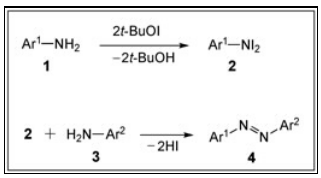
Noteworthy Chemistry

August 27, 2012

Use *tert*-butyl hypoiodite to make asymmetric azobenzenes. Conventional methods for preparing aromatic azo compounds often involve the use of heavy metals or highly reactive intermediates; and they are not useful for synthesizing asymmetric azo compounds. More recent protocols usually require harsh reaction conditions and excessive amounts of starting materials. To overcome these problems, Y. Takeda, S. Okumura, and S. Minakata* at Osaka University (Japan) developed a method for oxidatively homo- and cross-coupling aromatic amines under mild conditions. The method uses *tert*-butyl hypoiodite (*t*-BuOI) as the oxidant.



The authors believed that the powerful reagent *t*-BuOI would iodinate anilines (**1**) to generate *N*,*N*-diiodoanilines (**2**), which could react with a second mole of **1** or another aniline (**3**) to eliminate 2 mol HI and yield homo- or cross-coupled (**4**) azo compounds, respectively. They first treated unsubstituted aniline (**1**, Ar^1 = Ph) with 2 equiv *t*-BuOI in MeCN at room temperature for 1 h to make the homocoupled product azobenzene in 95% yield.

Next, the authors screened substituted anilines with electron-donating and electron-withdrawing groups (EDGs and EWGs) and found that most derivatives could be converted to the corresponding azo compounds in high yields (>80%) in <12 h at room temperature or –20 °C. Because of steric hindrance, only *o*-phenylaniline gave a lower yield (44%).

The authors then demonstrated azo cross-coupling between two anilines with *t*-BuOI. *p*-Toluidine and *p*-acetylaniline reacted with EDG- and EWG-substituted anilines to give the azo compounds in higher yields (52–72%) than with previous protocols. Unlike diazo coupling and the Mills reaction, this method is not limited to combinations of electron-rich and electron-poor anilines.

An initial mechanism study confirmed the formation of Ar^1NI_2, which is attacked by Ar^1NH_2 or Ar^2NH_2 to form the N–N bond. HI is eliminated to produce the symmetric or asymmetric azo compound. (*Angew. Chem., Int. Ed.* **2012,** *51,* **7804–7808**; **Xin Su**)

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Modified carboranes fluoresce efficiently in the solid state. A carborane is a cluster of boron and carbon atoms. The best-known examples of carboranes are 1,2-*closo*-dicarbadodecaboranes (*o*-carboranes), which have been studied for a variety of applications. L. Weber, M. A. Fox, and coauthors at the University of Bielefeld (Germany) and Durham University (UK) synthesized a series of *C*-diazaborolyl-*o*-carboranes with donor–acceptor characteristics and investigated their photoluminescence characteristics.

The cage molecules emit visible light in the long-wavelength region (523–631 nm) with large Stokes shifts (15,100–20,260 cm^{-1}) and fluorescence quantum yields of up to 65% in the solid state. These values are the highest reported for any solid carborane.

The authors assigned the low-energy fluorescence to the charge-transfer transition between the carborane cage and the diazaborolyl unit. Aggregation-enhanced emission caused by restricted molecular motion and intermolecular interaction in the solid state makes the crystalline carboranes more emissive than their solutions. (*Chem. Eur. J.* **2012,** *18,* **8347–8357**; **Ben Zhong Tang**)

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Bacteria "eat" glycerol to produce 1,3-propanediol. The increased use of biodiesel fuel has created a large surplus of glycerol, a waste product of biodiesel production. M. De May and co-workers at Ghent University (Belgium) wanted to find an efficient way to use this surplus glycerol by converting it biologically to 1,3-propanediol (PDO), an important building block for polymer synthesis.

The authors focused on *Citrobacter* spp. because they produce PDO in nature. Because PDO production is related to bacterial growth, they screened seven *Citrobacter* strains for their growth rates and their ability to produce PDO from glycerol. The strain *C. werkmanii* DSM17579 gave the best results.

In addition to converting glycerol to PDO, *Citrobacter* spp. consume it for cell maintenance and growth. Therefore, 100% conversion to PDO cannot be achieved if glycerol is the bacteria's only source of carbon. The authors then investigated supplementary carbon sources to maximize PDO yield. They tested 18 sugars and found that d-galactose and d-mannose were the best co-substrates. Adding them to glycerol gave 30% PDO yield increases compared with the yields from glycerol as sole carbon source.

Further optimization, such as fermentation processes and genetic engineering, is needed to achieve high enough yields for economical industrial production. But *C. werkmanii* bacteria are promising candidates for producing PDO from renewable carbon sources. (*Green Chem.* **2012,** *14,* **2168–2178**, **Chaya Pooput**)

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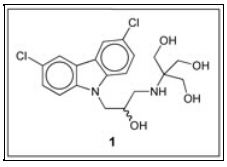
A new antibiotic targets bacterial cytoplasmic membranes. Prolonged infections are associated with slow-growing bacteria, which usually tolerate antibiotics such as β-lactams that require rapid cell growth. D. B. Weibel and coauthors at the University of Wisconsin–Madison and Philipps University (Marburg, Germany) used high-throughput screening to identify the molecule 2-{[3-(3,6-dichloro-9*H*-carbazol-9-yl)-2-hydroxypropyl]amino}-2-(hydroxymethyl)propane-1,3-diol (DCAP, **1**) that specifically targets the membranes of Gram-positive and Gram-negative bacteria.

The authors measured the transmembrane potentials (ΔΨ) of Gram-negative *Caulobacter crescentus* and Gram-positive *Bacillus subtilis* in the absence and presence of DCAP. The molecule reduced ΔΨ values of the bacteria's inner membranes. They then established that DCAPs facilitate ion transport across the membranes and general permeability of the lipid bilayer.



DCAP also inhibits the growth of *Escherichia coli* and *Pseudomonas aeruginosa*; it is superior to ampicillin against stationary-phase cells of *C. crescentus* and *Staphylococcus aureus*; and it eradicates biofilm-associated cells. The results show that membrane-active drugs eradicate slow-growing bacteria more efficiently than antibiotics with growth-dependent mechanisms. DCAP is only moderately toxic to rabbit red-blood cells. (*J. Am. Chem. Soc* **2012,** *134,* **11322–11325**; **José C. Barros**)

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Heating controls drug release from a hydrogel delivery system. J. H. van Esch and colleagues at the Delft University of Technology (The Netherlands) designed a

three-component therapeutic delivery system with thermally tunable release rates. The drug delivery system is a hydrogel network that consists of a fibrillar gelator with an enzymatically cleavable amide linker that is covalently attached to fluorogenic 6-aminoquinoline and a thermosensitive phospholipid loaded with protease.

Delivery is triggered by heating the system to the phase-transition temperature (42 °C) of the lipid liposome to liberate protease, which hydrolyzes an amide in the gelator to an amine and releases the fluorophore. The authors found a linear relationship between the degree of hydrolysis and the amount of protease incorporated if the gelator level is greater than its critical gelation concentration.

The rate of release of the protease enzyme can be controlled by heating the system for up to 5 min. The rate is monitored by fluorescence spectroscopy and increases with longer heating times. Beyond 5 min, no additional enzyme is released, and autodigestion occurs after 10 min.

The authors stress that the stability of the liposome in the network is linked to the age of the liposome solution. The hydrogel network stabilizes freshly prepared liposomes better than ones that are several days old. Microscopy and thermal studies confirmed that the delivery system assembles orthogonally. (*J. Am. Chem. Soc.* **2012,** *134,* **12908–12911**; **LaShanda Korley**)

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The right amine simplifies a pyridone synthesis workup. M. A. Graham, S. Raw, and co-workers at AstraZeneca (Macclesfield, UK) developed a scalable route to a group of deacetylase inhibitors. In one step of the process, a Mannich reaction of formaldehyde, a secondary amine, and 3-diemthylaminoacrolein gives an intermediate that is treated in situ with cyanoacetamide to give a 5-dialkylamino-3-cyano-2-pyridone in good yield.

Isolating the pyridone is affected by the secondary amine used. Basic amines such as Et_2NH and pyrrolidine give zwitterionic pyridones that can be isolated only by concentrating them to dryness. Less basic morpholine, in contrast, gives a pyridone that is more basic than the amine and does not form a zwitterion. The product is thus more amenable to conventional isolation. (*Org. Process Res. Dev.* **2012,** *16,* **1283–1292**; **Will Watson**)

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