

# **Noteworthy Chemistry**

April 13, 2009

- <u>A tandem one-pot reaction produces fused tricyclic amines</u>
- <u>Silver nanoparticles have photoreversible antimicrobial properties</u>
- <u>Amino acid sulfamides suppress epileptic convulsions</u>
- Freeze and emit!
- Photo effects: Deform the surfaces of azo diblock copolymers
- Diazepines are readily produced from maleimides

A tandem one-pot reaction produces fused tricyclic amines. A. J. M. Burrell\*, I. Coldham\*, and N. Oram at the University of Sheffield (UK) and Eli Lilly (Windlesham, UK) describe this process as a cascade reaction that includes condensation of an enolizable aldehyde and a primary amine, cyclization by N-alkylation, and azomethine ylide dipolar cycloaddition to create the desired tricyclic amine. This type of cascade sequence is especially efficient and provides rapid access to structurally and stereochemically complex molecules.

The key aldehyde reactant 1 is produced from a starting material such as 6-heptenenitrile, which is alkylated with the trimethylsilyl ether of 3-bromo-1-propanol. This is followed by chlorination and reduction to yield the desired 1.



The authors found that treating 1 with (tri-*n*-butylstannyl)methylamine (2) provides the target tricyclic amine 3 in a single step and as a single isomer with all-cis configuration. An enamine is formed as a byproduct of this reaction. To favor cycloaddition over enamine formation, the aldehyde structure was modified to include a terminal phenylsulfoxide group (4) to activate the dipolarophile. This change results in an efficient cycloaddition process that forms three tricyclic amine isomers (5–7) with no detectable enamine contaminant.

The authors extended this method to include dipolar cycloaddition of nitrone ylides derived from a similar enolizable aldehyde **8** and introduces an N–O bond in cycloadduct **9**. They demonstrated a practical application for this reaction sequence by first converting **9** to the amino alcohol **10**, then treating with paraformaldehyde and *p*-toluenesulfonic acid to form natural product myrioxazine A (**11**). The synthesis of **10** also completes a formal synthesis of two important antimalarial alkaloids, myrionidine and schoberine. (*Org. Lett.* **2009**, *11*, **1515–1518**; **W. Jerry Patterson**)

## Back to Top

**These silver nanoparticles have photoreversible antimicrobial properties.** R. Amal and co-workers at the University of New South Wales (Sydney, Australia) report a simple method to tune the antimicrobial activity of nanosilver deposited on a  $\text{TiO}_2$  semiconductor support. The authors used a one-step flame-spray pyrolysis technique to deposit finely dispersed nanosilver on the  $\text{TiO}_2$  support; they then used *Escherichia coli* to test its antimicrobial activity.

The as-prepared material consisted of  $Ag_2O$ , as determined by the X-ray photoelectron spectroscopy Ag  $3d_{5/2}$  binding energy shift. The suppression effect on the growth of *E. coli* increased with increasing amounts of  $Ag_2O$ . The authors attribute this mainly to the increased leaching of  $Ag^+$ , which can affect DNA replication and thus adenosine 5'-triphosphate production.

Upon UV-A irradiation, electrons in the valence band of TiO<sub>2</sub> are transferred to its conduction band, and then

to the nanosilver, reducing  $Ag^+$  to metallic silver. The samples that underwent longer UV irradiation showed less suppression of *E. coli* growth. The authors call this process "switching off" the antimicrobial activity. UVirradiated samples can be restored to high suppression activity by being exposed to visible light for 8 h, during which time electrons in the nanosilver return to the TiO<sub>2</sub> conduction band, and silver reoxidizes to Ag,

"switching on" antimicrobial activity. (Small 2009, 5, <u>341–344</u>; George Xiu Song Zhao)

## Back to Top

**These amino acid sulfamides suppress epileptic convulsions.** Current antiepileptic drugs (AEDs) are effective in only 70% of patients, and many drugs in this class have serious side effects. Because the cellular basis of epilepsy is not known and because most AEDs interact with more than one receptor, the rational design of new lead compounds is based on pharmacophoric patterns.



L. Gavernet, L. E. Bruno-Blanch, and coauthors at the National University of La Plata (Argentina) and the University of Notre Dame (Indiana) report the synthesis and pharmacological evaluation of amino acid– derived sulfamides as AEDs. The new compounds have a sulfamide pharmacophore that contains a polar group with well-determined charge distribution attached to a hydrophobic chain of at least three carbon atoms (Gavernet, L., et al. *Bioorg. Med. Chem.* **2007**, *15*, <u>5604–5614</u>). The authors incorporated amino acid substituents to improve pharmacokinetic properties.

Symmetrical sulfamides were prepared by condensing amino acid esters with  $SO_2Cl_2$ . The authors developed a new method to prepare unsymmetrical sulfamides starting from catechol sulfate and amino acid esters (Xaa; see figure).

The compounds were evaluated as anticonvulsives by using the maximal electroshock seizure and pentylenetetrazole tests, and for toxicity by the RotoRod test. The median effective dose  $(ED_{50})$  was measured

for the most promising compounds. The results indicate that compounds 1–4 at least duplicate the anticonvulsant activities of valrocemide and valproic acid, which were used as standards. This study may be useful for establishing new pharmacophoric requirements for an anticonvulsant activity. (*J. Med. Chem.* 2009, *52*, <u>1592–1601</u>, José C. Barros)

#### Back to Top



**Freeze and emit!** Freezing molecular motions can enhance light emission because the process of making molecular structures rigid blocks nonradiative decay channels. Following this design principle, K. Kokado and Y. Chujo\* of Kyoto University (Japan) synthesized a group of new organometallic polymers (1) that can be induced to emit light by restricting their intramolecular rotation.

Polymers 1 consist of alternating *o*-carborane and *p*-phenyleneethynylene units with various arylene (Ar) groups; two examples are shown. The polymers are almost nonluminescent in solution because of the intramolecular rotation of the aromatic units around the C–C bonds. When the molecular motion of the polymers is frozen in their aggregates in poor solvents or in solid thin films cast from their solutions, luminescence is activated. This novel aggregation-induced emission makes the polymers strong light emitters in the solid state. (*Macromolecules* 2009, 42, 1418–1420; Ben Zhong Tang)

#### Back to Top

**Photo effects: Deform the surfaces of azo diblock copolymers.** Z. Wang and co-workers at Tsinghua University (Beijing) used the phenomena of photoinduced mass migration to generate deformable colloids and surface relief gratings of amphiphilic diblock copolymers that contain azobenzene side chains. They wanted to understand the role of flexible spacer length (hexamethylene or ethylene) on the migration behavior of diblock systems irradiated with a linearly polarized  $Ar^+$  laser beam.

The authors used atom-transfer radical polymerization and an azo-coupling reaction to synthesize poly (ethylene glycol) (PEG)-*b*-poly( $2-\{N-ethyl-N-[4-(4'-cyanophenylazo)phenyl]amino\}ethyl methacrylate)$  (1)

and PEG-*b*-poly(2-{*N*-methyl-*N*-[4-(4'-cyanophenylazo)phenyl]amino}hexyl methacrylate) (2) with comparable hydrophilic and hydrophobic contents by weight. Copolymer 2 had a glass-transition temperature  $(T_g)$  of 60 °C, 57 °C lower than the  $T_g$  of 1. The crystallinity of the PEG block was suppressed in both diblock copolymers.



The researchers produced colloidal spheres of the copolymers with similar diameters by tuning water-feeding rates. Dynamic light-scattering studies resulted in a z-average hydrodynamic radius of ~169 nm for 2 and ~144 nm for 1; 2 had a broader particle size distribution. The spherical, colloidal azo diblock copolymers were deformed to ellipsoidal (polarization direction) particles when subjected to a polarized  $Ar^+$  laser beam. The authors note that the deformation rate below the saturation limit and the degree of deformation, at identical irradiation specifications, of 1 are lower than those of 2. The structural differences between the two are attributed to the spacer length connecting the azobenzene side chains to the methacrylate block.

To investigate these phenomena, the authors also probed photoinduced surface relief grating of spin-coated films (840–850 nm) of the copolymers. Atomic force microscopy images revealed a smaller modulation depth (131 nm) and lower diffraction efficiency (5.2%, 3600 s) for **2** compared with 225 nm and 13.7% (3600 s) for **1**. The intriguing structural differences between the two are attributed to the spacer length connecting the azobenzene side chains to the methacrylate block. (*Macromolecules* **2009**, *42*, **<u>2651-2657</u>; <b>LaShanda Korley**)

#### **Back to Top**

**Diazepines are readily produced from maleimides.** Various members of the diazepine class of nitrogen heterocycles are valuable as pharmaceuticals; for example, the widely used drug Valium is formed from the 1,4-benzodiazepine scaffold. K. L. Cubbage, A. J. Orr-Ewing, and K. I. Booker-Milburn\* at the University of Bristol (UK) report a photochemically mediated intramolecular [5 + 2] photocycloaddition of maleimides to C=N bonds that forms the 1,3-diazepine skeleton—a class of diazepine that is rarely reported.



The key to the synthetic strategy is the use of C=N tethered imide photoprecursors (2 and 3 in the figure), which lead to a wide range of highly functionalized 1,3-diazepines. The initial intermediate is aldehyde 1, which the authors prepared in a four-step sequence. Compound 1 is condensed with a variety of substituted hydrazines or oximes to form 2 or 3, respectively. Ts is *p*-toluenesulfonyl and THP is tetrahydropyranyl. The C=N tethered imides generally formed as a mixture of inseparable *E* and *Z* isomers, although several reactants produced the *E* isomers as the sole products.

The fused, polycyclic 1,3-diazepine targets **4** and **5** were prepared by photolysis of **2** and **3** under mild conditions, generally without side reactions. All reactions were carried out using a 125-W medium-pressure mercury lamp. Unexpectedly, no reaction was observed when hydrazones prepared from substituted hydrazines  $Me_2NNH_2$  and  $Ph_2NNH_2$  were irradiated.

The method tolerates a wide range of C=N systems and is carried out efficiently even when using bulky substituted hydrazones and oximes. Several mechanistic studies of this photocycloaddition led the authors to conclude that it proceeds from a maleimide singlet state rather than via a maleimide-sensitized C=N triplet state. (*Angew. Chem., Int. Ed.* 2009, 48, 2514–2517; W. Jerry Patterson)

### Back to Top