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Polymer-Supported Synthesis of Diverse Perhydro-1,4-diazepine-2,5-diones

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Abstract: The chemistry, synthesis of model compounds, selection of building blocks, and synthesis of a library of 1,4,7-trisubstituted perhydro-1,4-diazepine-2,5-diones are described. Secondary diamines and Fmoc protected amino alcohols were attached to chlorotrityl resin and the amino group acylated with Fmoc-Asp(OAll). The Fmoc group was cleaved, and the amino group alkylated. Then bromoacetic acid was coupled to the amino group and the bromide displaced by primary amines. After removal of the allyl ester function, the seven membered ring was closed upon mild activation of the carboxyl group. Products were cleaved from the resin by TFA vapor. © 1997 Elsevier Science Ltd.

The solid-phase synthesis of benzodiazepines, described by Bunin and Ellman,[2] represents the first combinatorial synthesis of small heterocyclic molecules. Since then, the literature has been flooded with descriptions of polymer-supported chemistries yielding various heterocyclic compounds for combinatorial libraries.[3] In this contribution we wish to report the straightforward solid-phase synthesis of diverse 1,4,7-trisubstituted perhydro-1,4-diazepine-2,5-diones (Scheme 1) using commercially available building blocks: diamines (or amino alcohols), aldehydes, and amines.

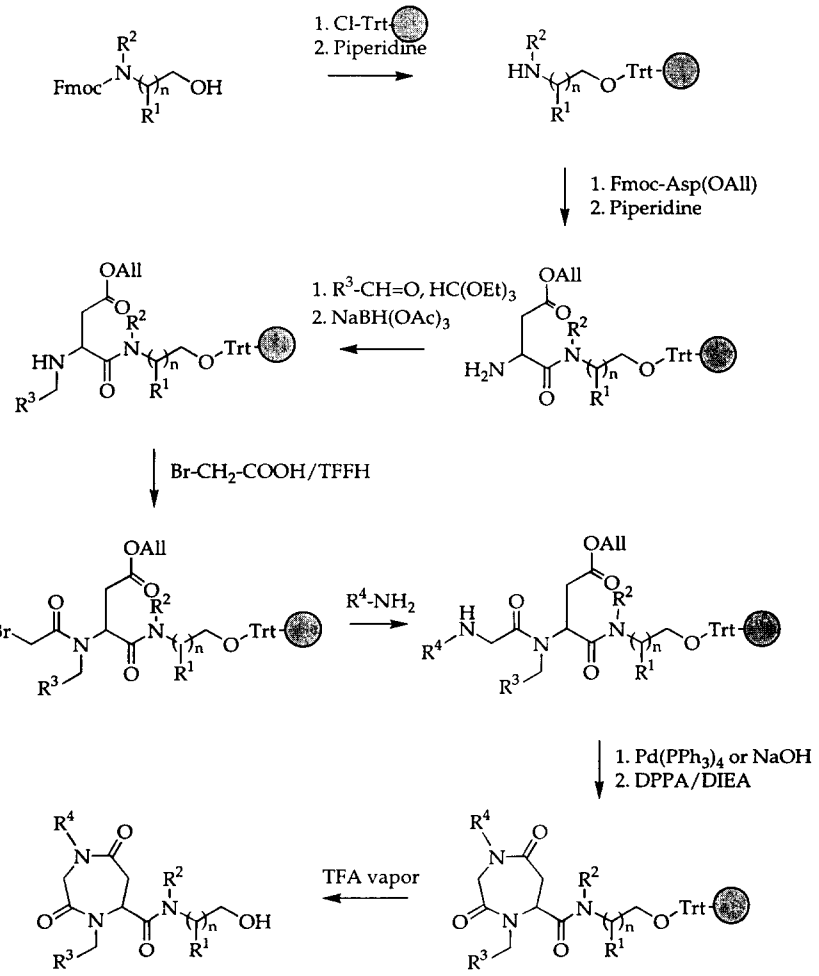
The synthesis was developed on TentaGel resin (Rapp Polymere, Germany, subst. 0.24 mmol/g) derivatized with either Rink or trityl (Trt) linker. The Trt linker allows the attachment of a variety of bifunctional building blocks such as amino acids, amino alcohols as well as diamines via the carboxyl, hydroxyl or amino groups, respectively. Thus, a polymer-supported amino group is available for further modification.[4] The linker is stable towards nucleophiles, a necessary condition in this case since primary amines are used in the last combinatorial step. The advantage of the Trt linker from the screening point of view is the ability to cleave compounds with TFA vapor or HCl gas applied to the dry beads. The beads can be handled after cleavage and the compounds released into solution only when the extracting solvent is applied.

The synthesis of perhydro-1,4-diazepine-2,5-diones begins with the attachment of the symmetrical secondary diamines and secondary Fmoc protected amino alcohols to the chlorotrityl resin. One can also use primary diamines or Fmoc protected primary amino alcohols, followed by reductive alkylation of the amino group. In this way the diversity of the library can be increased in combinatorial fashion (10 primary

diamines and 10 aldehydes provide 100 secondary diamines). Alternatively, amino acids are coupled to RAM TentaGel.

The presence of the secondary amino group is necessary. The primary amino group, acylated by Fmoc-Asp(OAll), undergo base catalyzed aspartimide formation during Fmoc deprotection (Scheme 2).[5] The formation of the five membered ring product is confirmed by MS and HPLC.

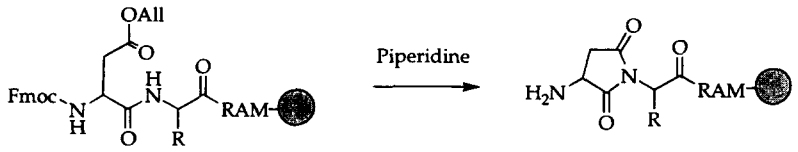
Scheme 1. Polymer-supported synthesis of 1,4,7-trisubstituted perhydro-1,4-diazepine-2,5-diones.



Acylation using Fmoc-Asp(OAll) is followed by piperidine deprotection and reductive alkylation of the α-amino group (the second combinatorial step using the set of aldehydes). The reaction is successful for a representative set of aliphatic, aromatic, and heteroaromatic aldehydes (Figure 1). We have used a modified procedure with triethylorthoformate and sodium triacetoxyborohydride as dehydrating and reducing agents, respectively.[6,7] The secondary amine thus formed is then acylated with bromoacetic acid activated

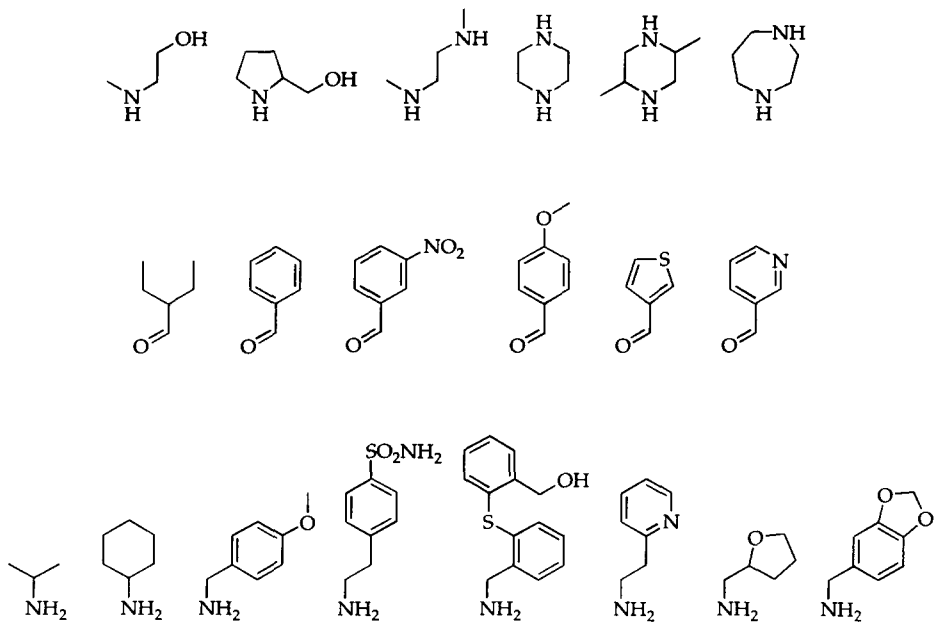
in situ with tetramethylfluoroformamidinium hexafluorophosphate (TFFH).[8] The otherwise difficult acylation of this secondary amino group[9] proceeded smoothly.

Scheme 2. Base catalyzed aspartimide formation



In the last combinatorial step the bromide is displaced using a 2 M solution of primary amine in DMSO at room temperature, following the procedure described by Simon et al.[10] It is worth mentioning that the allyl ester is stable under these conditions.

Figure 1. Building blocks used in individual combinatorial steps.



The next reaction step included the allyl ester removal with $Pd^0(PPh_3)_4$. Alternatively saponification easily occurs using 0.5% NaOH in MeOH/H_2O (20:80). The seven membered ring is closed by mild activation of the carboxyl group with diphenylphosphoryl azide overnight. The expected molecular ions are detected by mass spectrometry and the NMR spectra confirm the presence of the seven membered ring.[11]

The perhydro-1,4-diazepine-2,5-diones are then cleaved from the Trt resin by TFA vapor. A glass desiccator is saturated with TFA vapor by placing a Petri dish with neat TFA on the bottom of the desiccator. Dry resin beads in open vials are then exposed to TFA vapor at room temperature overnight.

The TFA dish is then removed from the desiccator, and the resin evacuated overnight. The product is then extracted three times with MeOH. Yields range from 73 to 84% of crude material. To assure that cleavage is complete, the resin beads are treated with neat TFA for 1 h, and the TFA solution is evaporated. The residue is dissolved in MeOH, and analyzed for the presence of product by analytical HPLC. Typically, when compared to the gaseous release, less than 5% of diazepines is detected.

We tested 8 symmetrical secondary diamines and amino alcohols, 17 aldehydes and 20 primary amines in model compounds prior to the library synthesis. Each building block was tested in the synthesis of at least two model compounds. The purity of the products was analyzed by HPLC at 215 nm and ranged from 76 to 96%.[12] The correct molecular weight was confirmed by mass spectrometry (PE-Sciex API III+ with an articulated ion spray sample inlet system). The first small library synthesized by split/mix technique with 8 secondary diamines and amino alcohols, 17 aldehydes, and 20 primary amines provided the final complexity of 2,720 compounds.

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References and notes

1. Present address: Trega Biosciences, Inc., 3550 General Atomics Court, San Diego, CA 92121
2. Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997-10998.
3. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600.
4. Barlos, K.; Chatzi, O.; Gatos, D.; Stavropoulos, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 513-520.
5. Offer, J.; Quibell, M.; Johnson, T. *J. Chem. Soc., Perkin Trans. I.* **1996**, 175-182, and references cited therein.
6. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937-2940.
7. Gordon, D. W.; Steele, J. *Bioorg. Med. Chem.* **1995**, *5*, 47-50.
8. Carpino, L. A.; Elfaham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401-5402.
9. Krchnak, V.; Weichsel, A.S.; Cabel, D.; Lebl, M. *Molecular Diversity and Combinatorial Chemistry for Drug Discovery;* Chaiken, I.; Janda, K. Eds.; ACS Books: Washington, 1996; pp. 99-117.
10. Simon, R. J.; Kaina, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Simon, N. G.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9367-9371.
11. Compound synthesized using sarcosine, 2-methylbutyraldehyde, and isopropylamine on RAM TentaGel provided the following ^{1}H NMR spectrum (300 MHz, DMSO-d$_6$) δ = 4.52-4.61 (m, 1 H), δ = 4.52-4.61 (m, 1 H), δ = 2.98-3.12 (m, 2 H), δ = 3.65 (d, J = 7 Hz, 1 H), δ = 5.07 (d, J = 7 Hz, 1 H), δ = 2.89 (s, 3 H), δ = 3.90-3.92 (m, 2 H), δ = 1.03-1.11 (m, 6 H).
12. Analytical gradient HPLC profile was run on a Protein & Peptide C18 4x250 mm analytical column (Vydac), gradient 0 - 60 % of ACN in 30 min. The purity was estimated based on analytical traces at 215 nm.

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