The Convenient Synthesis of Hydrogen-Bonded Ureidopyrimidinones

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Blocked isocytosine isocyanates are conveniently obtained by the reaction of 1,1′-carbonyldiimidazole (CDI) with isocytosines. The resulting precursors for quadruple hydrogen-bonded structures can be isolated and stored for further use. Reaction with either aliphatic or aromatic amines gives the corresponding mono-, bi-, or trifunctional ureidopyrimidinone derivatives in good to excellent isolated yields.

Introduction

Supramolecular polymers form a new class of polymers where the reversibility of the non-covalent bonds between the monomers gives rise to novel material properties.[1,2] We have developed supramolecular polymers in which the "monomers" are bifunctional molecules formed by connecting two strongly dimerizing quadruple hydrogen bonding 2-ureido-4-pyrimidinone (UPy) groups (Figure 1) via a linker.[3,4]

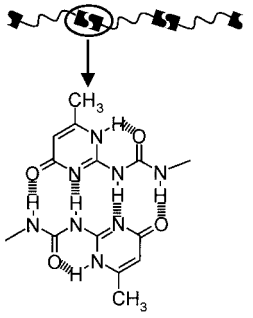
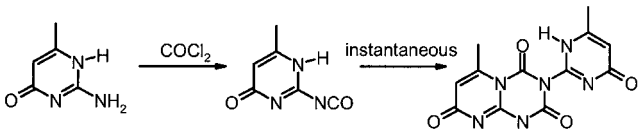


Figure 1. The self-complementary quadruple hydrogen-bonding ureidopyrimidinone (UPy) group in a supramolecular polymer

The linker in these monomers is most often connected to the UPy groups at the urea functionality through reaction of an isocytosine with isocyanate groups of the linker. However, for aromatic diisocyanates this method is not satisfactory and gives low yields, probably due to the low nucleophilicity of the amino group of isocytosine. Incomplete functionalization in bifunctional compounds leads to a lower degree of polymerization (DP) because of the formation of monofunctional UPys that can act as chain stoppers.[3,5] Furthermore, for the synthesis of multifunctional UPy derivatives, adding an excess of isocytosine isocyanate to a linker with multiple amino groups to ensure complete functionalization is a conceptually better strategy. Unfortunately, the isocyanate of isocytosine cannot be synthesized as was shown by Gizycki,[6] who showed that in attempts to form the isocyanate of pyridines and pyrimidines with diphenyl carbonate, dimeric ureas were obtained. In our attempts to form the isocyanate of isocytosine by phosgenation, only a covalent dimer could be isolated as shown in Scheme 1.[7]



Scheme 1. Formation of isocytosine dimers

The synthesis of "blocked" isocytosine isocyanates was attempted using a range of chloroformates[8] such as nitrophenyl and phenyl chloroformate. However, products with sufficient stability that could be isolated and stored for further use were not obtained. An alternative method to form ureas and carbamates is the use of 1,1′-carbonyldiimidazole (CDI),[9,10] which has been used in peptide synthesis,[11] heterocyclic synthesis,[12–15] small molecule synthesis,[16–18] and to prepare dendrimers and macromolecules.[19,20] Here, we report on the convenient synthesis of blocked isocytosine isocyanates using CDI, which can be isolated and stored. Furthermore, it is shown that the blocked isocytosine isocyanates are sufficiently reactive to react with both aliphatic and aromatic amines under mild conditions.

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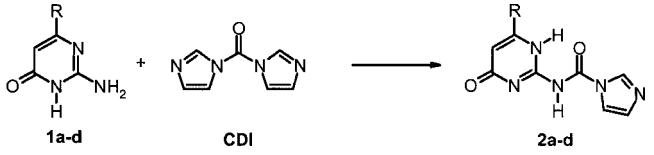
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Results and Discussion

Blocked isocytosine isocyanates **2a−d** were obtained by the reaction of the isocytosine derivatives **1a−d** with an excess (1.2 equiv.) of CDI (Scheme 2). Excess CDI was used to ensure complete activation of the isocytosine. Formation of bis(isocytosineurea) was not observed. Under these reaction conditions, the formed imidazolides are apparently not reactive towards the amino group of isocytosine (vide infra). High selectivity due to an asymmetric reactivity of CDI has also been observed for alcohols by Davis et al.[21]

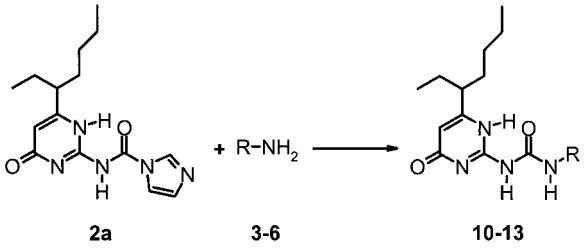


1a R = 1-ethylpentyl
1b R = *t*butyl
1c R = *n*butyl
1d R = $C_{13}H_{27}$

Scheme 2. Synthesis of blocked isocytosine isocyanates; throughout the paper this tautomeric form of **2a−d** is used, although the exact form has yet to be identified

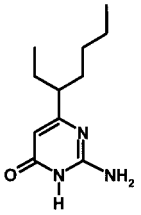
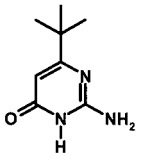
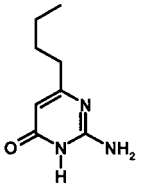
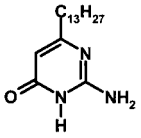
As shown by the reaction of **1a** with CDI in chloroform to give **2a** at room temperature (Table 1), high temperatures are not needed to prepare the imidazolide **2a**. At room temperature CDI is sufficiently reactive to react with the amino group of isocytosine which has a low nucleophilicity. It was necessary to use tetrahydrofuran and/or higher reaction temperatures for the synthesis of the imidazolides **2b−d** due to the limited solubility of the isocytosines **1b−d**.

The imidazolides **2b−d** were isolated by precipitation in acetone; the high solubility of **2a** did not allow for it to be precipitated, and the excess reagent and imidazole were therefore removed by washing twice with water. This was possible because the hydrolysis of imidazolide **2a** is slow and degradation does not take place. The dried imidazolides **2a−d** are stable and can be stored for several months at room temperature. The reactivity of the imidazolides towards amines was tested by reaction of **2a** with several amines of different reactivities (Scheme 3).



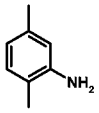
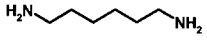
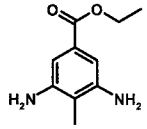
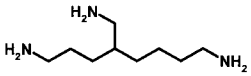
Scheme 3. Synthesis of monofunctional ureidopyrimidinones **10−13**

Table 1. Synthesis of the imidazolides

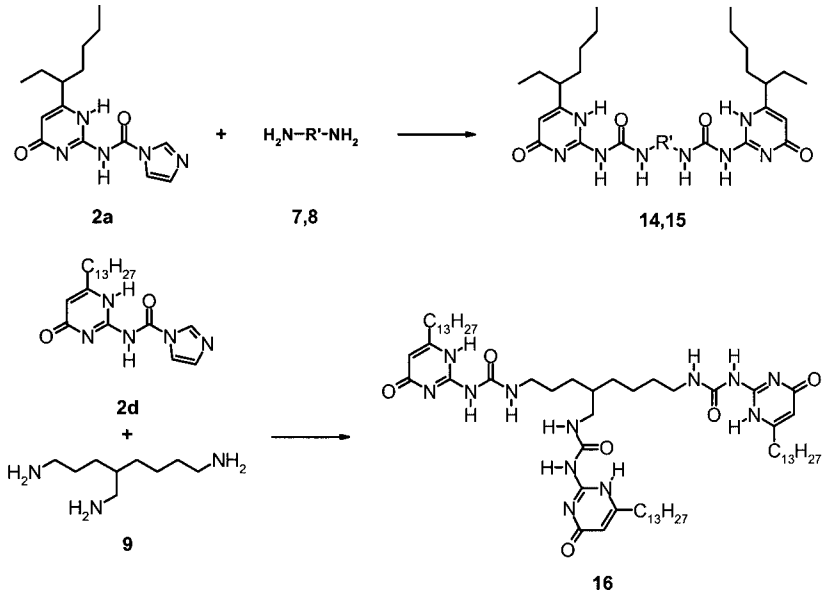
	Starting isocytosine	Solvent	Temperature (°C)	Isolated Yield (%)	Product
1a		chloroform	25	98	**2a**
1b		THF	65	88	**2b**
1c		chloroform	61	85	**2c**
1d		chloroform	50	91	**2d**

A slight excess (1.1 equiv.) of both the aliphatic and aromatic amines reacted smoothly with imidazolide **2a** to yield ureidopyrimidinones **10−13** (Table 2). A higher reaction temperature was used for the less nucleophilic aromatic amines **5** and **6**. The workup procedure involved washing with aqueous acid (1 N HCl) and aqueous base (sat. $NaHCO_3$), followed by either precipitation for **11−13** or column chromatography for **10**. The ureidopyrimidinones **10−13** were obtained as white powders in good isolated yields.

Table 2. Synthesis of the ureidopyrimidinones **10−16** from amines and **2a**

	Amine	Temperature (°C)	Isolated yield	Product
3		25	82	**10**
4		25	66	**11**
5		50	78	**12**
6		50	70	**13**
7		25	95	**14**
8		50	88	**15**
9		25	84	**16**[a]

[a] The trifunctional amine **9** was reacted with **2d** (Scheme 4).



Scheme 4. Synthesis of bi- and trifunctional ureidopyrimidinones

Bifunctional and trifunctional ureidopyrimidinones **14**, **15** and **16** were obtained by reaction of excess (1.15 equiv. per amine) **2a** or **2d** (in the case of **16**) with hexamethylenediamine (**7**), ethyl 3,5-diamino-4-methylbenzoate (**8**), and 4-aminomethyl-octane-1,8-diamine (**9**), respectively (Scheme 4).

The reaction conditions (Table 2) were the same as those for the synthesis of the monofunctional ureidopyrimidinones **10**−**13**. Bifunctional ureidopyrimidinones **14** and **15** were isolated after washing with acid (1 N HCl) and base (sat. $NaHCO_3$), followed by precipitation in acetone and methanol, respectively. The trifunctional ureidopyrimidinone **16** was isolated by slow addition of the reaction mixture to an excess of MeOH, which resulted in the precipitation of the product as a white powder.

Conclusion

In summary, we have shown that blocked isocytosine isocyanates can be obtained by reacting CDI with isocytosines, and that the reaction conditions are mainly dependent on the limited solubility of the isocytosines. The resulting imidazolides can be isolated and stored for further use. The blocked isocytosine isocyanates react smoothly with both aliphatic and aromatic amines to give the corresponding ureidopyrimidinone derivatives in good to excellent isolated yields.[22]

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[22] For experimental details see Supporting Information (see also the footnote on the first page of this article).

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