

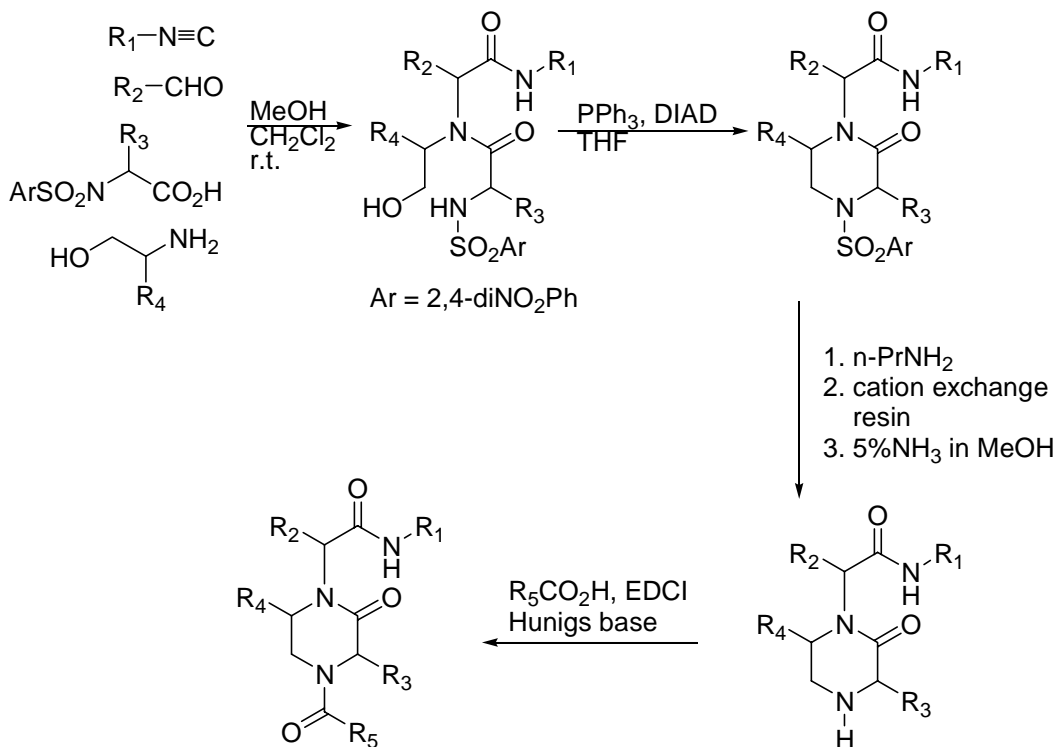
# Preparation of oxopiperazines utilizing an Ugi multi-component condensation followed by an intramolecular version of Fukuyama's amine synthesis. Paper #36167

Conrad W. Hummel and Anthony D. Piscopio

A common technique for determination of the bioactive conformation of a peptide is to constrain a portion of the linear peptide into a rigid ring system. The newly formed heterocycle not only may retain or enhance the desired biological effect of the parent but typically has the added advantage of greater metabolic stability. Our interest in generating diverse arrays of conformationally constrained dipeptide mimetics led us to explore the development of a combinatorial approach to the synthesis of oxopiperazines. Unfortunately, the previously described oxopiperazine preparations did not easily lend themselves to the rapid build up of a variety of analogs in a high throughput manner.<sup>1,2</sup> However, we were able to take advantage of the multi-component Ugi reaction, which has proven to be a general coupling technique for the production of large numbers of non-natural dipeptides from a relatively small number of each of its four inputs.<sup>3</sup> Further, due to the mild and chemoselective nature of this reaction we were able to append latent reactive groups to the side chain of the amine and acid components (see scheme), which were later used in an intramolecular Mitsunobu reaction, thereby generating a sulfonlated oxopiperazine. Removal of the 2,4-dinitrobenzenesulfonamide could then be effected by treatment with *n*-propylamine, as described by Fukuyama.<sup>4,5</sup> Purification of the resulting free amine was possible in solution either via acid-base work-up or with the aid of a cation exchange resin utilizing "catch and release" technology. Further functionalization of the cyclic amine has been carried out under standard amide bond forming conditions (EDCI and base).

We will discuss other solution and solid phase approaches, including solid phase attachment of the substrate via a convertible isonitrile<sup>6</sup> or via the 2,4-dinitrobenzenesulfonamide group of the acid input. Progress toward the use of polymer supported reagents in solution-phase synthesis will also be discussed, including the use of resin bound amines and thiols to cleave the above mentioned sulfonamide.

## Scheme.



## References

1. Bhatt, U.; Mohamed, N.; Just, G. *Tetrahedron Lett.* **1997**, 38, 3679.
2. Pohlmann, A.; Schanen, V.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1997**, 62, 1016.
3. Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I. Eds.; Pergamon: New York, 1991; Vol. 2, pp. 1083-1109.
4. Fukuyama, T.; et. al. *Tetrahedron Lett.* **1997**, 38, 5831.
5. Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1998**, 39, 2667.
6. Piscopio, A. D.; Miller, J. F.; Koch, K. Book of Abstracts, 214<sup>th</sup> ACS National Meeting, Las Vegas, NV, September 7-11, 1997.