ORGANIC LETTERS

2009
Vol. 11, No. 2
417−420

# Direct Preparation of Unsymmetrical Difunctionalized Cyclen Derivatives by an Ugi Multicomponent Reaction

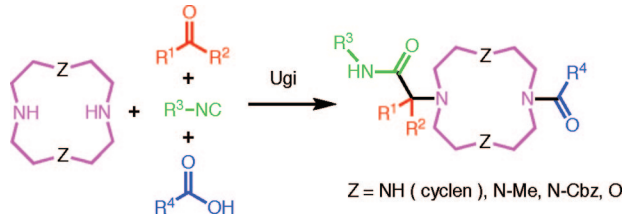
**Giovanni Piersanti,*,† Francesco Remi,† Vieri Fusi,‡ Mauro Formica,‡ Luca Giorgi,‡ and Giovanni Zappia*,†**

*Institute of Medicinal Chemistry, and Institute of Chemical Sciences, University of Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino (PU), Italy*

*giovanni.piersanti@uniurb.it; giovanni.zappia@uniurb.it*

**Received November 19, 2008**

## ABSTRACT




**A new and efficient synthetic protocol for the preparation of unsymmetrical difunctionalized cyclen and its close derivatives using a modified Ugi reaction (*N*-split Ugi) is described. The scope of this methodology is further extended by the successful use of various isocyanides, highly functionalized carboxylic acids, and aldehydes.**

Functionalized tetraazacycloalkanes have been widely studied, due to their ability to chelate a wide variety of metal cations.[1] Particularly, the N-functionalization of 12-membered saturated tetraazamacrocycles, such as 1,4,7,10-tetraazacyclododecane (cyclen), has been the subject of intense investigation, mainly due to their extensive use as MRI contrast agents,[2] radiodiagnostic and radiotherapeutic agents,[3] and fluorescent and luminescent sensors (Figure 1).[4] In addition, some cyclen metal complexes have been used in molecular recognition and catalysis[5] and as anti-HIV and anticancer agents.[6] All of these applications require fine-tuning of the chelating properties of the ligand derivative by changing the nature, the number, and the relative position of the functional groups. Moreover, many applications demand the synthesis of macrocycles bearing two distinct functional groups: one for coordination of the metal, and

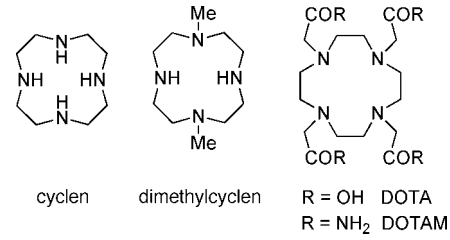



**Figure 1.** Structure of cyclen and some of its derivatives that have received special attention.

† Institute of Medicinal Chemistry.
‡ Institute of Chemical Sciences.

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10.1021/ol802674r CCC: $40.75 © 2009 American Chemical Society
**Published on Web 12/17/2008**

another for anchoring onto a solid support (silica gel, organic polymers) or a macromolecule (antibody, protein).[7] The synthesis of such bifunctional chelating agents (BCAs) has attracted increasing interest, but selective difunctionalization of cyclen is still difficult to achieve. Only a few methods have been reported,[8] although there is often poor selectivity in the formation of the mono-over the di-N-functionalized derivative. In general, N-derivatization has been accomplished by either direct derivatization or by a protection−derivatization−deprotection sequence of reactions.[8b] Literature reports on mono-, bis-, and triderivatization by either approach are known. However, bis-derivatization procedures are scarce and are of particular interest given the possibility of obtaining either symmetrical or unsymmetrical $N^1$,$N^4$ and/or $N^1$,$N^7$ polyazamacrocyclic derivatives. For all of these reasons, new and versatile methods, which simplify the preparation of regioselective unsymmetrical BCAs, are highly desiderable.

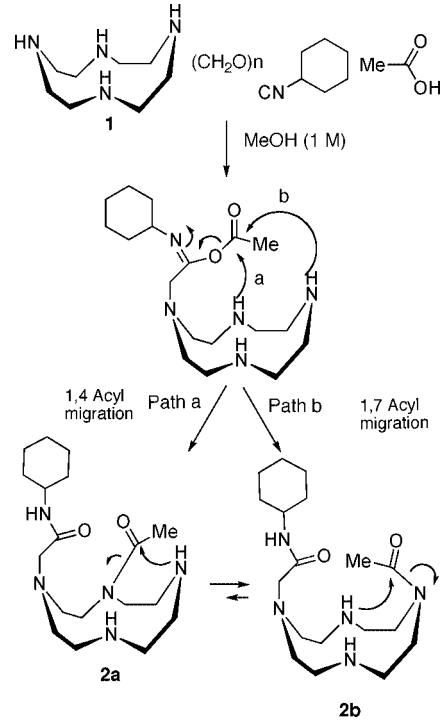
Multicomponent reactions (MCRs) are one of the best tools in modern organic synthesis to generate compound libraries for screening purposes because of their productivity, simple procedures, convergence, and facile execution.[9] Therefore, the design of novel MCRs has attracted great attention from research groups working in diverse areas such as drug discovery, supramolecular chemistry, and material science. In particular, MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds, and they form the basis of the well-known Passerini[10] and Ugi reactions.[11] The Ugi four-component reaction (Ugi 4CR) is one of the cornerstones in this field, and great efforts have been devoted to the exploration of the potential of this transformation.[12] The Ugi 4CR is a highly efficient process in which usually a primary amine, a carbonyl compound, a carboxylic acid, and an isocyanide react in one pot to give α-acylamino amides (peptoids). The incorporation of hostlike macrocycles into an Ugi-peptoid backbone represents a completely new and promising outlook for molecular recognition studies.[12e]

In the present paper, we report the first direct synthesis of unsymmetrical bis-functionalized cyclen and some of its analogues using an *N*-split-Ugi 4CR, a clever multicomponent variation recently described by Tron et al.[13] Thus, this application of novel Ugi 4CR gives access to a variety of unsymmetrical bis-functionalized cyclen derivatives, and the strategy can be varied to incorporate different substituents by simply changing the acid, carbonyl, and/or isocyanide component. In addition, a mechanism is proposed based on experiments using linear symmetrical secondary diamines.

Treatment of cyclen **1** with equimolar amounts of paraformaldehyde, acetic acid, and cyclohexylisocyanide in methanol (1 M) at room temperature for 16 h provided the macrocycles $N^1$,$N^4$ disubstituted **2a** and $N^1$,$N^7$ disubstituted **2b** in a 1:1 ratio (57% yield, Scheme 1).[14] However, when the reaction was performed under reflux conditions, the ratio of **2a/2b** obtained was a 1:2 ratio in comparable yield. This occurred even though, statistically, **2a** is twice as likely to form as **2b** as the major product. Two experiments have been performed to gain more insight into the reaction. When a 1:1 mixture of **2a/2b** was heated to reflux in methanol for 96 h, the ratio changed to 1:2 in favor of **2b**; the same result was obtained when pure **2a** or **2b** compounds were used.

Clearly, an equilibrium takes place between the $N^1$,$N^4$- and $N^1$, $N^7$-substituted compounds, with transfer of the acetyl group from one nitrogen to the other.

**Scheme 1.** Possibile Pathways for the Formation of **2a** and **2b**

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(14) Compounds **2a** and **2b** were separated, with difficulty, by normal phase chromatography using acetonitrile/ammonia as an eluent. Although the $^1$H NMR spectra of these compounds are quite complicated due to hindered rotations around the amide bonds, they were judged pure by elemental analysis and $^{13}$C NMR. The different symmetry between **2a** (less symmetrical) and **2b** (more symmetrical) allowed the correct assignment by comparison of the two $^{13}$C NMR.

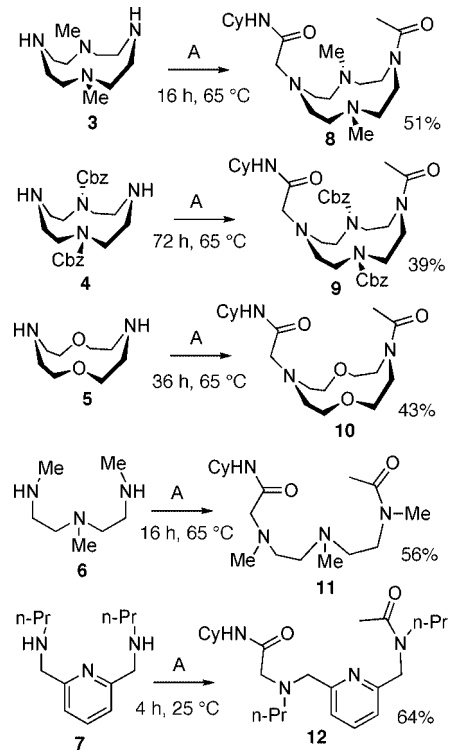
After screening numerous solvents, methanol was found to be the best. This solvent has ideal polarity for reagents solubility, therefore providing the highest yields and simplest workup of the reaction. No reaction took place when water was employed.[15]

The methodology was then extended to other 12-membered polyazamacrocycles such as 1,7-dimethylcyclen **3**,[16] 1,7-dioxacyclen **4**,[17] and 1,7-di-Cbz-cyclen **5**.[18] The choice was inspired by the relevance of these scaffolds used in molecular recognition and by their easy availability. All of these compounds contain the same substructure, namely, 1,7-bis secondary diamine separated by an aliphatic chain containing a heteroatom. As well as cyclen, **3**, **4**, and **5** were successfully subjected to the *N*-split-Ugi 4CR protocol using paraformaldehyde, cyclohexyl isocyanide, and acetic acid (Scheme 2). As shown, although the desired conversion always occurred, longer times were needed for **4** and **5** to give comparable yields. In addition, to further test the approach and to get more insight into the mechanism, two linear symmetrical secondary diamines **6** and **7** were used.[19] While compund **6** reacted similarly to cyclen **2** and dimethylcyclen **3**, pyridine derivative **7** furnished the corresponding product in less time at room temperature.

From these experiments, we can observe that the conformational flexibility of the linking moiety connecting the two secondary amines as well as the nature and the electronic properties of the internal heteroatoms evidently play a crucial role. However, precise rationalization cannot be given at this point.

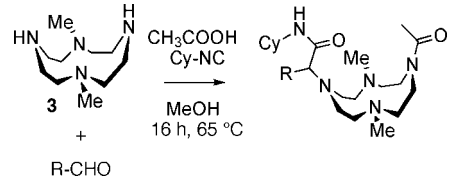
The generality for the functionalization of dimethylcyclen **3** was then validated by varying the single components.[6,16] Besides formaldehyde (Table 1, entry 1), butyraldehyde (Table 1, entry 2) and benzaldehyde (Table 1, entry 3) were successfully employed as the carbonyl compound. Ugi product formation was negligible or not observed when cyclopentanone (Table 1, entry 4) was employed, whereas the Passerini 3-CR (P-3CM) product **16** was isolated (see Supporting Information). Steric hindrance could be envisaged to explain the lack of the desired reaction, although the classical Ugi 4CR has been reported to be quite insensitive to steric hindrance.[12c] Notably, a lower yield was observed when benzaldeyde was used and the Passerini 3-CR product **15** was isolated and characterized (see Supporting Information). In this case, imine formation occurred quite readily, being favored by the conjugation, but slow α-addition of the isonitrile followed. For substrates with limited reactivity (aromatic aldehydes and ketones), Lewis acid catalysts have also been used.[20] The use of 10% quantities of $Sc(OTf)_3$, $Ti(OiPr)_4$, or $Mg(ClO_4)_2$ or molecular sieves did not enhance the yield of Ugi products.

**Scheme 2.** Compounds Obtained by Variation of the Bis-Secondary Amine[a]




[a] A: paraformaldehyde (1 equiv), cyclohexylisocyanide (1 equiv), acetic acid (1 equiv) in methanol (1 M). Yield of the isolated product.

**Table 1.** Compounds Obtained by Variation of the Carbonyl Component




| entry | R | Ugi 4CM product | P-3CM product |
|---|---|---|---|
| 1 | H- | **8** (51) | – |
| 2 | Pr- | **13** (31) | – |
| 3 | Ph- | **14** (21) | **15** (49) |
| 4 | cyclopentanone | traces | **16** (34) |

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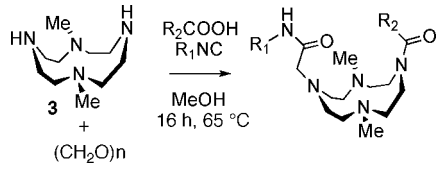
The isocyanide and the carboxylic acid components were also varied, and the results are listed in Table 2. As with the

**Table 2.** Compounds Obtained by Variation of the Isonitrile and Acid Component




| entry | $R_1$ | $R_2$ | yield | product |
|---|---|---|---|---|
| 1 | cHex | Me | 51 | **8** |
| 2 | cHex | Ph | 49 | **17** |
| 3 | cHex | Ph−CH=CH− | 56 | **18** |
| 4 | cHex | CbzNH−$CH_2$− | 62 | **19** |
| 5 | Bn | Me | 53 | **20** |
| 6 | t-Bu | Me | 42 | **21** |

parent Ugi 4CR, structural modification of one or both components did not affect either the progress or the yield of the corresponding reactions, which were still characterized by good overall efficiency. Furthermore, entry 4 (Table 2) exemplifies the synthetic power of this transformation: the product **19** was obtained using N-protected glycine as the acid component. This result allowed the peptide-like sequence to be extended into the macrocyclic system and potentially furnish easily homochiral unsymmetrical difunctionalized $N^1$,$N^7$ cyclen in a single step.

Although no detailed mechanistic studies have been carried out at this point, a possibile mechanism can be envisaged based on observed yields and reactivity.

In detail (Figure 2), one of the two secondary amines of the substrate reacts with the carbonyl group to afford an iminium ion which reacts via α-addition with the isocyanide and the carboxylate moiety. The resulting intermediate **A** undergoes a subsequent transacylation in which the acyl moiety migrates to the second $N^7$ secondary amine (Mumm rearrangement), either directly (path b) and/or through the intermediate acylated heteroatom **I**, that acts as a carrier of the acyl group (path a). The latter statement can be made by comparing the different reaction conditions used for substrates **4** and **7**. The more nucleophilic nitrogen of the pyridine in compound **7** allows the reaction to take place at room temperature in 4 h, whereas **4** required refluxing methanol and 3 days. When cyclen (Z = NH) is employed, an equilibrium is present between compounds **I** and **P**.

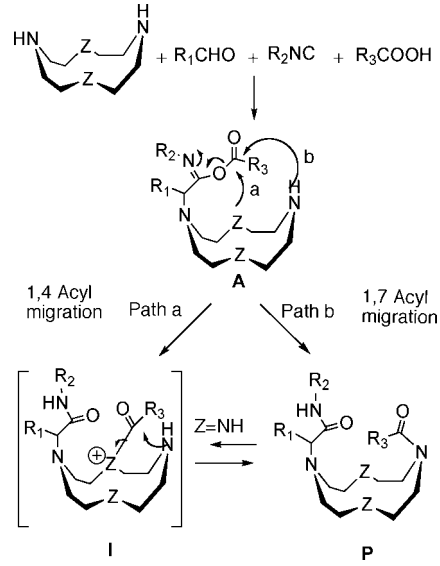



**Figure 2.** Proposed mechanism for the *N*-split-Ugi reaction in a polyazamacrocyclic system.

In summary, we have developed a new, simple, and efficient application of the Ugi multicomponent reaction that allows the one-pot direct preparation of unsymmetrical polyazamacrocycles, as well as their open-chain counterparts from readily available compounds. This approach avoids the time- and chemical-consuming steps necessary to discriminate the chemically equivalent nitrogen atoms of such polyamines.[21] The enabling methodology presented here will facilitate the synthesis of novel agents, improve conjugation efficiency of biopolymers bearing macrocycles to targeting moieties, and simplify functionalization of agents and intermediates.

**Acknowledgment.** Financial support from Universitàì degli Studi di Urbino "Carlo Bo" and M.I.U.R PRIN 2006 and PRIN 2007, Italy, is gratefully acknowledged.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802674R

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