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Efficient Synthesis of Substituted Oxopiperazines From Amino Acids

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***Abstract**: The synthesis of substituted oxopiperazines, which may act as conformationally constrained peptide mimics, is reported. The synthesis is based on the cyclization of sulfonamide dipeptides with dibromoethane as the 1,2-dielectrophile. Alternatively, these mimetics were prepared via a Mitsunobu reaction.*

We are interested in designing novel constrained peptidomimetics which could find use as potential therapeutic agents. The oxopiperazine ring was chosen as a model template in which the two nitrogen atoms of a dipeptide are linked by an ethylene bridge, thus restricting the ω, ϕ and φ torsion angles as shown in Figure 1.[1] We have earlier described a simple synthesis of 2-oxopiperazines as novel dipeptide mimics.[2] However, that methodology could not be successfully applied to synthesis on solid support. We now describe an efficient synthesis which can be adapted to solid phase synthesis.

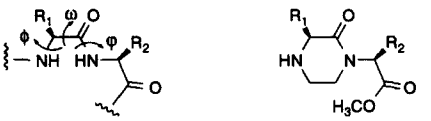

Figure 1

As reported,[2] we attempted cyclization of BOC dipeptides **1** using dibromoethane as the dielectrophile under several different conditions without any success. Using ethylene sulfate as a dielectrophile, Pohlmann *et al.*[3] initially tried to do a similar cyclization with a glycyl leucine dipeptide. Unfortunately, they did not observe the formation of the expected cyclic product and recovered the starting material completely. Later, they became aware of a synthesis of 1,2,4-triazinones by Gante *et al.*[4] involving N,N-cyclization by the use of ethylene glycol bis-triflate.[5] Pohlmann *et al.* were then able to successfully cyclize BOC-Gly-Leu-OMe **1a**, R_1=H using ethylene glycol bis-triflate and sodium hydride as the base in a 42 % yield, but reported only the cyclization of the above dipeptide. We then attempted to cyclize much

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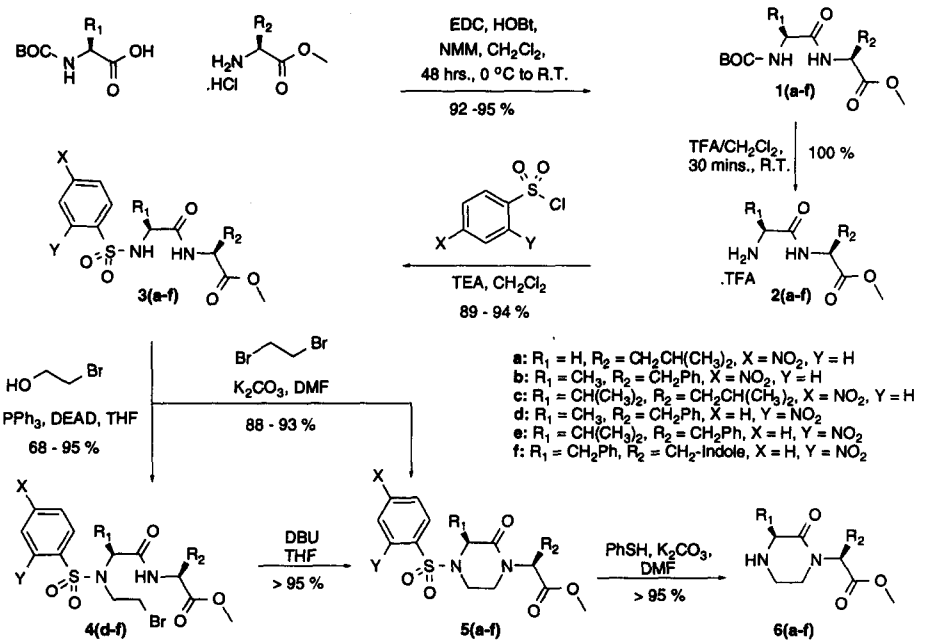
bulkier dipeptides, $R_1 \neq H$ using the same methodology as above. We were unable to obtain any of the desired cyclized product and recovered substantial amount of starting material and some unidentified products.

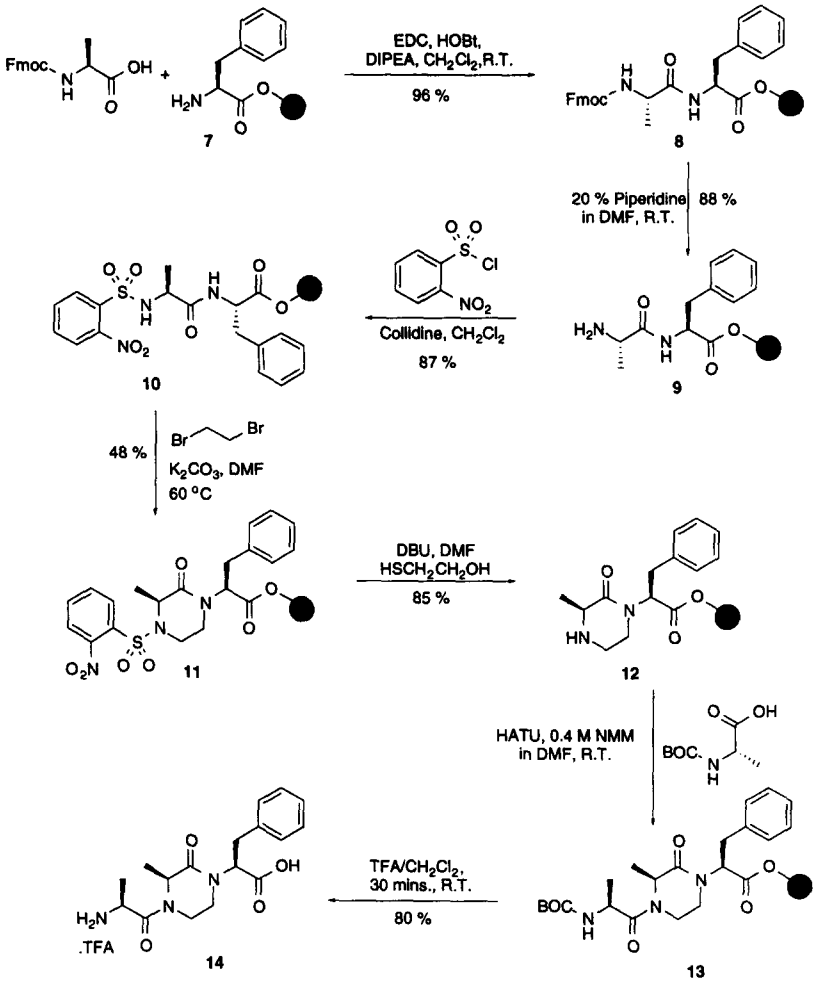
Our previous successful N-allylation of sulfonamides using Fukuyama's protocol[6] prompted us to use sulfonamide dipeptides instead of carbamate dipeptides. These sulfonamide dipeptides were prepared by an initial peptide coupling using EDC as shown in Scheme 1. BOC deprotection of **1(a-f)** with TFA followed by sulfonamide formation with 2- or 4-nitrobenzenesulfonyl chloride in the presence of triethylamine furnished the desired dipeptide sulfonamides **3(a-f)** without the use of chromatography in excellent yields. On reacting these sulfonamide dipeptides with excess 1,2-dibromoethane (10 eq.) and K_2CO_3 (10 eq.) in DMF at 60 ^{0}C, we were able to obtain the sulfonamide oxopiperazines **5(a-c)** in high yields (88 - 93 %). Deprotection with thiophenoxide yielded the desired oxopiperazines **6(a-c)**.



Scheme 1

Alternatively, the sulfonamide dipeptides **3(d-f)** were reacted with bromoethanol under standard Mitsunobu reaction conditions (PPh_3, DEAD, THF, 12 hr.) to generate the N-(bromoethyl) substituted intermediates **4(d-f)**. These intermediates could then be converted to the oxopiperazyl sulfonamides **5(d-f)** on

reaction with DBU in THF in nearly quantitative yields. Subsequent reaction with thiophenoxide furnished the desired oxopiperazines **6(d-f)**.[7]



Scheme 2

We then turned our attention to the synthesis of oxopiperazines on solid support. H-Phenylalanine-2-chlorotrityl resin **7**[8] was transformed to the 2-nitrobenzenesulfonamide dipeptide **10** in three steps by standard procedures as shown in Scheme 2. On reacting this dipeptide **10** with excess 1,2-dibromoethane in DMF in the presence of base at 60 °C, the cyclized sulfonamide **11** was obtained. The yield of this step could not be increased beyond 48 % using either K_2CO_3 or tetramethylguanidine as the base. Deprotection of the

sulfonamide gave the desired oxopiperazine **12** which was further derivatized by attaching a third amino acid via standard coupling conditions. Simultaneous cleavage of both the resin and BOC group with 50 % TFA/CH_2Cl_2 gave the highly functionalized 2-oxopiperazyl derivative **14**.[9] Unfortunately, despite our various attempts, the parallel approach using the Mitsunobu protocol could not be successfully repeated even on Rink Amide and Tenta-Gel resins. Apart from the standard reagents (PPh_3, DEAD), the use of TBP/TMAD system also failed to yield any of the desired product in the Mitsunobu reaction.

In conclusion we have described two efficient syntheses of the oxopiperazine peptide mimic. Preliminary studies on solid support have been carried out and this may open up the synthesis of a library of such constrained compounds.

Acknowledgments

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References and Notes

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7. All compounds gave satisfactory ^1H, ^{13}C NMR spectra as well as correct mass spectra.
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9. Structures of all solid phase reaction products were confirmed by LCMS.