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Cu-Catalyzed Multicomponent Polymerization To Synthesize a Library of Poly(*N*-sulfonylamidines)

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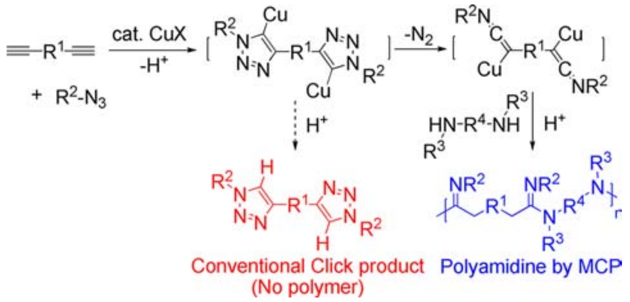
Supporting Information

ABSTRACT: We report a versatile Cu-catalyzed multicomponent polymerization (MCP) technique that enables the synthesis of high-molecular-weight, defect-free poly(*N*-sulfonylamidines) from monomers of diynes, sulfonyl azides, and diamines. Through a series of optimizations, we discovered that the addition of excess triethylamine and the use of *N*,*N*′-dimethylformamide as a solvent are key factors to ensure efficient MCP. Formation of cyclic polyamidines was a side reaction during polymerization, but it was readily controlled by using diynes or diamines with long or rigid moieties. In addition, this polymerization is highly selective for three-component reactions over click reactions. The combination of the above factors enables the synthesis of high-molecular-weight polymers, which was challenging in previous MCPs. All three kinds of monomers (diynes, sulfonyl azides, and diamines) are readily accessible and stable under the reaction conditions, with various monomers undergoing successful polymerization regardless of their steric and electronic properties. Thus, we synthesized various high-molecular-weight, defect-free polyamidines from a broad range of monomers while overcoming the limitations of previous MCPs, such as low conversion and defects in the polymer structures.

Multicomponent reactions (MCRs) such as the Cu-catalyzed three-component reaction (3CR),[1] the Mannich reaction,[2] the Passerini reaction,[3] and A^3 coupling,[4] have received great attention because of their ability to generate complex molecules economically. MCRs have recently been introduced into the field of polymer synthesis, and step-growth polymerization has provided access to various novel materials. For instance, polyester,[5] poly(ester–amide),[6] polyether,[7] poly(ester ether ketone),[8] polyurethane,[9] polythiourethane,[10] and π-conjugated polymers[11] such as poly(*p*-phenylenevinylene) have been synthesized by multicomponent polymerization (MCP). However, many of the previous MCPs are limited by a narrow monomer scope and afford low-molecular-weight polymers because of low conversion, low solubility, and various side reactions leading to defects in the polymer structure. Thus, the development of a new MCP that can generate both high-molecular-weight and defect-free polymers from a broad range of monomers would be desirable.

Polyamidines have attracted great attention because of their potential role as biomaterials,[12] metallic conductors,[13] and photosensitive semiconductors.[14] However, their syntheses have been limited to two-component step-growth polymerization reactions.[15] Thus, MCP is a promising synthetic strategy for producing various polyamidine structures. Recently, Chang's group reported an efficient Cu-catalyzed 3CR of alkynes, sulfonyl azides, and amines to generate a library of small-molecule amidines via Cu-catalyzed azide–alkyne cycloaddition (CuAAC) followed by a successive ring-opening process and nucleophilic attack by the amine (Scheme 1).[1a,c]

Scheme 1. Polymerization Scheme for Poly(*N*-sulfonylamidine) Synthesis



This synthesis generally resulted in moderate to excellent isolated product yields (generally 59–95%, with one example approaching 99%). Furthermore, excellent product selectivity for the 3CR (>99%) rather than more well-known click reaction leading to the formation of the triazole ring was observed.[1a,c] Although click reactions are widely used as a versatile route to two-component step-growth polymerization,[16] this new MCR has not been applied to polymerization reactions. Herein we report a versatile synthesis of a library of poly(*N*-sulfonylamidines) via a Cu-catalyzed MCP of various diynes, sulfonyl azides, and diamines. The main advantage of this method is its high selectivity for the 3CR over the click reaction, leading to defect-free polymer microstructures. Furthermore, all three kinds of monomers used are either readily available or easily accessible and, most importantly, stable under the reaction conditions employed. Thus, after the reaction conditions were optimized to maximize the conversion of the polymerization, 26 well-defined high-molecular-weight polyamidines were prepared from 26 different monomers, demonstrating the broad substrate scope of this methodology.

Utilizing the optimal conditions reported by Chang's group for the synthesis of small molecules, a model polymerization of diyne **A**, *p*-toluenesulfonyl azide, and *N*,*N*′-diisobutyl-1,6-

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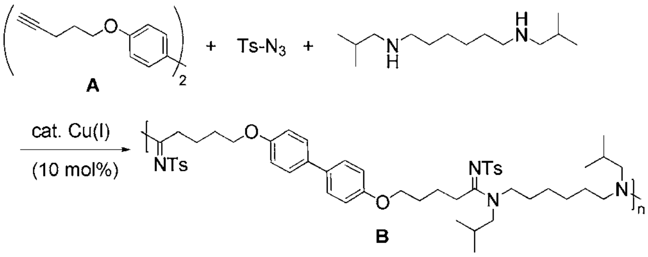
hexanediamine in tetrahydrofuran (THF) was attempted at room temperature.[1a] The stoichiometric balance between the diyne and the diamine was very important because both are involved in the chain-growth process of the step-growth polymerization. On the other hand, excess *p*-toluenesulfonyl azide (3 equiv) could be used to enhance the conversion of diyne **A** without limiting the molecular weight of the resulting polyamidine. Under these reaction conditions, a significant amount of precipitate formed during the course of the polymerization. To increase the solubility, the polymerization temperature was increased to 50 °C, which resulted in a more homogeneous reaction mixture. However, the number-average molecular weight (M_n) of the resulting poly(*N*-sulfonylamidine) **B** [2.7 kg/mol as determined by THF size-exclusion chromatography (SEC) calibrated using polystyrene (PS) standards] was still low (Table 1, entry 1), prompting further optimization of the synthetic procedure for highly polar polyamidines.

Table 1. Optimization of the Model MCP



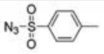
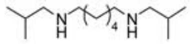
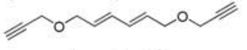
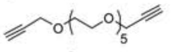
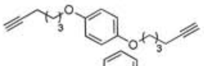
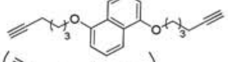
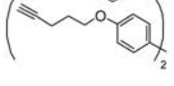
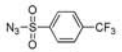
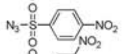
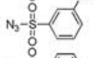
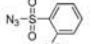
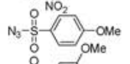
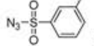
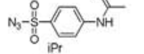
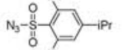
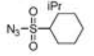
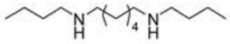
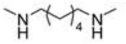
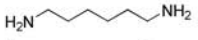
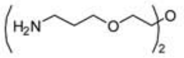
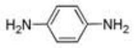
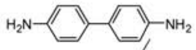
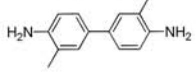
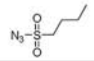
entry	catalyst	solvent	conc (M)	temp (°C)	additive (equiv)	M_n (PDI)[a]
1	CuI	THF	0.5	50	none	2.7 (1.22)
2	CuI	DMF	0.5	70	none	6.2 (1.71)
3	CuCl	DMF	0.5	70	none	7.5 (1.92)
4	CuCl	DMF	1.0	70	TBTA (0.1)	7.3 (1.73)
5	CuCl	DMF	1.0	70	TEA (5)	10.8 (2.81)

[a] Determined by THF SEC calibrated using PS standards. M_n is given in kg/mol.

Toward this goal, solvent screening at high temperatures was conducted. Polymerization in chloroform, 1,2-dichloroethane (DCE), and 1,4-dioxane resulted in unsatisfactory conversion. However, polymerization at 70 °C in the polar solvent *N,N′*-dimethylformamide (DMF) produced **B** with a doubled M_n [Table 1, entries 1 and 2; also see Table S1 in the Supporting Information (SI)], which was unexpected because DMF has been reported to be a poor solvent for 3CRs of small molecules.[1d] It seemed that the highly polar DMF increases the solubility of the polar poly(*N*-sulfonylamidines), resulting in high conversion. With optimized temperature and solvent conditions, several Cu(I) catalysts were screened because their counteranions and ligands could affect the catalytic activity in the MCP. Most catalysts showed good activity, and among them, CuCl showed the best results (Table 1, entries 2 and 3, and Table S1). Since the polymer showed excellent solubility in DMF, the polymerization concentration was increased to 1 M to facilitate higher conversion. In addition, to enhance the catalytic activity further, various additives were screened. The addition of tris(benzyltriazolylmethyl)amine (TBTA), a ligand reported to accelerate 3CRs,[1e] gave no noticeable improvement (Table 1, entry 4). Next, several amine bases were tried. The addition of 1 equiv of diisopropylethylamine (DIPEA) did not improve the polymerization, but excess DIPEA or 2,6-lutidine (5 equiv) significantly enhanced the conversion (Table S1). Ultimately, the best additive was found to be 5 equiv of triethylamine (TEA), which yielded the highest M_n (10.8 kg/mol; Table 1, entry 5); the absolute molecular weight determined by multiangle laser light scattering (MALLS) was much higher (30.8 kg/mol; Table 2, entry 6), suggesting that the conventional calibration method underestimated M_n. We speculate that TEA might play two important roles in enhancing the polymerization conversion. First, protons are generated in each coupling reaction. In the absence of an external base such as TEA, the diamine monomers are protonated to form ammonium salts, which are poor nucleophiles that do not facilitate conversion. In small-molecule synthesis, this problem is circumvented by adding excess amine reagent. However, in step-growth polymerization, where stoichiometric balance is extremely important, addition of external bases that do not interfere with the polymerization would be necessary to regenerate the active nucleophiles. Second, excess TEA would accelerate the formation of the Cu–acetylide complex from the Cu(I) catalyst and a terminal alkyne (Scheme 1), which in turn should increase the rate of polymerization and the molecular weights of the final polymers. ^{1}H and ^{13}C NMR analysis of the final polymer **B** (Figure S1 in the SI) confirmed that this MCP is highly selective for the 3CR over the conventional click reaction. This feature is indispensable for obtaining high-molecular-weight polymers because the click reaction between the diyne and the monofunctionalized sulfonyl azide would produce chain end-capping groups that would terminate the polymerization (Scheme 1).

Under the newly optimized polymerization conditions, various types of monomers were examined to expand the substrate scope of this MCP. First, we explored various diynes containing alkyl, diene, ethylene glycol, and aromatic groups and found that all of the diynes produced polyamidines with reasonable M_n ranging from 22 to 64 kg/mol as determined by MALLS (Table 2, entries 1–6). Initially, the polymerization of commercially available 1,6-heptadiyne with *p*-toluenesulfonyl azide and *N,N′*-diisobutyl-1,6-hexanediamine was explored, and a polymer with a relatively lower molecular weight was obtained (Table 2, entry 1). A closer analysis of the SEC trace revealed several sharp peaks in the low-molecular-weight region (Figure 1) even after rigorous purification through multiple precipitations for complete removal of the monomers. These low-molecular-weight contaminants were identified as cyclic dimers and oligomers by MALDI-TOF analysis, which revealed strong peaks corresponding to the molecular weights of these cyclic compounds (Figure S2). We hypothesized that suppressing the cyclization reactions would increase the molecular weights of the polyamidines, leading us to investigate how the structure of the alkyne could affect the degree of cyclization. We observed by SEC analysis that employing a less flexible diyne containing a diene moiety (**1b**) or a longer diyne (**1c**) as the monomer produced smaller amounts of cyclic products (Figure 1 and Table 2, entries 2 and 3). Furthermore, MCP from diynes containing highly rigid moieties such as phenyl, biphenyl, and naphthyl produced polyamidines with higher molecular weights (relative M_n up to 18 kg/mol and absolute M_n up to 64 kg/mol) and significantly smaller amounts of cyclic compounds (Figure 1 and Table 2, entries 4–6). Therefore, we could successfully suppress the cyclization

Table 2. Synthesis of Various Poly(*N*-sulfonylamidines)

entry	diyne	sulfonyl azide	diamine	M_n[a] (MALLS)[b]	PDI[a]	yield[c]
1	1a 	2a 	3a 	4.7k (22.4k)	1.52	72%
2	1b 	2a	3a	4.8k (23.4k)	1.54	98%
3	1c 	2a	3a	6.2k (22.8k)	1.50	79%
4	1d 	2a	3a	16.7k (56.1k)	2.99	84%
5	1e 	2a	3a	18.2k (63.9k)	2.53	78%
6	1f 	2a	3a	10.8k (30.8k)	2.81	76%
7	1f	2b 	3a	11.1k (21.5k)	2.16	74%
8	1f	2c 	3a	14.6k (–)[d]	3.51	90%
9	1f	2d 	3a	16.8k (–)[d]	5.07	85%
10	1f	2e 	3a	15.3k (–)[d]	5.92	90%
11	1f	2f 	3a	12.2k (20.1k)	1.85	87%
12	1f	2g 	3a	10.7k (25.7k)	1.51	93%
13	1f	2h 	3a	23.5k (–)[d]	1.77	91%
14	1f	2i 	3a	13.2k (44.7k)	1.69	78%
15	1f	2j 	3a	7.4k (34.6k)	2.77	66%
16	1f	2a	3b 	13.3k (19.9k)	2.97	74%
17	1f	2i	3b	9.7k (43.6k)	1.93	72%
18	1f	2i	3c 	8.9k (67.2k)	2.03	79%
19	1f	2i	3d 	19.2k (–)[d]	1.97	93%
20	1c	2i	3e 	14.5k (31.7k)	1.75	79%
21	1f	2i	3e	12.7k (44.0k)	2.10	77%
22	1f	2i	3f 	18.6k (75.1k)	1.91	72%
23	1f	2i	3g 	15.7k (–)[d]	2.37	76%
24	1c	2i	3h 	8.3k (50.9k)	1.73	71%
25	1f	2i	3h	15.7k (74.9k)	1.53	72%
26	1g 	2k 	3h	15.0k (–)[d]	1.99	86%

[a] Determined by DMF SEC calibrated using poly(methyl methacrylate) standards (entries 5, 7–14, 16–19, 21–23, 25–26) or THF SEC calibrated using PS standards (entries 1–4, 6, 15, 20, 24). M_n is given in g/mol. [b] Absolute molecular weights (in g/mol) determined by THF SEC ($CHCl_3$ SEC for entries 11 and 12) using a MALLS detector. [c] Isolated yields after precipitation from selected solvents. [d] The absolute molecular weight could not be obtained because the polymer was not soluble in THF or $CHCl_3$.

process by changing the rigidity or length of the diyne substrate, affording polymers with high molecular weights.

Next, we examined the feasibility of using different sulfonyl azides. At first, various phenylsulfonyl azides containing electron-donating groups (−OMe, −NHCOMe), electron-withdrawing groups ($-CF_3$, $-NO_2$), or a sterically hindered group (−iPr) at various positions on the aromatic ring were tested. Surprisingly, regardless of the position (ortho, meta, or para), electronic nature, or steric bulk of the substituent on the phenylsulfonyl azide, polymerization was successfully achieved (Table 2, entries 7–14). Although the absolute molecular weights of several highly polar polymers could not be determined by MALLS because of their poor solubility in THF and $CHCl_3$, they all had high molecular weights of over 10 kg/mol as determined by the relative calibration method. We believe that the corresponding absolute molecular weights would be much higher in view of the fact that for the other polymers the M_n values obtained from MALLS were at least 2 and generally 3–5 times larger than those obtained from standard calibration methods. In addition to aromatic sulfonyl azides, alkylsulfonyl azides (e.g., **2j** and **2k**) also afforded high-molecular-weight polymers (Table 2, entries 15 and 26). Thus, diverse sulfonyl azides with different functionalities were successfully introduced to the polyamidine structures. With

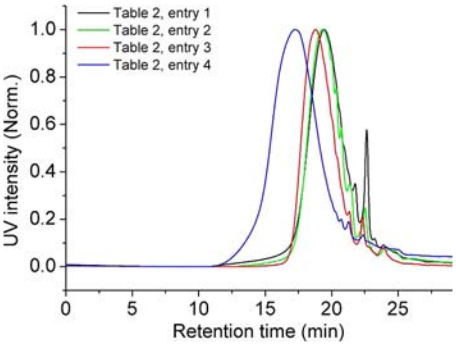


Figure 1. THF SEC trace monitored using a UV detector at 254 nm.

the successful introduction of various diynes and sulfonyl azides, we finally examined a variety of diamines to enrich the combination of monomers. Polymerization using primary dialkylamines and sterically demanding secondary dialkylamines successfully yielded polyamidines with absolute M_n values of up to 67 kg/mol, as measured by MALLS (Table 2, entries 16–21). In addition, even though aniline derivatives are much weaker nucleophiles than alkylamines, diarylamines (**3f**, **3g**, and **3h**) were excellent monomers for this MCP, affording the highest absolute M_n values of up to 75 kg/mol (Table 2, entries 22–25). From these observations, we can conclude that once the ketenimine species is formed via ring opening of the triazole, nucleophilic attack on the highly reactive ketenimine by the diamine readily occurs regardless of the electronic and steric nature of the diamine. Moreover, rigid diamines (**3f** and **3h**) produced the polyamidines with the highest molecular weights when polymerized with rigid diyne **1f** (absolute M_n of up to 75 kg/mol) (Table 2, entries 22 and 25) because the rigid monomers suppressed the cyclization reactions.

In summary, we have synthesized various poly(*N*-sulfonylamidines) via a Cu-catalyzed 3CR of diynes, sulfonyl azides, and diamines. This MCP shows high selectivity for the 3CR over the click reaction, affording defect-free polyamidines with highly regular structures. Conversion in the polymerization reaction was significantly enhanced by the addition of excess external base (5 equiv of TEA) with a polar solvent (DMF), while cyclic contaminants were reduced by incorporating long or rigid moieties into the diyne or diamine monomers. The significance of this work lies in the ability of the Cu-catalyzed MCP to facilitate the facile and efficient synthesis of highly diverse high-molecular-weight polyamidines from an electronically and sterically diverse range of diynes, sulfonyl azides, and diamines, which are not only readily available but also stable under the given reaction conditions. Therefore, diverse moieties such as alkyl, aryl, diene, and poly(ethylene glycol) could be incorporated into the polymer backbone. Ultimately, this MCP overcomes the common limitations of other MCPs, such as low conversion and narrow substrate scope.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental details, synthesis, complete table of optimization results, characterization data (TGA, DSC, SEC traces, etc.), and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347. (c) Yoo, E. J.; Ahlquist, M.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520. (d) Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745. (e) Hwang, S. J.; Cho, S. H.; Chang, S. *Pure Appl. Chem.* **2008**, *80*, 873. (f) Kim, S. H.; Park, S. H.; Choi, J. H.; Chang, S. *Chem.—Asian J.* **2011**, *6*, 2618.

(2) (a) Mannich, C.; Krosche, W. *Arch. Pharm* **1912**, *250*, 647. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(3) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231.

(4) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790.

(5) Kreye, O.; Tóth, T.; Meier, M. A. R. *J. Am. Chem. Soc.* **2011**, *133*, 1790.

(6) Deng, X. X.; Li, L.; Li, Z. L.; Lv, A.; Du, F. S.; Li, Z. C. *ACS Macro Lett.* **2012**, *1*, 1300.

(7) (a) Takenoya, K.; Yokozawa, T. *Macromolecules* **1998**, *31*, 2906. (b) Niimi, L.; Shiino, K.; Hiraoka, S.; Yokozawa, T. *Macromolecules* **2002**, *35*, 3490.

(8) Ihara, E.; Hara, Y.; Itoh, T.; Inoue, K. *Macromolecules* **2011**, *44*, 5955.

(9) Niimi, L.; Serita, K.; Hiraoka, S.; Yokozawa, T. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1236.

(10) Ochiai, B.; Ogihara, T.; Mashiko, M.; Endo, T. *J. Am. Chem. Soc.* **2009**, *131*, 1636.

(11) (a) Miyaki, N.; Tomita, I.; Endo, T. *Macromolecules* **1997**, *30*, 4504. (b) Choi, C. K.; Tomita, I.; Endo, T. *Macromolecules* **2000**, *33*, 1487. (c) Ishibe, S.; Tomita, I. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 3403. (d) Nakagawa, K.; Tomita, I. *Chem. Lett.* **2007**, *36*, 638. (e) Siamaki, A. R.; Sakalauskas, M.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6552.

(12) (a) Nastruzzi, C.; Gambari, R.; Menegatti, E.; Walde, P.; Luisi, P. L. *J. Pharm. Sci.* **1990**, *79*, 672. (b) Sharavanan, K.; Komber, H.; Fischer, D.; Böhme, F. *Polymer* **2004**, *45*, 2127.

(13) Ionov, A. N.; Rentzsch, R.; Nikolaeva, M. N. *Phys. Status Solidi C* **2008**, *5*, 730.

(14) (a) Aleksandrova, E. L.; Dudkina, M. M.; Ten'kovtsev, A. V. *Semiconductors* **2003**, *37*, 282. (b) Aleksandrova, E. L.; Dudkina, M. M.; Ten'kovtsev, A. V. *Semiconductors* **2004**, *38*, 1284.

(15) (a) Brand, R. A.; Bruma, M.; Kellman, R.; Marvel, C. S. *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 2275. (b) Sharavanan, K.; Komber, H.; Böhme, F. *Macromol. Chem. Phys.* **2002**, *203*, 1852. (c) Kholkhoev, B. Ch.; Burdukovskii, V. F.; Mognonov, D. M. *Russ. Chem. Bull., Int. Ed.* **2010**, *59*, 2159. (d) Kholkhoev, B. Ch.; Burdukovskii, V. F.; Mognonov, D. M. *Russ. J. Appl. Chem.* **2011**, *84*, 510.

(16) (a) Díaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4392. (b) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2010**, *39*, 2522.