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A Heterobifunctional Linker Bearing Azide-reactive Alkyne and Thiol-reactive Maleimide Connected with *N*-(2-Nitrobenzyl)imide to Synthesize Photocleavable Diblock Copolymers

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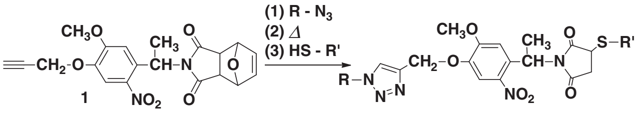
A novel heterobifunctional linker **1** connected with photocleavable *N*-(2-nitrobenzyl)imide has been developed. Hydrophobic polystyrene (PS), hydrophilic poly(ethylene oxide) (PEO), and thermosensitive poly(*N*-isopropylacrylamide) (PNIPAM) containing thiol or azide at the terminal, synthesized by a living radical polymerization or a transformation of terminal functional groups, were coupled with the alkyne and maleimide protected as the furan adduct at both terminals of **1** to synthesize three types of photocleavable diblock copolymers in high yields.

In the middle of the 1990s, atom-transfer radical polymerization (ATRP) by Matyjaszewski and Sawamoto[1,2] as well as different types of living radical polymerization[3] was developed to obtain many kinds of end-functionalized polymers and block copolymers very easily. In addition, a combination of click chemistry proposed by Sharpless[4] with living radical polymerizations promoted the synthesis and applications of a wide variety of polymers.[5] More recently, photosensitive structures were introduced into such polymers.[6] 2-Nitrobenzyl derivatives were mostly reported among the photosensitive units.[7] Polymers and block copolymers bearing 2-nitrobenzyl structure at the side chain, were synthesized to phototrigger micelle disruption and pattern thin films. Moreover, block copolymers connected with one photosensitive linker were also reportedly receiving attention as new materials such as a polymer assembly.[7,8] Most of block copolymers connected with 2-nitrobenzyl linkers were synthesized by living radical polymerization such as ATRP, reversible addition–fragmentation chain-transfer (RAFT) polymerization, and ring-opening polymerization.[9–12] However, it was reported that ATRPs of monomers containing 2-nitrobenzyl group were partially inhibited and that the control of molecular weights and their distributions was difficult.[13–15] Even in the case of the macroinitiator containing only one 2-nitrobenzyl group, there could be both difficulty in the control of molecular weight and limitation in the range of applicable monomers.

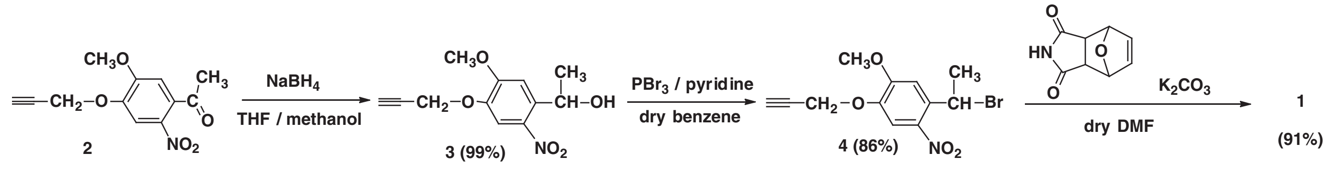
In this paper, a novel heterobifunctional linker **1** that is reactive to two types of click chemistry, the Huisgen cycloaddition and the Michael addition, connected with photocleavable 2-nitrobenzylimide was developed to synthesize photocleavable block copolymers in high yields and with control of the molecular weight. Alkyne and maleimide at the both terminals of **1** are highly reactive and mostly used for click chemistry with azido- and thiol-terminated polymers. Actually, the maleimide is protected as a Diels–Alder adduct with furan. Conceptual coupling reactions in three steps, including a deprotection step, are shown in Scheme 1. The alkyne reacts with azide at the terminal of $R–N_3$ to form a triazole ring by the Huisgen cycloaddition in the presence of Cu^IX and amine as the catalyst. After deprotection by the retro-Diels–Alder reaction, the generated maleimide undergo the Michael addition of R′–SH at the terminal in the presence of a tertiary amine. In this report, azido-terminated PS is synthesized by the reaction of sodium azide with bromo-terminated PS obtained by ATRP of styrene. Thiol-terminated PNIPAM is synthesized by aminolysis of terminal dithioester of PNIPAM obtained by RAFT polymerization of NIPAM. Azido- and thiol-terminated PEOs are employed for the coupling reaction. Three photocleavable block copolymers were synthesized by the two-step coupling reaction of end-functionalized PS, PNIPAM, and PEO. Three photocleavable block copolymers were synthesized by the two-step coupling reaction inserted with a deprotection step. The photosensitivity of the block copolymers was estimated and compared with that of a model compound **7a** synthesized separately. Turbidities of block copolymers containing PNIPAM as well as the homopolymer as a precursor in aqueous solutions were measured at different temperatures to determine the lower critical solution temperature (LCST).



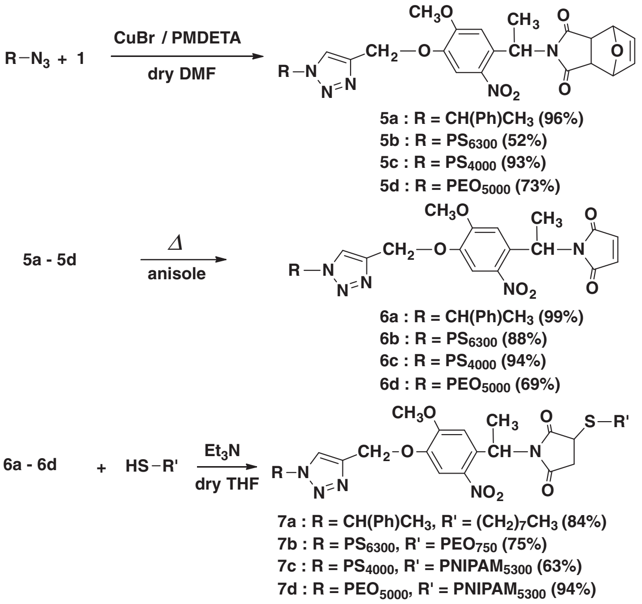
Scheme 1. Synthesis of photocleavable diblock copolymer using photodegradable heterobifunctional linker **1**.

Photocleavable linker **1** was synthesized as shown in Scheme 2. Compound **2**[16] synthesized in four steps from 4-hydroxy-3-methoxyacetophenone was reduced with $NaBH_4$ to alcohol **3** in 99% yield, reacting with PBr_3 to obtain bromide **4** in 86% yield. Finally, coupling of **4** and an adduct[17] of maleimide with furan in the presence of potassium carbonate afforded **1** in 91% yield identified by ^{1}H NMR, UV spectra, and elemental analysis.[18]

Synthetic route of a model compound **7a** and three different types of photocleavable block copolymers **7b**–**7d** are shown in Scheme 3. Prior to synthesis of photocleavable block copolymers using **1**, a model compound **7a** for the block copolymer was synthesized as shown in Scheme 3. The Huisgen cycloaddition of **1** and 1-azidoethylbenzene as the first click chemistry gave triazole **5a** in 96% yield, which was heated at 120 °C in anisole for removal of the protecting group to obtain maleimide **6a**, quantitatively. The Michael addition of **6a** with octane-1-thiol in the presence of triethylamine as the second click chemistry afforded model compound **7a** in 84% yield, as identified by ^{1}H NMR, UV spectra, and elemental analysis.[19]



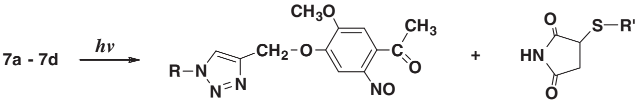
Scheme 2. Synthesis of photocleavable linker **1**.



Scheme 3. Synthesis of model compound **7a** and diblock copolymer **7b**–**7d**.

Table 1. Characterization of diblock copolymer **7b**–**7d**

	M_n				M_w/M_n (SEC)	Exposure dose/J cm^{-2}
	calcd	^{1}H NMR	UV	SEC		
7b	7380	7750	7700	8400	1.09	13
7c	9930	9900	9700	—	—	15
7d	10630	10600	10400	—	—	13



Scheme 4. Photolysis of model compound **7a** and diblock copolymer **7b**–**7d**.

The Huisgen cycloaddition of azido-terminated PS (molecular weights of 4000 and 6300)[20,21] and **1** with Cu^{I}Br and PMDETA was carried out to obtain **5b** and **5c** in 52% and 93% yields, respectively. The desired products were easily purified by reprecipitation against methanol followed by silica gel chromatography for removal of excess amount of PS used. Cycloaddition of azido-terminated PEO (molecular weights 5000)[21] synthesized from PEO via tosylated PEO[22] with **1** was similarly carried out to get **5d** in 73% yield. The products were purified by extraction with aqueous EDTA solution to remove Cu^{I}Br, followed by reprecipitation against ice-cooled diethyl ether. The resulting polymers **5b**–**5d** were characterized by ^{1}H NMR and SEC. The Diels–Alder adducts, **5b**–**5d** were heated for 4 h at 120 °C in anisole to remove the protecting group of *N*-maleimide through the retro-Diels–Alder reaction and to obtain *N*-maleimido-terminated polymers **6b**–**6d** in 88%, 94%, and 69% yields, respectively. The Michael addition of the maleimides **6b** and **6d** with excess amount of thiol-terminated PEO (molecular weight 750)[23] were carried out in the presence of triethylamine to synthesize **7b** in 75% yield, which was then purified by reprecipitation against methanol. Block copolymers **7c** and **7d** containing a PNIPAM segment were synthesized by the Michael addition of **6c** and **6d** in the presence of triethylamine to thiol-terminated PNIPAM generated in situ from a precursor, dithiobenzoate-terminated PNIPAM (molecular weight 5300),[24] by aminolysis using hexylamine.[25] A photocleavable block copolymer of PEO with PNIPAM **7d** was obtained in 94% yield by reprecipitation against diethyl ether, while block copolymer of PS with PNIPAM **7c** was afforded in 63% yield by a silica gel column chromatography because of no solvent adequate for reprecipitation. In ^{1}H NMR spectra of **7d** in $CDCl_3$ (Figure S1),[26] peaks originated from PEO, PNIPAM, and **1** were observed at 0.64–2.74, 3.42–3.91, and 5.48–7.18 ppm, confirming the structure of **7d**. Based on the integral ratio of the peaks of PEO and PNIPAM (at 3.7 and 3.9 ppm), the molecular weight of **7d** was determined. Molecular weights of the block copolymers **7b** and **7c** were similarly determined from ^{1}H NMR (Figures S2 and S3).[26] Molecular weights were also determined by UV using the value of $\varepsilon = 4100$ at 341 nm of a model compound **7a** for the block copolymers. Table 1 summarizes molecular weights of **7b**–**7d** determined by ^{1}H NMR and UV spectra as well as that determined from the polydispersity index from SEC. The molecular weights determined by different methods are consistent with one another, showing the ability to control the molecular weight of each block synthesized by living radical polymerizations. To our knowledge, **7c** and **7d** are the first examples of photocleavable block copolymers containing PNIPAM. Synthetic methods for **1**, **3**–**7**, and end-functionalized homopolymers are described.[26]

Photodecomposition of a model compound **7a** for **7b**–**7d** was monitored by UV spectroscopy and HPLC. Exposure dose of 12 J cm^{-2} was required for the complete photodecomposition, judging from no spectral change and disappearance of **7a** in HPLC. The nitroso compound was obtained from the photodecomposed mixture by a preparative TLC as shown in Scheme 4 (R = 1-phenylethyl).[27] This structure is consistent with those of products by the photoreaction of 2-nitrobenzyl derivatives such as esters of carboxylic and carbamic acids, and *N*-2-nitrobenzylamide reported previously.[28] UV spectral change of **7d** in THF upon photoirradiation for 0–120 s is shown in Figure 1. The absorption of original **7d** at 341 nm decreased,

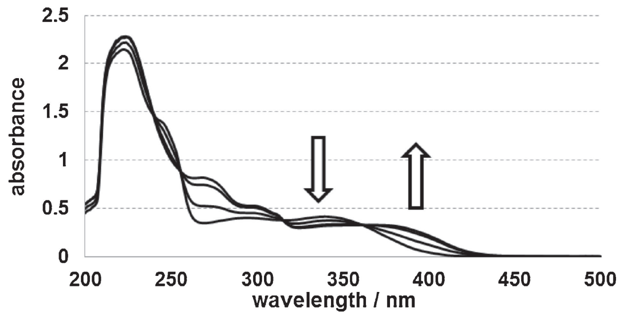


Figure 1. UV–vis spectral change of compound **7d** upon photoirradiation for 0, 30, 90, and 120 s.

and a new absorption at 370 nm close to that of the nitroso compound from **7a**[27] in Scheme 4 was observed. When the spectra have no change after photoirradiation for 120 s, there are still isosbestic points at 250, 315, and 362 nm, similar to the case of **7a**. This suggests that no side reaction occurs during photolysis of the 2-nitrobenzylimide of **7d**. Exposure doses of 13–15 J cm^{-2} are required for the photolysis of **7b**–**7d**, similar to that of **7a**, as shown in Table 1, indicating that the photoreaction rates are not significantly affected by the structures and molecular weights of the block copolymers.

LCSTs of end-functionalized PNIPAM and the block copolymers in an aqueous solution were determined by turbidity change with temperature. LCST of PNIPAM (molecular weight 5300) terminated with dithiobenzoate was 36 °C, higher than 33 °C of PNIPAM synthesized by a conventional radical polymerization.[29] LCST of **7d** was 39 °C comparable to 38 °C of PEO-*b*-PNIPAM without a photocleavable linker by synthesized by ATRP from a macroinitiator[30] and much higher than that of homopolymer.[29]

A novel photocleavable heterobifunctional linker **1** connected with *N*-(2-nitrobenzyl)imide has been developed, which is coupled with the Huisgen cycloaddition reaction and the Michael addition reaction. Polymers containing thiol or azide were coupled with alkyne and maleimide of **1** to synthesize photosensitive (and thermosensitive) diblock copolymers, PS-*b*-PEO, PS-*b*-PNIPAM, and PEO-*b*-PNIPAM connected with photocleavable 2-nitrobenzylimide in high yields. The energy needed for photolysis of diblock copolymer in solution was found to be 13–15 J cm^{-2}, regardless of the type and molecular weight of the polymers. It was demonstrated that **1** was very useful for the synthesis of a variety of photocleavable block copolymers applicable to functional polymer assembly such as photosensitive polymer micelles and polymersomes.[7,8]

References and Notes

1 J.-S. Wang, K. Matyjaszewski, *J. Am. Chem. Soc.* **1995**, *117*, 5614.

2 M. Kato, M. Kamigaito, M. Sawamoto, T. Higashimura, *Macromolecules* **1995**, *28*, 1721.

3 W. A. Braunecker, K. Matyjaszewski, *Prog. Polym. Sci.* **2007**, *32*, 93.

4 H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

5 N. Akeroyd, B. Klumperman, *Eur. Polym. J.* **2011**, *47*, 1207.

6 J.-M. Schumers, C.-A. Fustin, J.-F. Gohy, *Macromol. Rapid Commun.* **2010**, *31*, 1588.

7 H. Zhao, E. S. Sterner, E. B. Coughlin, P. Theato, *Macromolecules* **2012**, *45*, 1723.

8 P. Theato, *Angew. Chem., Int. Ed.* **2011**, *50*, 5804.

9 M. Kang, B. Moon, *Macromolecules* **2009**, *42*, 455.

10 J.-M. Schumers, J.-F. Gohy, C. A. Fustin, *Polym. Chem.* **2010**, *1*, 161.

11 H. Zhao, W. Gu, E. Sterner, T. P. Russell, E. B. Coughlin, P. Theato, *Macromolecules* **2011**, *44*, 6433.

12 E. Cabane, V. Malinova, W. Meier, *Macromol. Chem. Phys.* **2010**, *211*, 1847.

13 J. Jiang, X. Tong, D. Morris, Y. Zhao, *Macromolecules* **2006**, *39*, 4633.

14 J.-M. Schumers, C.-A. Fustin, A. Can, R. Hoogenboom, U. S. Schubert, J.-F. Gohy, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 6504.

15 S. Kumar, Y. L. Dory, M. Lepage, Y. Zhao, *Macromolecules* **2011**, *44*, 7385.

16 N. Umeda, T. Ueno, C. Pohlmeyer, T. Nagano, T. Inoue, *J. Am. Chem. Soc.* **2011**, *133*, 12.

17 H. Kwart, I. Burchuk, *J. Am. Chem. Soc.* **1952**, *74*, 3094.

18 ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (1H, s), 7.15 (1H, s), 6.51 (2H, s), 6.04 (1H, q, $J = 7.2$ Hz), 5.29 (1H, s), 5.22 (1H, s), 4.80 (2H, d, $J = 2.4$ Hz), 3.92 (3H, s), 2.88 (1H, d, $J = 6.6$ Hz), 2.79 (1H, d, $J = 6.6$ Hz), 2.57 (1H, t, $J = 2.4$ Hz), 1.84 (3H, d, $J = 7.2$ Hz). Anal. Calcd for $C_{20}H_{18}N_2O_7$: C, 60.30; H, 4.55; N, 7.03%. Found: C, 60.36; H, 4.55; N, 6.82%. UV measurement (in 0.10 mM THF solution): $\lambda_{max} = 335$ nm, $\varepsilon = 5200$.

19 ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.67 (1H, s), 7.54 (1H, s), 7.40–7.28 (6H, m), 6.01 (1H, q, $J = 7.1$ Hz), 5.81 (1H, q, $J = 7.1$ Hz), 5.25 (2H, s), 3.91 (3H, d, $J = 2.1$ Hz), 3.65 (1H, dtd, $J = 3.7$ Hz, $J = 3.8$ Hz, $J = 3.1$ Hz), 3.13–3.03 (1H, m), 2.90–2.63 (2H, m), 2.49 and 2.44 (1H, dd, $J = 3.3$ Hz, $J = 3.3$ Hz), 1.99 (3H, d, $J = 7.1$ Hz), 1.84 (3H, td, $J = 9.4$ Hz, $J = 4.4$ Hz), 1.62–1.53 (2H, br). 1.36–1.26 (10H, br), 0.87 (3H, td, $J = 7.6$ Hz, $J = 1.5$ Hz). Anal. Calcd for $C_{32}H_{41}N_5O_6S$: C, 61.62; H, 6.63; N, 11.23%. Found: C, 61.11; H, 6.71; N, 10.99%. UV measurement (in 0.10 mM THF solution): $\lambda_{max} = 341$ nm, $\varepsilon = 4100$.

20 M. Hikita, K. Tanaka, T. Nakamura, T. Kajiyama, A. Takahara, *Langmuir* **2004**, *20*, 5304.

21 S. Arseniyadis, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2002**, *43*, 9717.

22 Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, Y. Tanabe, *Tetrahedron* **1999**, *55*, 2183.

23 D. Wan, H. Pu, G. Yang, *React. Funct. Polym.* **2008**, *68*, 431.

24 B. Yu, J. W. Chan, C. E. Hoyle, A. B. Lowe, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3544.

25 X. Huang, C. Boyer, T. P. Davis, V. Bulmus, *Polym. Chem.* **2011**, *2*, 1505.

26 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

27 ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.50 (1H, s), 7.37–7.27 (5H, m), 6.22 (1H, s), 5.79 (1H, q, $J = 7.1$ Hz), 5.20 (1H, s), 4.02 (1H, s), 2.94 (3H, s), 1.98 (3H, d, $J = 7.1$ Hz). UV measurement (in THF solution): $\lambda_{max} = 376$ nm.

28 P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev.* **2013**, *113*, 119.

29 H. Wei, S.-X. Cheng, X.-Z. Zhang, R.-X. Zhuo, *Prog. Polym. Sci.* **2009**, *34*, 893.

30 K. H. Kim, J. Kim, W. H. Jo, *Polymers* **2005**, *46*, 2836.