A Concise Entry into Nonsymmetrical Alkyl Polyamines

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ABSTRACT

The synthesis of nonsymmetrical polyamines (PAs) has, up to now, been problematic due to lengthy synthetic procedures, lack of regioselectivity, and very poor atom economy. An innovative synthetic protocol for nonsymmetrical PAs using a modified Ugi reaction (N-split Ugi) which simplifies the synthesis of these tricky compounds is described. We believe that this new synthesis may open the door for the generation of new and pharmacologically active PAs.

Naturally occurring polyamines (PAs) play a pivotal role in the life of all organisms from bacteria to man.1 Although the precise role of the human PAs putrescine, spermidine, and spermine (Figure 1) is unclear, this is an expanding field of research,2 and there is already evidence that these molecules are fundamental for cell viability.3 For example, their involvement in the maintenance of nucleic acid conformation and membrane stability, control of gene expression, regulation of ion channel function, and cell motility has been described.1,3 Other natural PAs have been shown to possess fundamental properties. For example, thermophilic bacteria can survive under extreme conditions thanks to the presence of long-chain PAs which are able to stabilize DNA and participate in protein biosynthesis (e.g., caldohexamine, Figure 1).4

Figure 1. Structures of natural and synthetic PAs.
Conjugated polyamines such as acylpolyamine toxins\(^5\) isolated from natural sources have attracted much interest in neurobiology and stimulated elaborated approaches.\(^6\) Even more intriguing is the structural diversity of cyclic spermine and spermidine alkaloids, exemplified by the monocyclic macrolactams celacinnine\(^7\) and budmunchianines,\(^8\) the bicyclic macrolactams verbamethine\(^9\) and oncinotine,\(^10\) the diazocinones and diazepinones doyvialisins,\(^11\) and the azamacrocyclic motuporamins.\(^12\)

Over the past decades, it has also been demonstrated that synthetic PAs could have important functions in several fields of research. In oncology, it has been shown that the cellular requirement for natural PAs increases in cancer cells, thus providing a novel target for therapeutic intervention.\(^2,13\) For this reason, synthetic PA analogues, able to target the specific polyamine carrier but that do not display the typical biological activities of natural PAs, have been used as antimutagene agents, and some have reached phase II clinical trials (e.g., DENSpm, Figure 1).\(^13,14\)

In 1993, the first synthesis of nonsymmetrical \(N\)-alkyl derivatives of norspermine appeared and led to the discovery of cytotoxic agents in several tumoral cell lines. Indeed, these analogues have demonstrated lower toxicity and greater therapeutic efficacy than the symmetrically substituted PAs.\(^15\) Despite these promising activities, a limited number of nonsymmetrical PAs have been synthesized to date. The reason lies in the more challenging availability of the appropriate diamine. The preparation of their nonsymmetrically substituted counterparts is more demanding since orthogonal protection of internal and lateral nitrogen atoms is required, while the purification of these highly polar compounds is not always straightforward.\(^16\) For this reason, new and versatile approaches to the synthesis of nonsymmetrical PAs are needed. We present here a novel application of multicomponent reactions (MCRs) that can provide a direct access to nonsymmetrical alkyl PAs in only two synthetic steps (Scheme 1).

Scheme 1. Two-Step Synthesis of Nonsymmetrical PAs by an N-Split Ugi Multicomponent Reaction/Amide Reduction and Hydrogenolysis

To accomplish this, we leveraged on a recently described multicomponent protocol\(^17\) where symmetrical secondary diamines are fed into the four-component Ugi reaction. This variation “splits” the typical Ugi backbone within the two diamine nitrogen atoms, with one nitrogen atom undergoing acylation and the other alklylation.

To combine proof-of-principle and relevance, we investigated the combination of butylisocyanide (2), \(N^1, N^3\)-dibenzyl-1,3-propanediamine (13), paraformaldehyde, and \(N\)-acetyl \(\beta\)-alanine (10). This choice was inspired by the relevance of the 1,3-propanediamine leitmotif in antitumoral PAs\(^1,14\) and by the inhibitory of the classic Ugi reaction to provide this type of compounds.\(^18\) The \(N\)-split Ugi reaction (MeOH, reflux, 16 h) directly provided the required polyamide scaffold; next, the hurdle of the reduction of the amides was studied, as the presence of sterically hindered tertiary amides occasionally leads to low yields and unwanted byproduct formation.\(^19\) After several attempts with different reducing agents, we finally identified BH\(_3\)·THF\(^20\) (3 equiv for amide group; 60 °C, 120 h) as the most efficient

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(18) It should be noted that although PAs containing the 1,2-ethylenediamine skeleton may be obtained using the classical Ugi reaction, this strategy has never been reported in the literature.
reducing agent able to reduce these polyamides without causing hydrolytic cleavage. An additional problem was represented by the extreme stability of the borane—amine Lewis salt,21 which prevented us from releasing the free PAs. In this regard, we finally found that direct addition of the Pearlman catalyst (Pd(OH)2/C)22 to the reaction mixture cleanly cleaved the borane—amine adduct and concurrently hydrogenolyzed the benzylic groups, disclosing the desired PA (19).

The efficacy of this methodology required an efficient purification protocol which can keep the pace with this fast two-step procedure, and simple chromatographic conditions (silica gel 60, eluant: CH3CN/NH4OH in different ratios) gave the desired PAs with a purity higher than 95% by NMR. To demonstrate the generality of this methodology, different isocyanides, carboxylic acids, and diamines were used (Figure 2).

After the split-Ugi reaction, the corresponding polyamides (31–87% yield),23 only starting materials, and sometimes the aminal were submitted to the reduction protocol, and in all entries the desired PAs were successfully obtained (Figure 3). It is worth mentioning that, when sterically hindered isocyanides were used (1 and 3), the isocyanide-derived amide group was not reduced.

To evaluate whether these novel nonsymmetrical PAs had antitumoral potential, we decided to investigate cytotoxicity in a human prostate cancer cell line (DU-145) via a MTT assay which evaluates the mitochondrial activity. The most potent of these compounds displayed IC50’s for cytotoxicity in the low micromolar range (16: 1.2 µM ± 0.2; 18: 1.2 µM ± 0.3). In conclusion, we described a concise and convenient application of MCRs toward the synthesis of nonsymmetrical PAs in only two synthetic steps. As the approach conjugates efficiency and practicality, we think that it will be of help for all people involved in the PAs field. Continuation of this work for the synthesis of symmetrical and nonsymmetrical PAs with different spacers is in progress, as well as investigations into their potential applications in medicinal chemistry.

Figure 2. Isocyanide, carboxylic acid, and diamine building blocks.

Figure 3. Nonsymmetrical alkyl PAs synthesized.
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Supporting Information Available: Experimental procedures and characterization data for all new compounds and concentration–response curve for cytotoxicity of all novel PAs synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Only the starting materials and sometimes the aminal were detected.