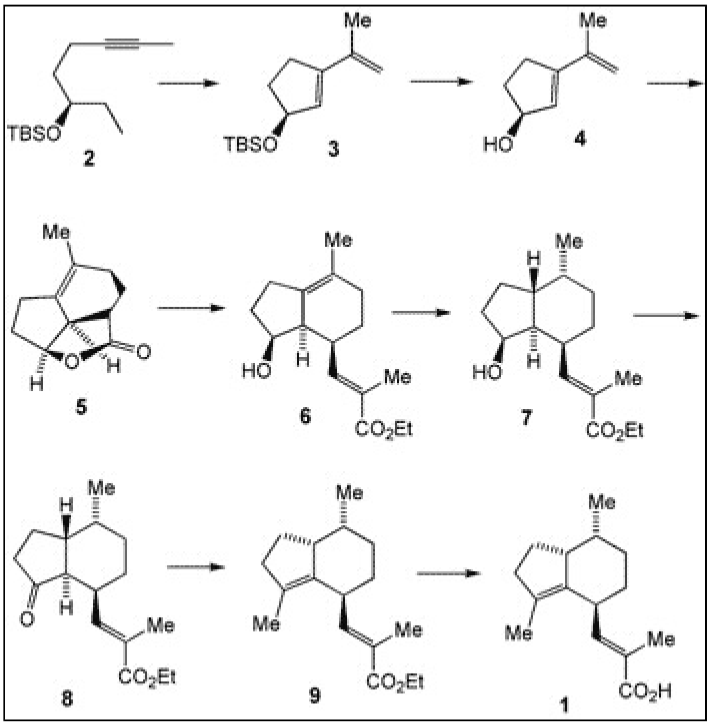
Noteworthy Chemistry

March 9, 2009

- First synthesis of valerenic acid, a potent $GABA_A$ receptor modulator
- The right solvent improves conversion of an amine to a hydroxylamine
- Pyrolysis in a template gives a large-pore nanostructured ceramic
- Create ordered mesoporous silver by controlling template hydrophobicity
- Use a lithium acetate catalyst for mild deprotection of aryl silyl ethers
- Create functional colloidal particles with a degradable nanogel template
- This furan synthesis uses successive metal-catalyzed processes

Here is the first synthesis of valerenic acid, a potent GABA type A receptor modulator. The sesquiterpenoid valerenic acid (**1**) is isolated from the roots of the herb valerian (*Valeriana officinalis*); it has important interactions with neurotransmitters in the mammalian brain. Specifically, **1** is a potent modulator of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain. GABA mediates its action by interacting with GABA type A ($GABA_A$) receptors.

J. Ramharter and J. Mulzer* at the University of Vienna suggest that this function of **1** may provide useful activity against central nervous system disorders such as panic attacks, learning deficits, and epileptic seizures. They note that no total synthesis of **1** has been reported until now.



The authors' synthesis uses readily available racemic 3-*tert*-butyldimethylsilyloxy-1-octen-6-yne (**2**) as a starting material. The structural arrangement of **2** allows smooth ring-closing metathesis to yield cyclopentene **3**. Deprotection of the TBS group using Bu_4NF gives alcohol **4**, which is treated with $MgBr_2$ and methyl acrylate to undergo a metal-coordinated, stereoselective Diels–Alder reaction that yields tricyclic lactone **5**. Next, **5** is reduced to a lactol (not isolated) with *i*-Bu_2AlH, followed by a Wittig reaction with $Ph_3P{=}CMeCO_2Et$ to produce bicyclic enoate **6**.

Crabtree's catalyst (an indium complex) is then used under reducing conditions (H_2, 1 bar) to form hydrindane

7 stereo- and chemoselectively. The hydroxyl group on **7** is oxidized with 2-iodoxybenzoic acid to the corresponding ketone **8**, followed by sequential deprotonation to the enolate, formation of a vinyl trifluoromethanesulfonate, and Negishi coupling with $Pd(PPh_3)_4$ and Me_2Zn to give olefinic ester **9**. Finally, base-catalyzed hydrolysis leads to racemic **1**.

The authors completed their stereoselective synthesis by repeating the procedure using enantiomerically pure (*S*)-**2**, which leads to the natural enantiomer (–)-**1**. They note that the initial stereochemical conformation at the carbinol center in **2** controls the stereogenic centers in the target molecule up to the point where it is discarded in favor of an endocyclic double bond. This synthesis should provide researchers with a source of useful quantities of **1** to further assess its efficacy in modulating the $GABA_A$ receptor. (*Org. Lett.* **2009,** *11,* 1151–1153; **W. Jerry Patterson**)

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The right solvent improves a three-step conversion of an amine to a hydroxylamine. Several three-step protocols for converting α-methylbenzylamine to (*S*)-*N*-(1-phenylethyl)hydroxylamine have been published. For example, alkylating α-methylbenzylamine with $BrCH_2CN$, followed by *m*-chloroperbenzoic acid oxidation of the amine to a nitrone and finally aminolysis with NH_2OH at elevated temperature effects the desired conversion.

However, this route uses four solvents and requires the isolation of three solids. I. Patel*, N. A. Smith, and S. N. G. Tyler at AstraZeneca (Bristol, UK) report that all three steps can be carried out in ethyl acetate to avoid having to isolate the intermediates. The use of ethyl acetate also allows the final step to be carried out under milder conditions: heating the aqueous ethyl acetate solution of the nitrone with *p*-toluenesulfonic acid at 40 ° C. (*Org. Process Res. Dev.* **2009,** *13,* 49–53; **Will Watson**)

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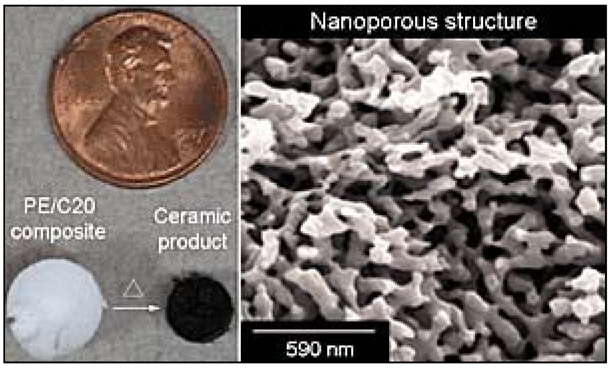
Pyrolyzing polysilazane in a polyethylene template gives a large-pore nanostructured ceramic. Inorganic ceramics are useful materials, but they are difficult to process into complex structures and shapes. Nonoxide ceramics have been made from readily processible organic polymers, but the pore sizes of the resultant ceramics are small (≤5 nm). B. H. Jones and T. P. Lodge* at the University of Minnesota (Minneapolis) developed a new process that replicates the structure of a polymeric bicontinuous microemulsion (BμE) and makes it possible to prepare a nanoporous ceramic monolith with large pore size (60–100 nm).

The BμE is a polymer blend that consists of polyethylene (PE), poly(ethylene-*alt*-propylene) (PEP), and poly (ethylene-*b*-ethylene-*alt*-propylene) (PE-PEP). Soaking the polymer blend in THF removes the PEP polymer component. Polysilazane Ceraset 20 (C20, KiON Corp.) is introduced into, and cross-linked within, the resulting nanoporous PE template. The PE–C20 composite is pyrolyzed at 1000 °C to give a ceramic that retains the original shape, structure, and pore size of the BμE template.



The advantage of this process over the silica and carbon templates used by other researchers is that ceramic conversion and template removal is accomplished in a single step because of the thermal degradability of the organic polymers. The result is a pore structure entirely unprecedented in ceramic materials: It is disordered and continuous in three dimensions, and it has a previously unattainable size range. The procedure is simple and flexible, and it preserves the structure of the original polymer blend. This work may pave the way toward the production of nanoporous ceramics with tunable sizes and shapes. (*J. Am. Chem. Soc.* **2009,** *131,* 1676–1677; **Ben Zhong Tang**)

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Create highly ordered mesoporous silver by controlling template surface hydrophobicity. J. M. Kim, J.-N. Kim, and coauthors at Sungkyunkwan University (Suwon, Korea) and Korea Institute of Energy Research (Daejeon) synthesized silver with ordered mesopores by using a hard-template method. Cubic mesoporous silica KIT-6 was used as the template.

According to the authors, the key to synthesizing mesoporous silver is control over the surface hydrophobicity of KIT-6. $AgNO_3$ is impregnated into the pores of methyl group–modified KIT-6 by an incipient wetness method. The impregnated material is then dried and reduced at high temperatures. The hard silica template is dissolved in aqueous NaOH.

The hydrophobic surface of the silica plays an important role in forming the mesoporous silver structure because it causes the $AgNO_3$ to aggregate and retards the mobility of the silver ions. In contrast, the surface of unmodified pure silica KIT-6 has hydrophilic silanol groups, which allow even dispersion of $AgNO_3$. Upon reduction, isolated silver nanoparticles form instead of a network. Transmission electron microscope images confirm the importance of a hydrophobic surface for making the mesoporous silver. (*Chem. Commun.* **2009,** **650–652**; **George Xiu Song Zhao**)

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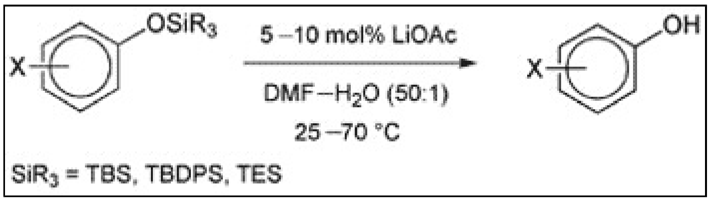
Use a lithium acetate catalyst for mild deprotection of aryl silyl ethers. Silyl ethers are well-recognized protecting groups for alcohols and phenols that have applications in natural product synthesis. Removing a phenolic *tert*-butyldimethylsilyl (TBS) ether usually requires stoichiometric fluoride sources, acids, or strong bases. Z.-H. Sun and coauthors at Fudan University and Shanghai Saijia Chemicals (both in Shanghai) developed a mild deprotection method for aryl silyl ethers that uses LiOAc.

When the authors used the TBS ether of 4-*tert*-butylphenol as a model substrate, they initially noticed that weak bases such as acetates are effective catalysts. LiOAc was superior to the corresponding potassium and sodium salts. LiBr and LiCl failed to catalyze the deprotection, confirming the need to use a base. DMF was the best solvent, but water is also necessary for the catalytic reaction. This permits the use of inexpensive $LiOAc{\cdot}2H_2O$.



Free or *tert*-butoxycarbonyl–protected amino, epoxide, and halogen groups are well tolerated by this method, which can also be used in enols and heterocyclic systems. In terms of selectivity, phenolic TBS ethers are deprotected in presence of aliphatic TBS ethers, phenolic *tert*-butyldiphenylsilyl (TBDPS) ethers, and triethylsilyl (TES) ethers at room temperature. Full deprotection is achieved at 70 °C. The method is operationally simple, mild, selective, and tolerant to many functional groups. (*J. Org. Chem.* **2009,** *74,* **1781–1784**; **José C. Barros**)

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Create functional colloidal particles with a degradable nanogel template. X.-Z. Zhang and co-workers at Wuhan University (China) have prepared mesoporous silica colloids by using a degradable nanogel templating method. They synthesized the monodisperse and spherical nanogels by using Michael addition to cross-link the *N,N*’-bis(acryloyl)cystamine (BAC) monomer with triethylenetetramine (TETA) or tetraethylenepentamine (TEPA) under controlled stoichiometric conditions (1:2 mol ratio of amine to acrylate) and moderate concentrations.

The authors attribute differences in particle sizes as determined via a particle size analyzer (190 nm) and transmission electron microscopy (TEM, 50 nm) to the evaporation of water and subsequent nanogel shrinkage during TEM analysis. The nanogel framework catalyzes the formation of core–shell hybrid silica colloids (190 nm) by hydrolysis of $(EtO)_4Si$. The size of the hybrid colloidal particles depends on the size of the nanogel and is influenced by the choice of amine (TEPA or TETA) used in nanogel synthesis.

Calcination at 400 °C for 24 h results in the loss of the characteristic N–H bending and C–H asymmetric bending vibrations of the nanogel, confirming the removal of the organic template. The authors show that the S–S bonds in the nanogel can be cleaved by 1,4-dithiothreitol without affecting the shape and uniformity of the colloidal particles, but this degradation mechanism creates a rough surface and a mesoporous structure (245.4 m^2/g specific surface area). The researchers state that this hybrid templating technique is versatile and lends itself to developing functional colloidal silica particles. (*Langmuir* **2009,** *25,* 1923–1926; LaShanda Korley)

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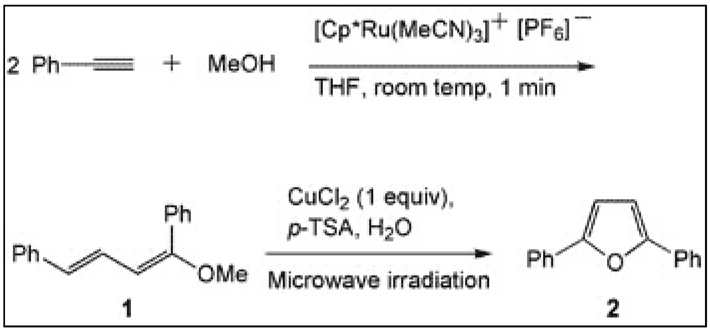
This furan synthesis uses successive metal-catalyzed processes. Functionalized furans are important components of bioactive molecules. M. Beller, P. H. Dixneuf, and coauthors at the University of Rennes (France), the South China University of Technology (Guangzhou), and the University of Rostock (Germany) describe a novel way to prepare 2,5-disubstituted furans directly from terminal aryl alkynes in one pot.

The synthesis begins with ruthenium catalysis to form an intermediate 1,3-dienyl ether (**1**) via a "click" dimerization of the terminal alkynes. This is followed by copper-catalyzed cyclization to the desired aryl-substituted furan ring (**2**). Cp* is pentamethylcyclopentadienyl; *p*-TSA is *p*-toluenesulfonic acid.



Unexpectedly, compound **1** forms very efficiently, with yields up to 92% after a reaction time of only 1 min. The conversion to **2** proceeds with yields as high as 99%.

This reaction sequence appears to be highly stereoselective when forming the dienyl ethers and the subsequent 2,5-substituted furans. The authors suggest that the procedure could be extended to mixed aryl–furan polymers based on aromatic diynes. (*Angew. Chem., Int. Ed.* **2009,** *48,* 1681–1684; W. Jerry Patterson)

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