

## Supramolecular Polymers

## Convenient Synthesis of Functionalized Bis-ureidopyrimidinones Based on Thiol-yne Reaction

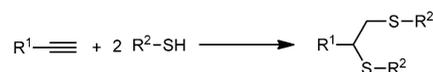
Hui-Qing Peng,<sup>[a, b]</sup> Cai-Li Sun,<sup>[a, b]</sup> Jiang-Fei Xu,<sup>[a, b]</sup> Li-Ya Niu,<sup>[a]</sup> Yu-Zhe Chen,<sup>[a]</sup> Li-Zhu Wu,<sup>[a]</sup> Chen-Ho Tung,<sup>[a]</sup> and Qing-Zheng Yang<sup>\*[a]</sup>

**Abstract:** The preparation of functionalized bis-ureidopyrimidinones (**Bis-UPy**) through the thiol-yne reaction is described. Various **Bis-UPys** with different functional groups were synthesized by using the readily available functionalized alkynes and UPy-thiol to affirm the simplicity and versatility of the methodology.

The self-complementary 2-ureido-4[1H]-pyrimidinone (UPy) quadruple H-bonding motif developed by Meijer is one of the most commonly used building blocks in supramolecular polymers due to its great binding strength ( $K_{\text{ass}} = 6 \times 10^7 \text{ M}^{-1}$ ) and directionality.<sup>[1]</sup> Bis-ureidopyrimidinones (**Bis-UPy**) containing functional groups have been used for constructing functional supramolecular polymers.<sup>[2,3]</sup> To date, **Bis-UPy** have mainly been synthesized by two different methods; either by reaction of activated isocytosine with diamines or by reaction of isocytosine with diisocyanates.<sup>[4]</sup> Their mild reaction conditions and high yields have boosted developments of **Bis-UPy** based supramolecular polymers in areas such as biomaterials, smart materials and light-emitting devices.<sup>[2,3]</sup> Unfortunately, diamines containing functional groups are not usually available and need to be prepared by multistep synthesis, such as by the introduction and reduction of nitro<sup>[2a]</sup> or azide<sup>[3]</sup> groups under harsh reaction conditions. Protection and deprotection of amino groups are also necessary for storage or further molecular functionality due to its high reactivity. In the second strategy, the reaction is performed under high temperature probably due to the low nucleophilicity of the amino group in the isocytosine.<sup>[4]</sup> An alternative method that can efficiently prepare **Bis-UPy** with functional groups is highly desirable.

The thiol-yne radical reaction has received significant interest as the new click chemistry due to its mild reaction condition, rapid reaction rate and high yield.<sup>[5,6]</sup> It tolerates a wide range of functional groups. In particular, this reaction involves

addition of two thiols to one alkyne, which makes it perfectly suitable for synthesis of bis-adduct products (Scheme 1). Impressive progress has been achieved in the construction of dense functional polymer materials by using this accelerated synthesis.<sup>[6]</sup> However, the synthesis of **Bis-UPy** by the thiol-yne reaction remains unexplored. Herein, we reveal the use of the thiol-yne reaction for the synthesis of **Bis-UPy** to be an extremely simple synthetic approach. The easily available starting alkynes were used to prepare promising **Bis-UPys** that are difficult to prepare by conventional synthetic strategies.



**Scheme 1.** Synthesis of bis-adducts from thiol-yne reaction.

The synthesis of **Bis-UPy** with the thiol-yne reaction is shown in Scheme 2. Disulfide-thiol chemistry was employed to provide UPy-functionalized thiol (UPy-thiol) for the thiol-yne reaction, since disulfides are stable for storage and can be easily cleaved to afford corresponding thiols in the presence of reducing agents.<sup>[7]</sup> The commercially available cystamine dihydrochloride (**A**) was selected as the starting material to react with the activated ureidopyrimidinones (**B**) to afford **Bis-UPy** disulfide (**C**) in excellent yield. UPy-thiol was obtained by the reduction of **C** with 1,4-dithiothreitol (DTT) quantitatively.<sup>[8]</sup>

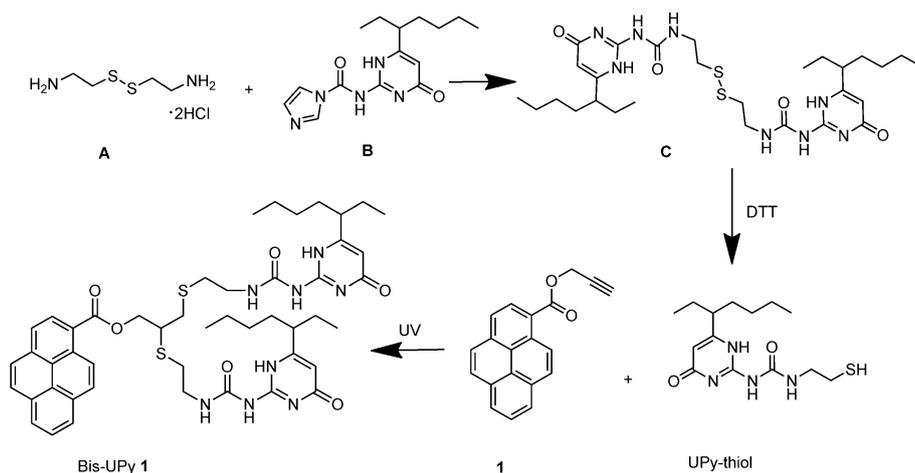
Alkyne **1** (43 mM), UPy-thiol (6 equiv) and a catalytic amount of 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photoinitiator were combined in 1,2-dichloroethane (1.2 mL). The resulting solution was irradiated under a high pressure Hg lamp at room temperature. The functionalized alkyne precursor was depleted in 2 h. We removed the solvent and obtained the pure **Bis-UPy 1** by column chromatography with a high yield of up to 94%. Each alkyne group reacts firstly with a single UPy-thiol to form a vinyl sulfide stage followed by reaction of the vinyl sulfide with another UPy-thiol to yield the 1,2-disubstituted adduct (Scheme S1 in the Supporting Information).<sup>[9]</sup>

To prove the general suitability of this method, alkynes **2–5** containing different functional groups were selected as precursor to prepare **Bis-UPys** (Table 1 and Table 2). The starting materials were mixed together with photoinitiator in photostable 1,2-dichloroethane, except **Bis-UPy 3**, which was synthesized in chloroform due to the limited solubility of **3** in 1,2-dichloroethane. All the **Bis-UPys** were thoroughly characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and high-resolution mass spectrom-

[a] H.-Q. Peng, C.-L. Sun, J.-F. Xu, Dr. L.-Y. Niu, Dr. Y.-Z. Chen, Prof. Dr. L.-Z. Wu, Prof. Dr. C.-H. Tung, Prof. Dr. Q.-Z. Yang  
Key Laboratory of Photochemical Conversion and Optoelectronic Materials  
Technical Institute of Physics and Chemistry, Chinese Academy of Sciences  
Beijing 100190 (P.R. China)  
E-mail: qzyang@mail.ipc.ac.cn

[b] H.-Q. Peng, C.-L. Sun, J.-F. Xu  
University of the Chinese Academy of Sciences Beijing 100049 (P.R. China)

Supporting information for this article is available on the WWW under  
<http://dx.doi.org/10.1002/chem.201402955>.



**Scheme 2.** Illustration for synthesis of bis-ureidopyrimidinones by disulfide-thiol chemistry and thiol-yne reaction.

etry (see the Supporting Information).  $^1\text{H}$  NMR spectra of **Bis-UPys 1–5** showed large downfield shifts of the UPy N–H signals, indicating the dimerization of the UPy units, which is the prerequisite for constructing supramolecular polymers (Figure S1 in the Supporting Information).<sup>[1b]</sup>

Although impressive progress has been made using the thiol-yne reaction, most of these studies have focused on new materials synthesis and have rarely been concerned with the experimental conditions affecting the reaction outcome.<sup>[6]</sup> One intriguing observation in this methodology is that different molar ratio of alkynes to UPy-thiol is required to complete the reaction for different functional groups in **1–5** in 2 h. At UPy-thiol concentration of 260 mM, we tuned the concentration of alkynes to change their molar ratio. We found that a slight excess of UPy-thiol (2.5 equiv) was needed to maximize the bis-adducts for alkyne **3–5**. It should be noted that 6 and 10 equiv of UPy-thiol were used to complete the reaction in 2 h for alkyne **1** and **2**, respectively. This may be attributed to the fact that the functional groups of these alkynes absorb light of similar wavelength as the photoinitiator DMPA, which reduces the initiation efficiency.<sup>[10]</sup> However, the completion of **Bis-UPy 1** required 6 equivalents of UPy-thiol, but for **Bis-UPy 2**, with the lower extinction coefficient, 10 equivalents of UPy-

thiol were needed to deplete alkyne **2** in 2 h (see the Supporting Information). We speculate that steric hindrance is responsible for this deviation. The longer ester linkage was favorable for the addition of UPy-thiol radical to give a bis-sulfide adduct. In contrast, alkyne **2** was linked to a large aromatic substrate by a short ether groups. The addition of UPy-thiol may be blocked to yield 1,2-disubstituted adducts.

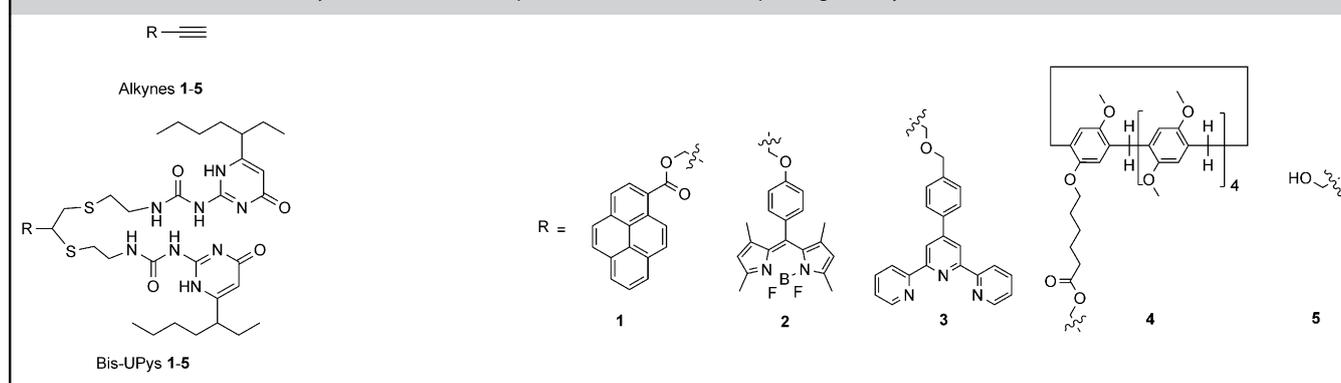
The influence of steric hindrance on the thiol-yne reaction is supported by two facts. First, alkyne **1** gave **Bis-UPy 1** in 94%

or even higher yields and alkyne **2** only gave **Bis-UPy 2** in 84% yield. The steric factor may lower the reactivity of **2** at the vinyl sulfide stage, and consequently decrease the yield of bis-adduct. The low reactivity of our thiol-yne reaction for the substrates with the alkyne group directly linked to an aromatic group provides the second solid evidence. Under identical conditions, 1-ethynylpyrene treated with 6 equivalents UPy-thiol for 2 h yielded no bis-adducts and only a small amount of monoadduct. This result may be attributed to the steric hindrance of the pyrene group to the bulk UPy-thiol radicals, which further verified our speculation on synthesis of **Bis-UPy 1** and **Bis-UPy 2** requiring different equivalents of UPy-thiol.

**Table 2.** Summary of the **Bis-UPys 1–5** synthesized by thiol-yne reactions in 2 h under air.

Bis-UPy	UPy-thiol [mM]	Alkyne [mM]	UPy-thiol/alkyne	Solvent	Yield [%]
1	260	43	6	$\text{ClCH}_2\text{CH}_2\text{Cl}$	94
2	260	26	10	$\text{ClCH}_2\text{CH}_2\text{Cl}$	84
3	260	104	2.5	$\text{CHCl}_3$	74
4	260	104	2.5	$\text{ClCH}_2\text{CH}_2\text{Cl}$	87
5	260	104	2.5	$\text{ClCH}_2\text{CH}_2\text{Cl}$	97

**Table 1.** Chemical structures of alkyne-functionalized compounds **1–5** and their corresponding **Bis-UPys 1–5**.



In addition to the study of the influence of the molar ratio of the starting materials, we took the whole reaction concentration into account to obtain insights into **Bis-UPy** synthesis. The result shows that thiol-yne reaction for preparing **Bis-UPy** is sensitive to the concentration of the UPy-thiol. As the UPy-thiol concentration was diluted from 260 to 43 mM under the same molar ratio of alkynes to UPy-thiols, the reaction mixture, as monitored by TLC after 2 h, clearly showed much of the unreacted functionalized alkyne. However, 65 mM of UPy-thiol was enough to complete the reaction. It is most likely that the high reaction concentration is favorable to the radical transfer in radical-mediated thiol-yne reaction. These correlations enabled us to prepare **Bis-UPy** with satisfactory yield under appropriate conditions.

To further optimize the reaction conditions, we studied the influence of oxygen and solvent on the reaction for preparing **Bis-UPy**. **Bis-UPy 1** was prepared in a solution exposed to air and a solution degassed with nitrogen, respectively. It turned out that our reactions are insensitive to oxygen, which is usually a factor in radical-mediated thiol-yne reaction.<sup>[6b]</sup> This leads to a more simplified preparation method without tedious degassing procedures. Moreover, in addition to nonpolar solvents (e.g., 1,2-dichloroethane and chloroform), the efficiency of the reaction was satisfied by using a polar solvent, such as a mixture of THF/water (9:1, v/v), indicating that this new methodology for the preparation of **Bis-UPy** was not restricted to a particular solvent (Table S2 in the Supporting Information).

To illustrate the application of our **Bis-UPys** for construction of supramolecular polymers, we took **Bis-UPy 1** as an example to study its self-assembly behavior in  $\text{CHCl}_3$ . As shown in Figure 1, the double logarithmic plot of specific viscosity versus concentration of **Bis-UPy 1** was linear with a slope of 2.10 over the whole concentration range (5–75 mM), indicating the propensity of **Bis-UPy 1** to supramolecular polymerize even at low concentrations (Scheme S2 in the Supporting Information).<sup>[11]</sup> This result combined with the NMR spectroscopy result shown above, confirmed the formation of supramolecular polymers in chloroform from **Bis-UPy 1**.

In our work, **Bis-UPys 1–5** with different functional groups are potentially useful for constructing novel supramolecular polymers. **Bis-UPys 1–2** containing chromophores with high quantum yields can be employed to fabricate luminescent supramolecular polymers. Terpyridine as a classical metal

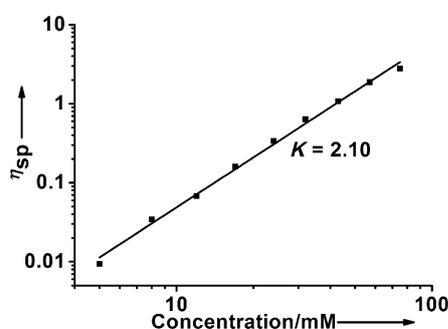


Figure 1. Specific viscosity of compound **Bis-UPy 1** in  $\text{CHCl}_3$  solutions versus the concentration at 298 K. The  $K$  value indicates the slope of the line.<sup>[11]</sup>

ligand in **Bis-UPy 3** will allow to introducing metal-ligand binding which approaches the strength of covalent bonds to afford a supramolecular polymer networks.<sup>[12]</sup> The combination of host-guest chemistry of pillar[5]arene moiety<sup>[13]</sup> with quadruple H-bonding from **Bis-UPy 4** may be useful for fabricating novel supramolecular polymers by orthogonal self-assembly. Moreover, the thiol-yne reaction results in the functional groups as pendants in side chains, which will endow the supramolecular polymers with special properties, such as convenient further modification of the **Bis-UPy**. For example, the hydroxyl in **Bis-UPy 5** as a new reactive site can be used to graft another functional group. The length of the linker between two UPy groups in **Bis-UPy** could be tuned by adjusting the linkage between amino and disulfide groups of the starting compound. Studies of applications of these new **Bis-UPys** are now ongoing in our laboratory.

In conclusion, we describe the preparation of bis-ureidopyrimidinones by using the thiol-yne reaction. Five **Bis-UPys** with different functional groups were synthesized successfully from readily available alkyne precursors and **Bis-UPy** disulfide (**C**) in excellent yields. The yield was not influenced by oxygen and solvent, but was sensitive to molar ratio of alkynes/thiols and the whole reaction concentration. The extremely simple synthetic approach may offer great opportunities in preparing new **Bis-UPy** for construction of useful functional supramolecular polymers. Further studies in our laboratory are aimed at developing a library of **Bis-UPy** and their use to construct supramolecular polymers for various applications.

## Acknowledgements

We are grateful for the financial support from the 973 Program (2013CB933800, 2013CB834505), the National Natural Science Foundation of China (21222210, 91027041, 21272243) and the Chinese Academy of Sciences (100 Talents Program).

**Keywords:** bis-ureidopyrimidinones · hydrogen bonds · supramolecular chemistry · supramolecular polymers · thiol-yne reaction

- [1] a) R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. Ky Hirschberg, R. F. M. Lange, J. K. L. Lowe, E. W. Meijer, *Science* **1997**, *278*, 1601–1604; b) F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, *120*, 6761–6769; c) S. H. M. Söntjens, R. P. Sijbesma, M. H. P. van Genderen, E. W. Meijer, *J. Am. Chem. Soc.* **2000**, *122*, 7487–7493.
- [2] a) S. P. Dudek, M. Pouderoijen, R. Abbel, A. P. H. J. Schenning, E. W. Meijer, *J. Am. Chem. Soc.* **2005**, *127*, 11763–11768; b) J. Hentschel, A. M. Kushner, J. Ziller, Z. Guan, *Angew. Chem.* **2012**, *124*, 10713–10717; *Angew. Chem. Int. Ed.* **2012**, *51*, 10561–10565; c) J.-F. Xu, Y.-Z. Chen, D. Wu, L.-Z. Wu, C.-H. Tung, Q.-Z. Yang, *Angew. Chem.* **2013**, *125*, 9920–9924; *Angew. Chem. Int. Ed.* **2013**, *52*, 9738–9742; d) N. Hosono, M. A. J. Gillissen, Y. Li, S. S. Sheiko, A. R. A. Palmans, E. W. Meijer, *J. Am. Chem. Soc.* **2013**, *135*, 501–510; e) Z.-M. Shi, C.-F. Wu, T.-Y. Zhou, D.-W. Zhang, X. Zhao, Z.-T. Li, *Chem. Commun.* **2013**, *49*, 2673–2675.
- [3] a) R. Abbel, C. Grenier, M. J. Pouderoijen, J. W. Stouwdam, P. E. L. G. Leclère, R. P. Sijbesma, E. W. Meijer, A. P. H. J. Schenning, *J. Am. Chem. Soc.* **2009**, *131*, 833–843; b) S.-L. Li, T. Xiao, W. Xia, X. Ding, Y. Yu, J. Jiang, L. Wang, *Chem. Eur. J.* **2011**, *17*, 10716–10723; c) X. Yan, B. Jiang, T. R. Cook, Y. Zhang, J. Li, Y. Yu, F. Huang, H.-B. Yang, P. J. Stang, *J. Am. Chem.*

- Soc. **2013**, *135*, 16813–16816; d) R. E. Kieltyka, A. C. H. Pape, L. Albertazzi, Y. Nakano, M. M. C. Bastings, I. K. Voets, P. Y. W. Dankers, E. W. Meijer, *J. Am. Chem. Soc.* **2013**, *135*, 11159–11164; e) X. Yan, S. Li, J. B. Pollock, T. R. Cook, J. Chen, Y. Zhang, X. Ji, Y. Yu, F. Huang, P. J. Stang, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 15585–15590; f) H.-Q. Peng, J.-F. Xu, Y.-Z. Chen, L.-Z. Wu, C.-H. Tung, Q.-Z. Yang, *Chem. Commun.* **2014**, *50*, 1334–1337.
- [4] a) H. M. Keizer, R. P. Sijbesma, E. W. Meijer, *Eur. J. Org. Chem.* **2004**, 2553–2555; b) A. Tessa ten Cate, H. Kooijman, A. L. Spek, R. P. Sijbesma, E. W. Meijer, *J. Am. Chem. Soc.* **2004**, *126*, 3801–3808.
- [5] a) R. M. Hensarling, V. A. Doughty, J. W. Chan, D. L. Patton, *J. Am. Chem. Soc.* **2009**, *131*, 14673; b) C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, *39*, 1355–1387; c) A. B. Lowe, C. E. Hoyle, C. N. Bowman, *J. Mater. Chem.* **2010**, *20*, 4745–4750.
- [6] a) D. Konkolewicz, A. Gray-Weale, S. Perrier, *J. Am. Chem. Soc.* **2009**, *131*, 18075–18077; b) D. Konkolewicz, C. K. Poon, A. Gray-Weale, S. Perrier, *Chem. Commun.* **2011**, *47*, 239–241; c) V. X. Truong, A. P. Dove, *Angew. Chem. Int. Ed.* **2013**, *52*, 4132–4136.
- [7] a) M. H. Lee, J. H. Han, P.-S. Kwon, S. Bhuniya, J. Y. Kim, J. L. Sessler, C. Kang, J. S. Kim, *J. Am. Chem. Soc.* **2012**, *134*, 1316–1322; b) M. H. Lee, Z. Yang, C. W. Lim, Y. H. Lee, D. Sun, C. Kang, J. S. Kim, *Chem. Rev.* **2013**, *113*, 5071–5109.
- [8] a) W. W. Cleland, *Biochemistry* **1964**, *3*, 480–482; b) W. J. Lees, G. M. Whitesides, *J. Org. Chem.* **1993**, *58*, 642–647.
- [9] B. D. Fairbanks, T. F. Scott, C. J. Kloxin, K. S. Anseth, C. N. Bowman, *Macromolecules* **2009**, *42*, 211–217.
- [10] a) A. Thander, B. Mallik, *Chem. Phys. Lett.* **2000**, *330*, 521–527; b) Y. Li, K. Guo, H. Su, X. Li, X. Feng, Z. Wang, W. Zhang, S. Zhu, C. Wesdemiotis, S. Z. D. Cheng, W.-B. Zhang, *Chem. Sci.* **2014**, *5*, 1046–1053.
- [11] For characterization of supramolecular polymer please see references: a) Y. Liu, Z. Wang, X. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 5922–5932; b) F. Huang, D. S. Nagvekar, X. Zhou, H. W. Gibson, *Macromolecules* **2007**, *40*, 3561–3567.
- [12] a) H. Hofmeier, A. El-ghayoury, A. P. H. J. Schenning, U. S. Schubert, *Chem. Commun.* **2004**, 318–319; b) G. Gröger, V. Stepanenko, F. Würthner, C. Schmuck, *Chem. Commun.* **2009**, 698–700.
- [13] a) T. Ogoshi, K. Kitajima, T. Yamagishi, Y. Nakamoto, *Org. Lett.* **2010**, *12*, 636–638; b) Y. Yao, M. Xue, J. Chen, M. Zhang, F. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 15712–15715; c) M. Xue, Y. Yang, X. Chi, Z. Zhang, F. Huang, *Acc. Chem. Res.* **2012**, *45*, 1294–1308; d) J.-F. Xu, Y.-Z. Chen, L.-Z. Wu, C.-H. Tung, Q.-Z. Yang, *Org. Lett.* **2013**, *15*, 6148–6151; e) H. Zhang, Y. Zhao, *Chem. Eur. J.* **2013**, *19*, 16862–16879.

Received: April 4, 2014

Published online on July 23, 2014