ORGANIC LETTERS

2006
Vol. 8, No. 3
383−385

Synthesis of 3,6-Diaminophthalimides for Ureidophthalimide-Based Foldamers

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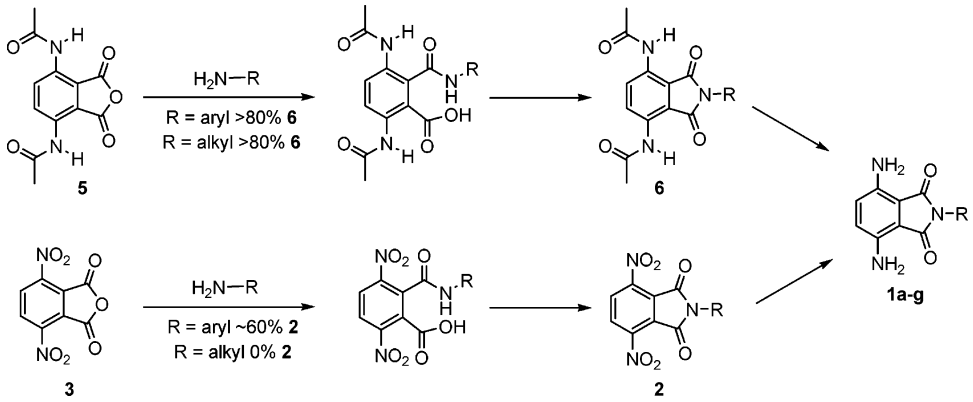
Received October 12, 2005

ABSTRACT



Herein, we report an improved methodology for the synthesis of a variety of 3,6-diaminophthalimides in high yields. This enables decoration of the periphery of foldamers with a wide range of functionalities.

Natural as well as synthetic helical architectures have attracted great interest recently. Of all helical architectures, the foldamer most resembles natural systems.[1] Appropriate functionalization of the covalent backbone of an oligomer or polymer allows for dynamic intramolecular interactions. Within the area of foldamer research, many classes have been described ranging from the hydrogen-bond-based peptides and peptidometics to systems in which $\pi-\pi$ interactions determine the secondary architecture.[2−4] Recently, we have reported on the synthesis of a ureidophthalimide-based foldamer which has been synthesized by the reaction of a 3,6-diaminophthalimide (**1a**) with its corresponding diisocyanate (Scheme 1).[5] The polyurea has proven to fold in THF and heptane but not in $CHCl_3$. To expand the scope of the current system, decoration of the core with a variety of functionalities has been envisaged. Incorporation of chromophores and functionalities that simultaneously ensure solubility in water form an important part of the scope.

However, synthesis of phthalimides with the 1,2,3,6-substitution pattern, as in **1**, is not trivial. A general method is not available. Despite the availability of several approaches to 3,6-disubstituted phthalic acid derivatives, such as a Diels−Alder adduct of 1,4-disubstituted 1,3-butadiene with alkynes[6] and of 2,5-dimethylfuran with *N*-methylmaleimide,[7]

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(2) (a) Huc, I. *Eur. J. Org. Chem.* **2004**, 17. (b) Estroff, L. A.; Incarvito, C. D.; Hamilton, A. D. *J. Am. Chem. Soc.* **2004**, *126*, 2. (c) Sandford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Gong, B. *Eur. J. Biochem.* **2004**, 1416. (d) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587.

(3) Berl, V.; Kirsche, M. J.; Huc, I.; Lehn, J. M.; Schmutz, M. *Chem.−Eur. J.* **2000**, *6*, 1938.

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(5) van Gorp, J. J.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem. Commun.* **2004**, 60.

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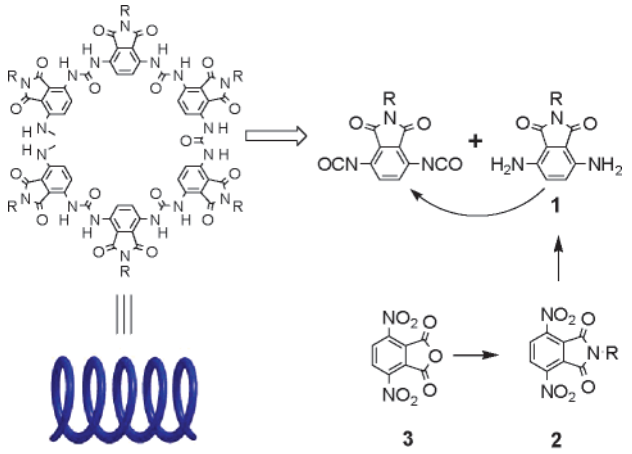
10.1021/ol0524757 CCC: $33.50
Published on Web 01/10/2006

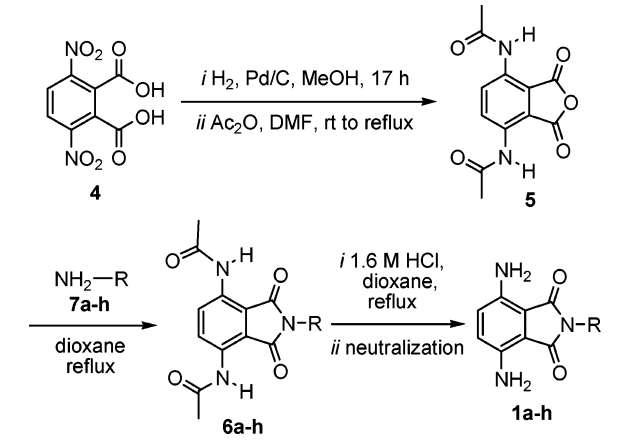
Scheme 1



these approaches do not lead to the required substituents. Moreover, the imidation of 3,6-dinitrophthalic anhydride **3** leading to **2** (Scheme 1) only works with specific amines.

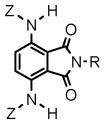
In this paper, we present a general methodology for the synthesis of 3,6-diaminophthalimide building blocks employing 3,6-bis(acetylamino)phthalic anhydride (**5**) as a starting material. The latter is obtained via the palladium-mediated catalytic reduction of 3,6-dinitrophthalic acid (**4**),[8] followed by exposure of the unstable diaminophthalic acid to acetic anhydride[9] (Scheme 2). Subsequent reaction of **5** with

Scheme 2



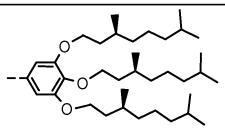
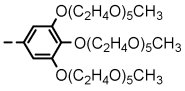
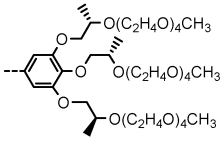
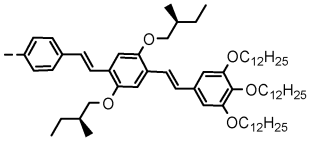
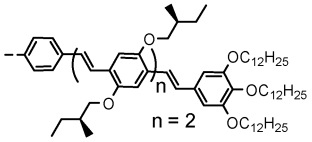
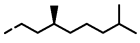
primary amines in dioxane at reflux affords a variety of 3,6-bis(acetylamino)phthalimides (**6a**−**h**) in good to almost quantitative yields (Table 1). All phthalimides have been purified by column chromatography or crystallization.

Table 1. Two-Step Conversion of 3,6-Bis(acetylamino)phthalic Anhydride **5** to 3,6-Diaminophthalimides **1a**−**g**



6, Z = $COCH_3$

1, Z = H

	R	imides **6** yield (%)[a]	imides **1** yield (%)[b]
a		86	91
b		80	83
c		90	95
d		85	~70[c]
e		91	81
f		87	75
g		83	90
h		86	--

[a] Isolated yield for the 3,6-bis(acetylamino)phthalimides. [b] Isolated yield for the 3,6-diaminophthalimides. [c] Based on NMR.

The final step toward the desired monomeric building blocks for the foldamer is the removal of the *N*-acetyl functionalities. Exposure of 3,6-bis(acetylamino)phthalimides (**6a**−**g**) to a 1.6 M solution of HCl in aqueous dioxane at reflux furnishes the corresponding 3,6-diaminophthalimides in 70−95% yield, without noticeable imide hydrolysis.

We have found that the outcome of imide formation is strongly governed by the substituents on both the anhydride and the N-source and have revealed that 3,6-bis(acetylamino)phthalic anhydride (**5**) is more suitable than 3,6-dinitrophthalic anhydride (**3**). Primary aromatic amines can be reacted with 3,6-dinitrophthalic anhydride (**3**) affording the corresponding functionalized phthalimide (**2**) in a yield typically between 40 and 60%.[5] However, this strategy cannot be applied for the introduction of primary aliphatic amines. This may be rationalized by the mechanism of the

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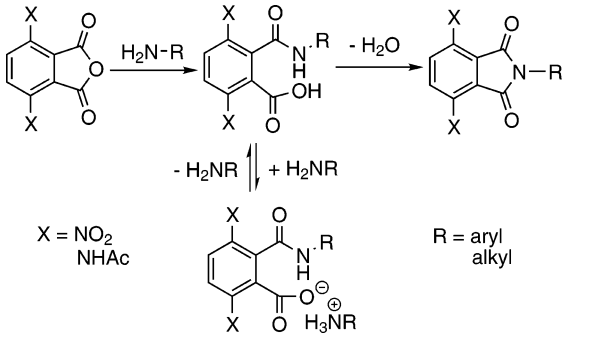
reaction (Scheme 3). Moreover, during incorporation attempts of aliphathic amines, substitution of one of the nitro functionalities was observed.

Scheme 3



The formation of the phthalimide most likely proceeds via two steps, starting with a ring-opening reaction involving the nucleophilic attack of the amine on the carbonyl carbon of the phthalic anhydride. The second step is the ring closure to the phthalimide system with concomitant release of water. The remaining carboxylic acid functionality of the amic acid intermediate readily protonates the amine giving an organic salt, as is observed in ^{1}H NMR. Although not observed in our research, the formation of an isoimide by dehydration of the amic acid followed by rearrangement to the imide has also been reported.[10] In the case of aromatic amines, the organic salt is in equilibrium with the free acid.

However, when aliphatic amines are employed, the intermediate is trapped as the organic salt. This is due to the combination of the electron-withdrawing nature of the nitro groups, which enhances the acidity of the carboxylic acid, and the basicity of the aliphatic amines, compared to the aromatic ones. Consequently, conversion of the electron-withdrawing nitro function into the electron-donating acetamide strongly improves the ring-closure reaction. In addition, the intramolecular hydrogen-bonding ability of the acetamido group may influence the ring opening of the anhydride as well as the ring closure to the imide.[11]

As seen in Table 1, the broad scope of the methodology toward imides **6** and **1** is obvious. Not only were weakly nucleophilic aromatic amines **7a**−**f** successfully incorporated but also were strongly nucleophilic aliphatic amines **7g**−**h**. Even the more sterically demanding amine **7h** was integrated in good yield. In addition, in the case of synthon **6h**, derivatization prior to removal of the acetyl groups is envisaged. The scope covers the introduction of hydrophobic **7a** and **7d**−**h**, as well as hydrophilic **7b**−**c**, functionalities. The current strategy via 3,6-bis(acetylamino)phthalic anhydride (**5**) has proven to be superior to our previously reported approach (Scheme 1) starting from 3,6-dinitrophthalic anhydride (**3**). To summarize, with this library of novel 3,6-diaminophthalimides in hand, the synthesis and study of a wide range of appealing foldamers are viable.

Acknowledgment. For financial support, we thank NWO. We kindly acknowledge Xianwen Lou and Henk Eding for their measurements concerning the MALDI-TOF MS and elemental analysis, respectively. Guy Koeckelberghs is a postdoctoral fellow of FWO-Vlaanderen (Fund for Scientific Research-Vlaanderen).

Supporting Information Available: Experimental procedures of all synthesized compounds including their characterization (^{1}H NMR, ^{13}C NMR, FT-IR, UV−vis, MALDI-TOF MS, and elemental analysis). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0524757

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(11) The relevance of intramolecular hydrogen bonding by the acetamido group was kindly suggested by a reviewer.