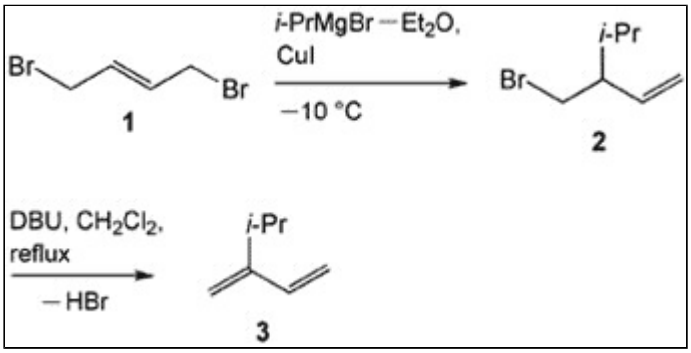
Noteworthy Chemistry

May 11, 2009

Here's a simple, practical synthesis of 2-substituted 1,3-butadienes. The 1,3-diene structure is an important building block for organic synthesis, but few butadienes substituted at C-2 are commercially available. Existing procedures for preparing simple 2-substituted derivatives in multigram quantities have various problems that limit their usefulness. S. Sen, S. Singh, and S. M. Sieburth* at Temple University (Philadelphia) overcame this limitation with a simple two-step procedure that starts from commercially available *trans*-1,4-dibromo-2-butene (**1**).

A key to the process is treating **1** with a Grignard reagent in diethyl ether in the presence of CuI. These conditions promote S_N2' (rather than S_N2) substitution and place the alkyl group at the desired 2-position (**2**).

Dehydrohalogenating **2** with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) completely consumes the intermediate bromide and leads to the target substituted 1,3-diene (**3**) with overall yields of 51–72%. Because some variants



of **3** are volatile and not easily handled, product yields in these cases were determined by trapping them as the Diels–Alder adduct using *N*-phenylmaleimide as the dienophile.

The authors verified that this two-step process can easily be conducted on a multigram scale. They also carried out the dehydrohalogenation step by using a triisopropylsilanol-catalyzed KOH method, which they consider preferable to DBU when low–molecular weight diene products must be isolated. (*J. Org. Chem.* **2009,** *74,* 2884–2886; W. Jerry Patterson)

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Explore the behavior of polypeptides under confinement. G. Floudas* and colleagues at the Max Planck Institute for Polymer Research (Mainz, Germany), the University of Ioannina (Greece), the Biomedical Research Institute (Ioannina), and the Max Planck Institute of Microstructure Physics (Halle, Germany) explored the influence of cylindrical confinement on the assembly behavior and segmental dynamics of poly(γ-benzyl-L-glutamate) (PBLG) in well-defined, nanoporous templates.

The authors synthesized PBLG via amine-initiated BLG *N*-carboxy anhydride polymerization in anodic aluminum oxide (AAO) membranes (25, 35, 60, 200, and 400 nm pore diam) that were surface-functionalized with 3-aminopropyltriethoxysilane. They investigated PBLG nanorods that were released (by etching the AAO with acid) and supported (surface uncovered, but AAO confined). All pore diameters contained an α-helical secondary structure arranged in a hexagonal unit cell.

By using dielectric spectroscopy, the authors observed a difference between the released and supported PBLG nanorods in the temperature dependence of the segmental dynamics. For supported PBLG nanorods (25, 45, and 65 nm diam), the relaxation behavior relative to the bulk depends on whether the temperature is above or below the glass-transition temperature of bulk PBLG (T_g ~11 °C). For example, supported PBLG nanorods (35 nm) had slower segmental dynamics when measured 60 °C, but faster relaxation phenomena at –10 °C relative to bulk PBLG. The released PBLG nanostructures and supported PBLG nanorods (200 and 400 nm) showed strong temperature dependence—"fragile" segmental dynamics—relative to bulk PBLG. The supported PBLG nanorods (≤65 nm) displayed weaker temperature dependence of the segmental relaxation behavior—"strong" dynamics—and a reduction in T_g by as much as 50 °C.

The authors note that the observed segmental dynamics of the supported PBLG confined at pore diameters ≤65 nm is mostly likely influenced not only by cylindrical confinement, but also by the presence of the AAO pore walls, which may have silanol groups on the surface that are capable of hydrogen bonding with PBLG and disrupting the peptide conformation. (*Macromolecules* **2009,** *42,* **2881–2885**; **LaShanda Korley**)

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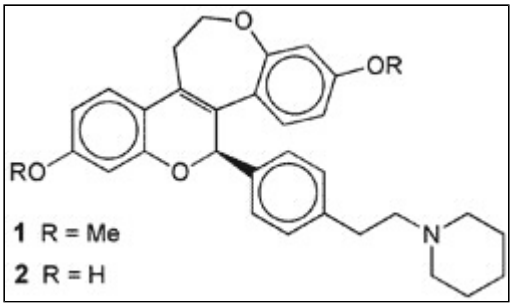
The choice between base- and acid-catalyzed racemization depends on the substrate. The (*R*)-enantiomer of tetracyclic compound **1** has high selective estrogen receptor modulator activity, whereas its (*S*)-counterpart does not. The enantiomers can be separated by chiral chromatography, and the efficiency of this process can be improved by racemizing and recycling the unwanted (*S*)-enantiomer.



Although phenolic precursor **2** racemizes under basic conditions (e.g., LiOH in DMF at 80 °C), these conditions have no effect on compound **1**. But X. Li and co-workers at Johnson & Johnson Pharmaceutical Research and Development (Raritan, NJ, and Beerse, Belgium) show that the acid-catalyzed racemization of **1** or its enantiomer proceeds smoothly. Optimized conditions (1 M HCl in EtOH) give near-racemic material in 99% isolated yield and >95% chemical purity. (*Org. Process Res. Dev.* **2009,** *13,* **102–105**; **Will Watson**)

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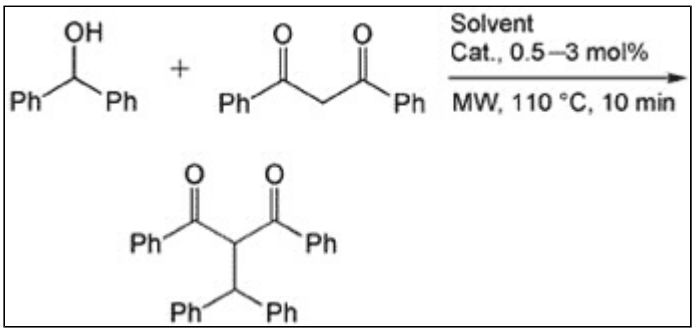
Perform microwave organic synthesis in chromatography vials. Microwave-assisted organic synthesis (MAOS) helps shorten reaction times and permits rapid reaction optimization by parallel screening of variables such as catalyst concentration, solvents, and additives. However, analysis of reaction mixtures involves transferring samples from reaction vessels to chromatography vials; this time-consuming process can cause sample contamination.

M. Damm and C. O. Kappe* at Karl Franzens University Graz (Austria) use standard HPLC–GC vials as reaction vessels for microwave synthesis. They fashioned sintered SiC plates that can hold 20 vials in a 5 x 4 matrix. Four plates can be used so that 80 reactions can be run at a time. The SiC plate is chemically inert, has a low thermal expansion coefficient, and strongly absorbs microwaves, making the microwave-absorption properties of solvents in reaction mixtures irrelevant.

Initial experiments established the best vial septa (PTFE-coated silicone) and the optimum reaction volume (0.5–1.5 mL), and showed that heating is homogeneous across the SiC plate. In a second set of experiments,

the authors compared three methods of esterifying carboxylic acids: MeOH–$Yb(OTf)_3$, $MeC(OMe)_3$, and MeI–DBU; all require homogeneous conditions to facilitate CG analysis of the reaction mixture. Finally, the authors screened catalysts and solvents for the metal-catalyzed C–C bond formation between alcohols



and active methylene compounds (see figure).

This parallel reaction design provides excellent temperature and reaction homogeneity for high-throughput reaction optimization. The studies could not be performed without the SiC plate because the microwave absorption characteristics of each solvent produce different reaction temperatures. (*J. Comb. Chem.* **2009**, *11,* **460-468**; **José C. Barros**)

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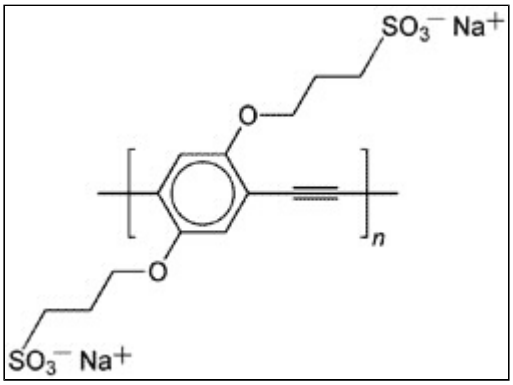
Poly(*p*-phenyleneethynylene) chains helically wrap carbon nanotubes. Carbon nanotubes (CNTs) have exotic properties but are difficult to process. Wrapping CNTs noncovalently with soluble polymers can make CNTs soluble and preserve their excellent properties. Poly(*m*-phenylenevinylene) and poly(phenylacetylene) helically wrap CNTs.

D. A. Bonnell, J. G. Saven, M. J. Therien, and coauthors at the University of Pennsylvania (Philadelphia), Seoul National University, and Duke University (Durham, NC) found that poly(*p*-phenyleneethynylene) (PPE) also helically wraps CNTs, adding another member to the family of π-conjugated polymers that form CNT–polymer nanohybrids with well-defined morphologies.



The polymer used by the researchers is amphiphilic, disulfonated, water-soluble PPE derivative **1**. It disentangles CNTs from their bundled forms under ultrasonication conditions and disperses them into the aqueous phase as highly individualized strands. The polymer chain wraps the CNT wall helically with a pitch of 13 ± 2 nm, in good agreement with the theoretically predicted pitch value. Given that conjugated polymer–CNT hybrids often show synergistic optoelectronic effects, this work may stimulate the development of superhelical assemblies of CNTs with other technologically important semiconducting polymers. (*Nano Lett.* **2009,** *9,* **1414–1418**; **Ben Zhong Tang**)

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Ionic liquids help make photonic crystals with high dielectric constants. To prepare 3-D photonic crystals with complete band gaps, the refractive index contrast must be sufficiently high. In other words, the matrix material must have a high dielectric constant. Because of this requirement, germanium photonic crystals with high dielectric constants have received a great deal of attention.

3-D germanium photonic crystals have been made by using several techniques, including template-assisted electrodeposition. The electrochemical deposition method is difficult to operate, however, because of hydrogen evolution during the process.

According to Y. Li, F. Endres, and coauthors at the Harbin Institute of Technology (China) and the Clausthal University of Technology (Clausthal-Zellerfeld, Germany), the ionic liquid 1-ethyl-3-methylimidazolium bis (trifluoromethanesulfonyl)amide can be used as a solvent in the germanium electrodeposition process. The electrochemical reduction properties in the ionic liquid were characterized by cyclic voltammetry. The reduction peak from Ge(IV) to Ge(0) appeared at a more positive potential than when the ionic liquid contained the 1-hexyl-3-methylimidazolium cation. Thus it is possible to deposit germanium in an ionic liquid.

Scanning electron microscopy images showed uniform germanium structures. The thickness, quality, and pore size of the germanium structure can be controlled by adjusting the ionic liquid, the template, and the concentration of $GeCl_4$. (*Angew. Chem., Int. Ed.* **2009,** *48,* **2703–2707**; **George Xiu Song Zhao**)

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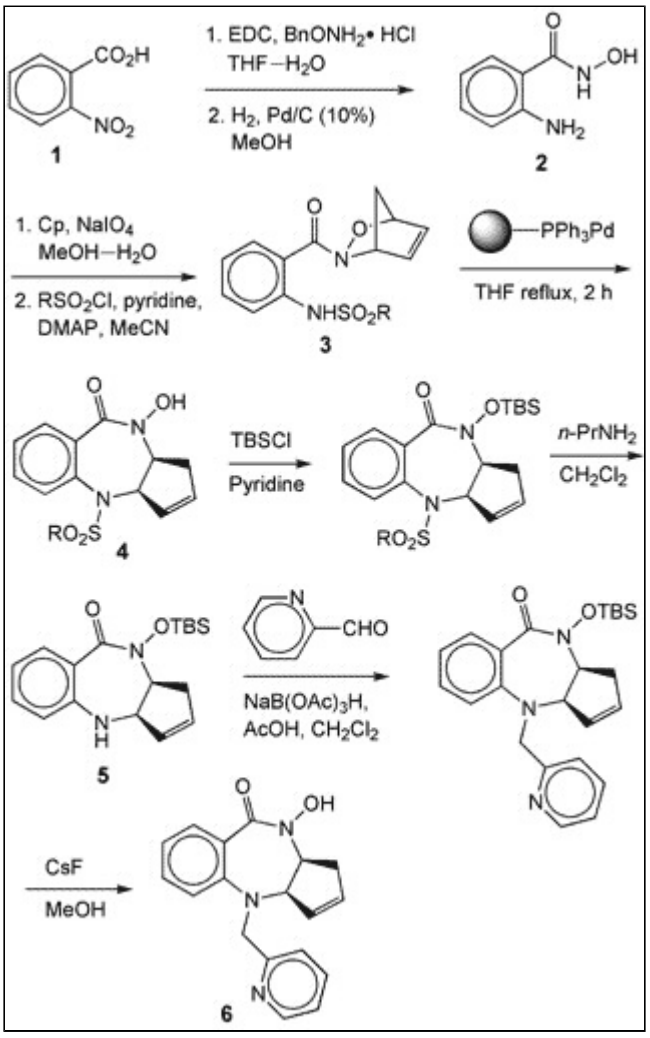
A hydroxamic acid group enhances the bioactivity of benzodiazepines. The 1,4-benzodiazepine scaffold promotes a variety of biological and therapeutic functions that can lead to antibiotic, anticancer, antimalarial,



and anti-HIV agents. L. P. Tardibono, Jr., and M. J. Miller* at the University of Notre Dame (IN) recognized the potential value of hydroxamate within the benzodiazepine structure to facilitate metal binding, making the modified benzodiazepines potential inhibitors of metalloenzymes such as the farnesyltransferase protein.

The authors' synthesis strategy begins with a simple compound, *o*-nitrobenzoic acid (**1**), which leads to hydroxamic acid **2**, then conversion to the key functionalized cycloadduct (**3**). Polymer-bound Ph_3PPd promotes the rearrangement of **3** that leads directly to the substituted 1,4-benzodiazepine skeleton (**4**). Protection of the hydroxamic acid hydroxyl group is followed by treatment with an alkylamine to allow mild deprotection of the dinitrobenzenesulfonamide and regeneration of the amine moiety in the diazepine ring (**5**). Alkylation of the now-free amine in **5** with an aldehyde, followed by deprotection of the hydroxamic acid, gave target compound **6**. In the reaction scheme, EDC is ethylene dichloride, Cp is cyclopentadiene, R

represents dinitrobenzene, DMAP is 4-(*N*,*N*-dimethylamino)pyridine, and TBS is *tert*-butyldimethylsilyl.

Several variants of **6** demonstrate growth-inhibiting activity in the micromolar range in breast and prostate tumor cell assays. The results of this study demonstrate that hydroxamate is a necessary functionality for effective bioactivity in this class of benzodiazepines. (*Org. Lett.* **2009,** *11*, **1575–1578**; **W. Jerry Patterson**)

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