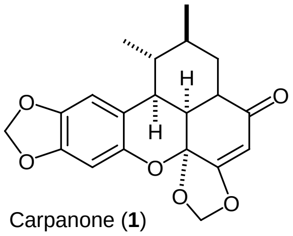

Carpanone (**1**)

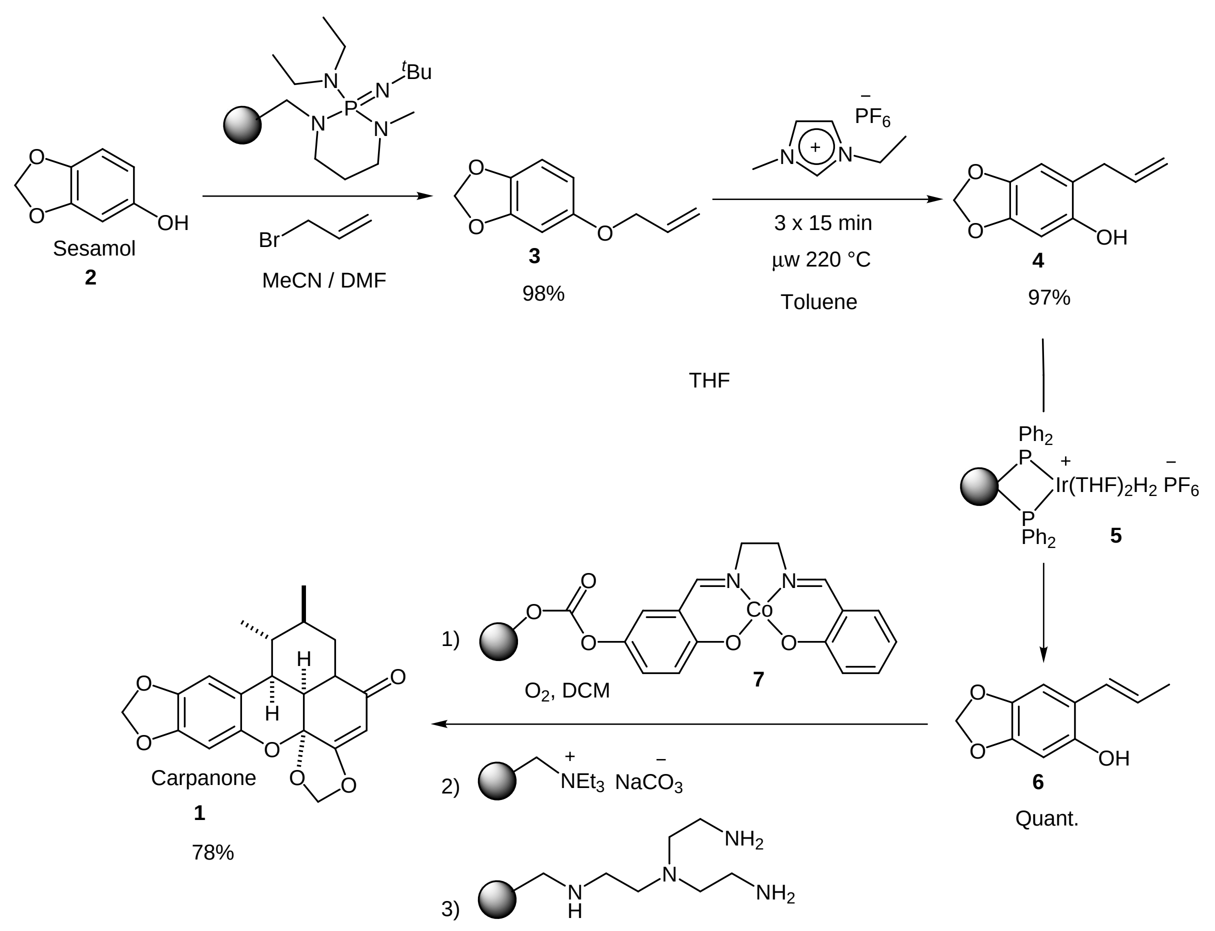
Figure 1 Structure of the natural product carpanone.

We became interested in these systems for several reasons. Firstly these types of compounds had not been extensively evaluated for their biological significance, they possess attractive complex architectures that can be generated from simple starting materials and, moreover, they could potentially be obtained using a combination of supported-reagents and scavengers in a multi-step process.[3]

We have shown previously that this approach is very effective for natural product synthesis[4] and in the generation of libraries of heterocyclic compounds.[5] The key advantages of these methods are the ability to run reactions at reasonable scale yet be able to obtain pure products by the simple task of filtration and solvent removal. The reactions can be convergent, mutually incompatible reagents, when immobilised, can be used simultaneously and scavenger resins can be used to clean-up poorer reactions. Here we report the concise preparation of carpanone **1** using these concepts, although one should also recognise the opportunities that could arise by simple variation of the starting material inputs leading to other unique structures.[2]

The synthesis begins from commercially available sesamol **2** which is readily allylated in acetonitrile containing a small quantity of dimethylformamide, using allyl bromide and a polymer-supported phosphazene base (PS-BEMP)[6] to give the aryl ether **3** in 98% yield (Scheme 1). The product **3** was then subjected to Claisen rearrangement. This was best achieved using toluene and an ionic liquid (1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate[7]) and heating in a focussed microwave well system[8] (3 × 15 min) at up to 220°C. The pure substituted phenol **4** was obtained in better than 97% conversion. This microwave assisted Claisen process has proven to be extremely successful in related examples; these results will be reported separately. Next, smooth isomerisation of the double bond in compound **4** to give the conjugated material **6** was achieved using an immobilised version of Felkin's iridium catalyst developed for in solution isomerisation.[9] In this particular example we chose to first complex the catalyst onto polymer-supported triphenylphosphine **5**.[10] This was then used to effect the isomerisation of **4** in THF at ambient temperature to give conjugated system **6** quantitatively and with a *trans* to *cis* ratio of 11:1.[11] We believe this new supported catalyst should find numerous applications in organic synthesis. Finally, the conversion of styrene **6** to carpanone **1** was investigated using various polymer-supported oxidants.[12] The most satisfactory of which was the supported-cobalt salen complex **7** which, in the presence of oxygen, in dichloromethane, gave carpanone **1** in 78% yield (Scheme 1).[12c] The clean product was obtained after filtration of the spent catalyst and brief scavenging with PS-trisamine[13] and polymer-supported carbonate resin.[14] The product was identical in all respects to previously characterised and reported material.[15]

The short synthesis reported above constitutes a further demonstration of the power of using these immobilised systems to provide complex products without requiring conventional work-up procedures such as chromatography, crystallisation or distillation. We believe it is possible to use these reagents in many more elaborate one-pot multi-step, multi-reagent combinations, even with the aim of discovering new chemical transformations. These attractive concepts open up phenomenal future opportunities for organic synthesis.



Scheme 1 Synthesis of the natural product carpanone.

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References and Notes

(1) (a) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, 6696. (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437. (c) Nishiyama, A.; Eto, H.; Tevada, Y.; Iguchi, M.; Yamamura, S. *Chem. Pharm. Bull.* **1983**, *31*, 2834. (d) Iyer, M. R.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1662.

(2) Lindsley, C. W.; Chan, L. K.; Goess, B. C.; Joseph, R.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 422.

(3) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (b) Thompson, L. A. *Curr. Opin. Chem.* **2000**, *4*, 324. (c) Kobayahi, S. *Curr. Opin. Chem.* **2000**, *4*, 338. (d) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 650.

(4) (a) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251. (b) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253.

(5) (a) Baxendale, I. R.; Brusotti, G.; Matsunka, M.; Ley, S. V. *J. Chem. Soc. Perkin Trans. 1* **2001**, submitted. (b) Ley, S. V.; Lumeras, L.; Nesi, M.; Baxendale, I. R. *Comb. Chem. High Throughput Screening* **2001**, submitted. (c) Caldarelli, M.; Baxendale, I. R.; Ley, S. V. *J. Green Chem.* **2000**, *43.* (d) Baxendale, I. R.; Ley, S. V. *Biorg. Med. Chem. Lett.* **2000**, *10*, 1983. (e) Caldarelli, M.; Habermann, J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 107. (f) Caldarelli, M.; Habermann, J.; Ley, S. V. *Biorg. Med. Chem. Lett.* **1999**, *9*, 2049. (g) Habermann, J.; Ley, S. V.; Smits, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2421. (h) Habermann, J.; Ley, S, V.; Scicinski, J. J.; Scott, J. S.; Smits, R.; Thomas, A. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2425. (i) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1. (J) Haunert, F.; Bolli, M. H.; Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2235. (k) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A.-G.; Hall, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239. (l) Bolli, M. H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2243. (m) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3127.

(6) The reagent polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP) had a loading of 2.3 mmol g^{-1} and was purchased from Fluka; Cat. No. 20026.

(7) Purchased from Aldrich Cat. No. 44,466-9.

(8) A fully automated *Coherent Synthesis System* microwave machine was used. This was supplied by Personal Chemistry: Hamnesplanaden 5, SE-753 19 Uppsala, Sweden; www.personalchemistry.com.

(9) (a) Yamamoto, R.; Fujikawa, N.; Miyanra, N. *Synth. Commum.* **2000**, *30*, 2383. (b) Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc. Chem. Commun.* **1978**, 694. (c) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Chem. Soc. Chem. Commun.* **1976**, 716.

(10) **Polymer-supported Iridium isomerisation catalyst**
Triphenylphospine on polymer support (Fluka, 3mmol/g, 1 g, 2.98 mmol) was added to a suspension of chloro(1,5-cyclooctadiene)iridium(I)dimer (250 mg, 0.37 mmol) in THF (8 mL). The resulting suspension was agitated under an atmosphere of argon at ambient temperature for 24 h. During this time the polymer slowly turned a dark red-brown colour. A solution of ammonium hexafluorophosphate (500 mg, 2.98 mmol) in THF (9 mL) was then added and the resulting suspension agitated for a further 24 h. The polymer was filtered and washed sequentially with ether and DCM and dried in vacuo. Elemental analysis indicated 9.2% Iridium, corresponding to a theoretical loading of 0.47 mmol/g.

(11) Only the *trans* isomer is able to subsequently react to form carpanone **1**, with the unreactive *cis* form being scavenged in the penultimate clean-up step using polymer suported carbonate.

(12) (a) Thoma, H.; Morioka, H.; Takizawa, S.; Arisawa, M.; Kita, Y. *Tetrahedron* **2001**, *57*, 345. (b) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc. Perkin Trans. 1*. **1999**, 669. (c) Annis, D. A.; Jacobsen, E. N.; *J. Am. Chem. Soc.* **1999**, *121*, 4147. See also ref 1 above.

(13) Polyamine resin HL (200-400 mesh) 3.30 mmolg^{-1}; and the alternative polymer-supported tris-(2-aminoethyl)-amine (Cat. No. 01-64-0170) was 2.1 mmol g^{-1};Novabiochem.

(14) Carbonate on polymer support 3.5 mmolg^{-1} $NaCO_3$; Fluka; Cat. No. 21850.

(15) Brophy, G. C.; Mohandas, J.; Slaytor, M.; Sternhell, S.; Watson, T. R.; Wilson, L. A. *Tetrahedron Lett.* **1969**, 5159.

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